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

NCT Number: NCT05091567

Document Date: Protocol Amendment Version 8: 05-Mar-2025

PROTOCOL

PROTOCOL 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**
PROTOCOL NUMBER:	GO43104
STUDY NAME:	IMforte
VERSION NUMBER:	8
TEST COMPOUNDS:	Lurbinectedin (PM01183/JZP712) Atezolizumab (RO5541267)
STUDY PHASE:	Phase III
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 156,531 EudraCT Number: 2021-001930-20 EU CT Number: 2023-503868-16-00 NCT Number: NCT05091567
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 *4058* Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
8	See electronic date stamp on the final page of this document.
7	27 November 2023
6	23 February 2023
5	19 September 2022
4	18 February 2022
3	3 December 2021
2	22 September 2021
1	11 August 2021

PROTOCOL AMENDMENT, VERSION 8: RATIONALE

Protocol GO43104 has been amended to align the risks and management guidelines with the Atezolizumab Investigator's Brochure, Version 21. In addition, given that the clinical cut-off date for the final overall survival analysis has been reached and some study analyses are now complete, certain changes as outlined below have been implemented to alleviate the burden on participants and sites.

Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- [redacted]
- [redacted]
- Collection of demographic data, including information on race and ethnicity, is of importance to the future interpretation of results from the clinical trial. A rationale has been provided in Section 4.2.7.
- The estimated length of the study from first participant screened for enrollment into the induction phase to last participant, last visit has been updated from approximately 60 months to approximately 90 months (Section 4.4).
- Text in Section 6.6 has been modified to align with updates to the Roche Global Policy on Continued Access to Investigational Medicinal Products.
- The responsibilities of the investigator and the role of the Medical Monitor in study conduct have been clarified (Section 7.1).
- The Sponsor's policy on trade secrets has been described in Section A1-10 to increase transparency.
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 21 (Section A6-2.4.2).
- The adverse event management guidelines have been streamlined by removing standard of care information and restructured, for consistency with regulatory guidelines and industry standards (Section A6-2.4.2).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL 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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SPONSOR NAME:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL 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**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 156,531 EudraCT Number: 2021-001930-20 EU CT Number: 2023-503868-16-00 NCT Number: NCT05091567

STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of lurbinectedin, an alkylating drug that binds guanine residues in the minor groove of DNA, in combination with atezolizumab for the maintenance treatment of extensive-stage small-cell lung cancer (ES-SCLC) in participants whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin, and etoposide.

Despite the improved efficacy observed with programmed death-ligand 1 (PD-L1) inhibitors in combination with platinum-based chemotherapy in first-line ES-SCLC, most patients eventually experience disease progression and upon relapse, their prognosis is poor. Therefore, novel combination strategies are needed to deliver better long-term outcomes.

The early introduction of other agents active in small-cell lung cancer (SCLC), and with a complementing pathway to the current treatment approach, is an appealing strategy to further improve the prognosis of patients with advanced SCLC.

OBJECTIVES AND ENDPOINTS

Primary Objective	Corresponding Endpoints
• To evaluate the efficacy of lurbinectedin in combination with atezolizumab compared with atezolizumab	• Population: individuals with ES-SCLC who have ongoing CR, 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 • Endpoint: IRF-assessed PFS after randomization, defined as the time from randomization to the date of first documented disease progression (as assessed by the IRF according to RECIST v1.1) or death, whichever occurs first • Treatments: – Experimental arm: atezolizumab 1200 mg IV + lurbinectedin 3.2 mg/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 for IRF-assessed PFS • Population: as defined above • Endpoint: OS after randomization, defined as the time from randomization to the date of death from any cause • Treatments: as defined above • Intercurrent events and handling strategies: as defined above • Population-level summary: hazard ratio for OS
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 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 • 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 • PFS rates at 6 months and 12 months, defined as the proportion of participants who have not experienced disease progression or death from any cause at 6 months and 12 months after randomization, as determined by the IRF according to RECIST v1.1 • PFS rates at 6 months and 12 months, defined as the proportion of participants who have not experienced disease progression or death from any cause at 6 months and 12 months after randomization, as determined by the investigator according to RECIST v1.1 • 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 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
• To evaluate the health-related quality of life of participants treated with lurbinectedin in combination with atezolizumab compared with atezolizumab	• TTCD from randomization in patient-reported physical functioning and global health status as measured by the EORTC QLQ-C30

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; IRF = Independent Review Facility; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PRO = Patient-Reported Outcome; QLQ-C30 = Quality of Life Questionnaire–Core 30; RECIST = Response Evaluation Criteria in Solid Tumor; SD = stable disease; TTCD = time to confirmed deterioration.

OVERALL DESIGN AND STUDY POPULATION

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.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase III	**Population Type:**	Adult patients
Control Method:	Active comparator	**Population Diagnosis or Condition:**	ES-SCLC
Interventional Model:	Single group induction phase, parallel group maintenance phase	**Population Age:**	≥18 years
Test Compounds:	Lurbinectedin, Atezolizumab	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Atezolizumab	**Study Intervention Assignment Method:**	Randomization and stratification
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Induction phase: approximately 690 Maintenance phase: approximately [redacted]

ES-SCLC = extensive-stage small-cell lung cancer.

STUDY TREATMENT

STUDY TREATMENT IN THE INDUCTION PHASE

Once participants are screened for the induction phase and have been determined to be eligible, participants will be enrolled to receive 4 cycles of standard of care treatment with carboplatin, etoposide and atezolizumab unless unacceptable toxicity, disease progression or a participant's decision to discontinue occur, with each cycle being 3 weeks (21 days) in length. All participants will receive a fixed dose of 1200 mg atezolizumab administered by IV infusion on Day 1 of each 21-day cycle.

STUDY TREATMENT IN THE MAINTENANCE PHASE

Arm A: Atezolizumab + Lurbinectedin

Atezolizumab and lurbinectedin will be administered in the following order for Arm A:

Atezolizumab → Lurbinectedin

Atezolizumab 1200 mg IV + Lurbinectedin 3.2 mg/m^2 IV on Day 1 of each 21-day cycle.

Prophylactic anti-emetic medication and primary prophylaxis with pegylated G-CSF will be administered.

All participants will receive atezolizumab administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity, disease progression per RECIST v1.1, or any other discontinuation criterion has been met. The atezolizumab dose is fixed and is not dependent on body weight or body surface area. There will be no dose modifications such as dose reductions, for atezolizumab. Treatment with atezolizumab may be temporarily suspended as appropriate for management of adverse events.

All participants in Arm A will receive 3.2 mg/m^2 lurbinectedin administered by IV infusion on Day 1 of each 21-day cycle. The lurbinectedin dose is dependent on body surface area (BSA). It is recommended to calculate BSA using the DuBois formula.

The dose of lurbinectedin will be based on the participant's maintenance baseline weight (measured ≤28 days prior to randomization into the maintenance phase) and will remain the same throughout the study unless the participant's weight changes by >10% relative to the weight recorded at the time of the previous dose calculation. However, treating physicians may choose to re-calculate the dose of lurbinectedin based on the actual weight assessed prior to each dosing.

Up to 2 lurbinectedin dose reductions will be allowed (first dose reduction: 2.6 mg/m^2 Q3W; second dose reduction: 2 mg/m^2 Q3W). Once the dose has been reduced for an individual participant, it must not be re-escalated again. If the participant receives a lurbinectedin dose of 2 mg/m^2 and experiences a toxicity that would warrant a lurbinectedin dose reduction, treatment with lurbinectedin must be permanently discontinued.

If study treatment has to be temporarily interrupted or permanently discontinued to manage toxicity, atezolizumab and lurbinectedin can be interrupted or discontinued independently from each other (i.e., an interruption or discontinuation of lurbinectedin does not necessarily result in a simultaneous interruption or discontinuation of atezolizumab; an interruption or discontinuation of atezolizumab does not necessarily result in a simultaneous interruption or discontinuation of lurbinectedin), depending on the toxicity and suspected causality.

Arm B: Atezolizumab

Atezolizumab will be administered to participants in Arm B:

Atezolizumab 1200 mg IV on Day 1 of each 21-day cycle

Prophylactic anti-emetic medication and primary G-CSF prophylaxis is not required for atezolizumab administered alone.

Prophylactic Medications

All participants in the atezolizumab + lurbinectedin arm (Arm A) will receive the following anti-emetic and G-CSF prophylactic medication for lurbinectedin treatment:

- Anti-emetic treatment on Day 1 of the first cycle will be administered as per local standard practice (before or after infusion of atezolizumab, but at least 15–30 minutes before the infusion of lurbinectedin):
  - Corticosteroids (dexamethasone 8 mg IV or equivalent)

    AND
  - 5-HT$_3$ antagonists (Zofran® [ondansetron hydrochloride] 8 mg IV or equivalent), with or without metoclopramide 10 mg IV or equivalent

Other possible additional prophylactic medications:

- Extended treatment with oral prednisone not exceeding 10 mg/day or equivalent and/or oral ondansetron 4–8 mg or equivalent, at the investigator's discretion if required
- Additional anti-emetics may be used, if required

Aprepitant and equivalent agents (e.g., fosaprepitant) are not permitted in participants treated with lurbinectedin. The requirement for premedication for anti-emetic prophylaxis for the subsequent cycles (i.e., Day 1, Cycle 2 and subsequent cycles) should be evaluated on an individual basis, and its administration left to the investigator's judgment, taking into account the potential impact of corticosteroids on the beneficial immunologic effects of treatment with atezolizumab.

Primary prophylaxis with pegylated G-CSF is mandated in participants receiving lurbinectedin. It is strongly recommended to use pegylated instead of non-pegylated G-CSF; however, if pegylated G-CSF cannot be obtained at the site, the use of non-pegylated G-CSF is permitted. Type, dose, and scheme may vary according to institutional standard practices or guidelines. Home self-administration of G-CSF is permitted according to institutional standard practice. A mandatory window of at least 24 hours to up to 48 hours from lurbinectedin administration must be allowed until G-CSF prophylaxis is started.

DURATION OF PARTICIPATION

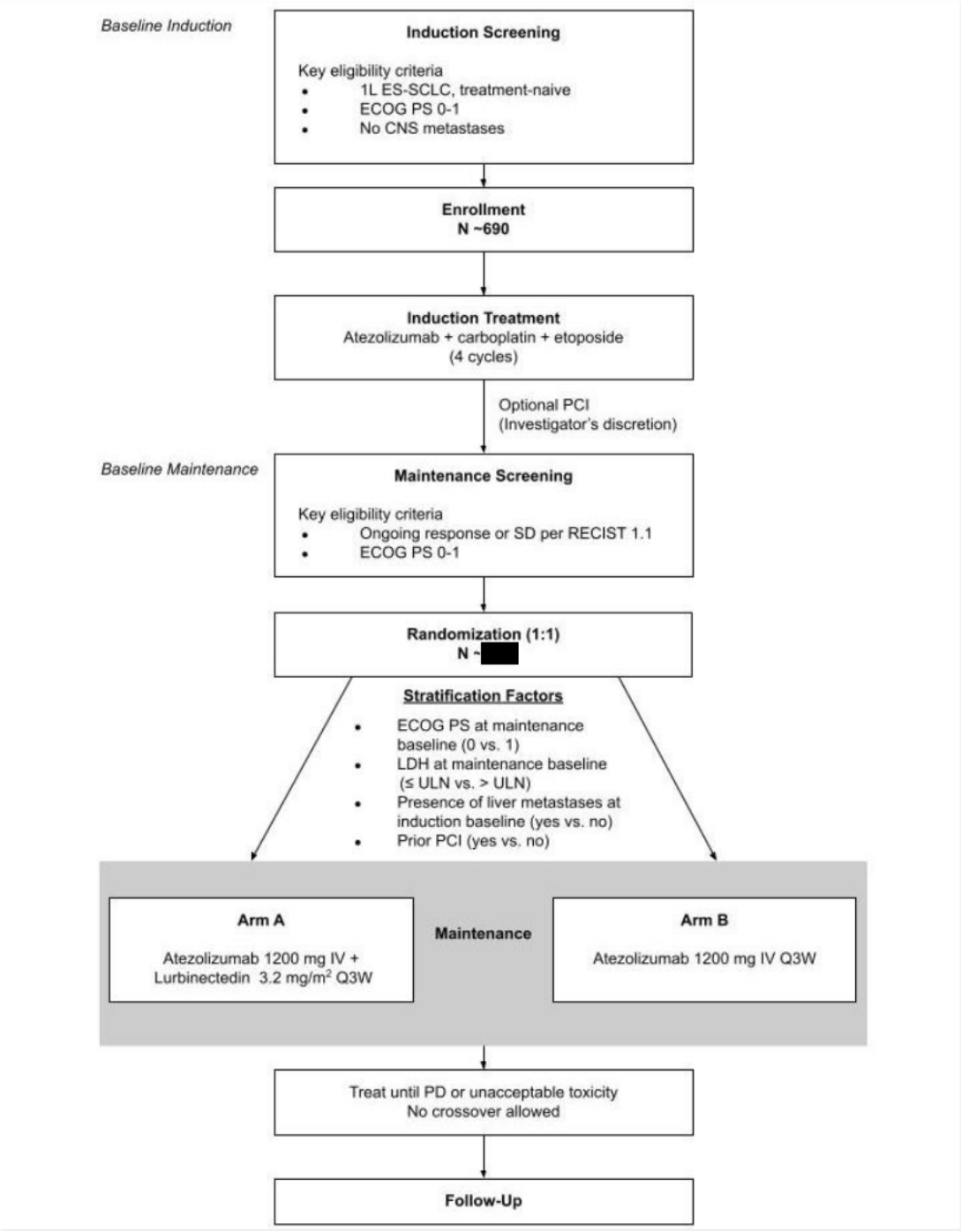
The total duration of study participation for each individual is expected to range from 1 day to more than 2 years.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee

1.2 STUDY SCHEMA

Figure 1 Study Schema



1L = first-line; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ES-SCLC = extensive-stage small-cell lung cancer; 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.

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities during the Induction Phase

Procedure	Induction Screening Days –28 to –1	Induction Phase (Cycles 1–4) [a] Day 1 of Every 21-Day Cycle (±3 Days) [b]
Informed Consent	x	
Demographic data	x	
Medical history and baseline conditions	x	
SCLC history and treatments	x	
Vital signs [d]	x	x
Weight	x	x
Height	x	
Complete physical examination	x	
ECOG Performance Status	x	
ECG	x	
Hematology [e]	x [f]	x [g, h]
Serum chemistry [i]	x [f]	x [g, h]
Coagulation test (aPTT and INR)	x	
Pregnancy test (female participants of childbearing potential only) [j]	x	x
TSH, free T3, free T4 [k]	x	
HIV, HBV, HCV serology [l]	x	
C-reactive protein (CRP) per local testing	x	

Table 1 Schedule of Activities during the Induction Phase (cont.)

Procedure	Induction Screening Days –28 to –1	Induction Phase (Cycles 1–4) [a] Day 1 of Every 21-Day Cycle (±3 Days) [b]
Induction treatment administration (Atezolizumab, Carboplatin, Etoposide) [m]		x
Tumor assessment	x [n]	Per local standard of care [o]
[redacted]		
Optional blood sample for RBR [p]		x
Adverse events [q]	x	x [h]
Concomitant medications [r]	x	x [h]
Patient-reported outcomes (EORTC QLQ-C30, EORTC QLQ-LC13, EORTC IL46, PRO-CTCAE [select items], and EQ-5D-5L) [s]		x

ADA = anti-drug antibody; CT = computed tomography (scan); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; HBcAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IL46 = Item List 46; MRI = magnetic resonance imaging (scan); PK = pharmacokinetic; PRO = patient-reported outcomes; PRO-CTCAE = Patient-Reported Outcomes–Common Terminology Criteria for Adverse Events; QLQ-C30 = Quality of Life Questionnaire–Core 30; QLQ-LC13 = Quality of Life Questionnaire–Lung Cancer Module; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; SCLC = small-cell lung cancer.

Note: Results of standard-of-care tests or examinations performed prior to obtaining informed consent and which fall into the specified screening window may be used; such tests do not need to be repeated for screening. Participants who are not randomized into the maintenance phase are not required to undergo a treatment discontinuation visit and will not go into follow-up.

Table 1 Schedule of Activities during the Induction Phase (cont.)

[a] Assessments should be performed before study treatment infusion unless otherwise noted.

[b] Enrolled participants will receive their first dose of study treatment the day of enrollment, if possible. Cycle 1 must be performed within 5 days after the participant is enrolled. Screening assessments performed ≤ 4 days before Cycle 1, Day 1 are not required to be repeated for Cycle 1, Day 1. Day 1 dose administrations are to be performed within a ±3-day window, unless treatment is delayed or on hold to manage adverse events. If the scheduled dose administration coincides with a weekend or holiday that precludes administration, administration should be performed as soon as possible but within 7 days following the scheduled D1 dose administration.

[c] [redacted]

[d] Vital signs include pulse rate, respiratory rate, blood pressure, and temperature. Vital signs should be recorded as described in Section 8.2.2.

[e] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils) and platelet count.

[f] At screening, the participant must have adequate hematologic and end-organ function defined by laboratory test results obtained within 14 days prior to enrollment. See Section 5.1 for details.

[g] Local laboratory assessments may be obtained ≤ 4 days before Day 1 of each cycle.

[h] For participants at participating sites who have signed Informed Consent to take part in mobile nursing visits, this assessment or procedure may be performed by a trained nursing professional at the participant's home or another suitable location.

[i] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide, sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH. A CPK assessment is required at screening.

[j] A serum pregnancy test is required within 14 days prior to enrollment. On Day 1 of each cycle, a urine pregnancy test is required.

[k] TSH, free T3 (or total T3 for sites where free T3 is not preferred), and free T4 can be assessed after enrollment but must be assessed before drug administration on Day 1 of Cycle 1.

[l] All participants will be tested for HIV prior to inclusion into the study. Participants who have a negative HIV test at screening are eligible. Participants with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count ≥ 200/μL, and have an undetectable viral load. Participants with active HBV (chronic or acute; defined as having a positive HBsAg test result at screening) will be excluded from the study. Participants with past or resolved HBV infection (defined as the presence of HBcAb and absence of HBsAg) are eligible; HBV DNA should be obtained in these participants prior to randomization. Participants with active HCV will be excluded from the study; participants who test positive for HCV antibody are eligible only if a PCR test is negative for HCV RNA.

Table 1 Schedule of Activities during the Induction Phase (cont.)

[m] For atezolizumab, the initial dose will be administered over 60 (± 15) minutes. If the first infusion is well-tolerated, subsequent infusions may be administered over 30 (± 10) minutes (see Section 6.1.1). The order of infusions should be as per local standard of care. Atezolizumab and carboplatin will be administered on Day 1 of each induction treatment cycle, etoposide will be administered on Day 1, Day 2, and Day 3 of each induction treatment cycle.

[n] CT scans (with IV contrast unless contraindicated and oral contrast as appropriate per institutional standards) of the chest, abdomen and pelvis. A CT (with contrast) or MRI scan of the head is required to evaluate CNS metastasis in all participants. Target and non-target lesions must be assigned to allow tumor response assessments per RECIST v1.1. See Section 8.1.1.1 for details.

[o] Please see requirements for tumor assessment scans at maintenance screening in Table 2.

[p] The optional RBR whole blood sample requires an additional Informed Consent signature. If the optional blood sample for the RBR was not collected on Day 1 of Cycle 1 of the induction phase, it can be collected at any other time during the study after the RBR optional consent has been signed.

[q] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported. After initiation of study treatment, all adverse events must be reported. Please see Section 8.3.1 for the adverse event reporting period.

[r] From 7 days prior to enrollment until the treatment discontinuation visit. All such medications must be recorded on the Concomitant Medications eCRF.

[s] EORTC QLQ-C30, EORTC QLQ-LC13, EORTC IL46, PRO-CTCAE (select items), and the EQ-5D-5L questionnaires will be completed by the participants at the start of the clinic visit before discussion of the participant's health state, laboratory results, or health record; before administration of study treatment; and/or prior to the performance of any other study assessments that could bias the participant's responses. In scenarios where laboratory assessments (e.g., blood draws) are done in a different clinic than the one providing treatment or when they are done on a different day than study treatment administration, laboratory assessments can be completed before the completion of PROs as long as results have not been discussed with the participant. If the participant comes to the clinic for study drug administration, completes the PRO questionnaires and then does not receive study treatment (i.e., a decision is made that study treatment cannot be administered on that day due to the participant's health status), the collected PROs should be kept and questionnaires for this timepoint should not be re-administered on the day of the delayed study drug administration. All questionnaires will be completed during the induction phase on Cycle 1, Day 1 only. The PRO instruments will be self-administered by the participant via electronic PRO device at the investigational site.

Table 2 Schedule of Activities during the Maintenance Phase

Procedure	Maintenance Screening [a]	Maintenance Phase (21-Day Cycles) [b]		Treatment Discontinuation Visit	Post-Treatment Follow-Up [e]
	Days –28 to –1	Day 1 (±3 Days) [c]	Day 10 (±3 Days) of Maintenance Cycles 1 and 2 only	≤30 Days after the Last Dose of Study Treatment [d]	
Review of eligibility criteria for the maintenance phase	x				
Vital signs [f]	x	x		x	
Weight	x	x		x	
Complete physical examination	x				
Limited physical examination [g]		x [h]		x	
ECOG Performance Status	x	x [h]		x	
ECG	x	Perform if clinically indicated			
Hematology [i]	x [j]	x [h, k]	x [k]	x	
Serum chemistry [l]	x [j]	x [h, k]		x	
Coagulation test (aPTT and INR)	x			x	
Pregnancy test (female participants of childbearing potential only)	x [m]	x [n]		x [n]	x [k, n]
TSH, free T3, free T4	x	x [k, o]		x	
Urinalysis [p]	x	Perform if clinically indicated [k]			
Serum sample for AGP assessment		x [q]			

Table 2 Schedule of Activities during the Maintenance Phase (cont.)

Procedure	Maintenance Screening [a]	Maintenance Phase (21-Day Cycles) [b]		Treatment Discontinuation Visit	Post-Treatment Follow-Up [e]
	Days –28 to –1	Day 1 (±3 Days) [c]	Day 10 (±3 Days) of Maintenance Cycles 1 and 2 only	≤30 Days after the Last Dose of Study Treatment [d]	
Maintenance treatment administration [r] Arm A: atezolizumab + lurbinectedin Arm B: atezolizumab		x			
Tumor assessment	x [s]	x [t]			x [u]
[redacted]					
Optional tumor biopsy after induction/prior to maintenance treatment [v] (if participant signs the Consent Form and if clinically feasible)	x				
Optional tumor biopsy at the time of radiographic disease progression [v] (if the participant signs the Consent Form and if clinically feasible)		At the time of radiographic disease progression			

Table 2 Schedule of Activities during the Maintenance Phase (cont.)

Procedure	Maintenance Screening [a]	Maintenance Phase (21-Day Cycles) [b]		Treatment Discontinuation Visit	Post-Treatment Follow-Up [e]
	Days –28 to –1	Day 1 (± 3 Days) [c]	Day 10 (±3 Days) of Maintenance Cycles 1 and 2 only	≤30 Days after the Last Dose of Study Treatment [d]	
Adverse events	x	x [k]	x [k]	x [w]	x [k, w]
Cancer-related procedures and treatments (medical, surgical, radiation)	To be reported throughout				
Concomitant medications [x]	x	x [k]		x	
Patient-reported outcomes (EORTC QLQ-C30, EORTC QLQ-LC13, EORTC IL46, and EQ-5D-5L) [y]		x *No longer collected from Protocol Version 8 onwards.*		x *No longer collected from Protocol Version 8 onwards.*	x [k] *No longer collected from Protocol Version 8 onwards.*
Patient-reported outcomes (PRO-CTCAE [select items]) [z]		x *No longer collected from Protocol Version 8 onwards.*	x [k] *No longer collected from Protocol Version 8 onwards.*	x *No longer collected from Protocol Version 8 onwards.*	
Survival and anti-cancer therapy follow-up [aa]					x [k]

ADA = anti-drug antibody; AGP = α-1-acid glycoprotein; CT = computed tomography (scan); ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC = European Organisation for Research and Treatment of Cancer; IL46 = Item List 46; MRI = magnetic resonance imaging (scan); MUGA = multiple-gated acquisition; PCI = prophylactic cranial irradiation; PK = pharmacokinetic; PRO = *patient*-reported outcomes; PRO-CTCAE = *patient*-reported outcomes–Common Terminology Criteria for Adverse

Table 2 Schedule of Activities during the Maintenance Phase (cont.)

Events; QLQ-C30 = Quality of Life Questionnaire–Core 30; QLQ-LC13 = Quality of Life Questionnaire–Lung Cancer Module; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Maintenance screening can be started as early as all Cycle 4 induction treatment administrations have been completed. The maintenance screening window is up to 28 days. Randomization must occur within 5 weeks (35 days) from the day of the administration of the last dose of induction treatment with atezolizumab, carboplatin, and/or etoposide (whichever occurs last), but Cycle 1, Day 1 of the maintenance phase must not be administered less than 3 weeks (21 days) from Cycle 4, Day 1 of the induction treatment phase. Participants receiving PCI must be randomized within 9 weeks (63 days) from the last dose of induction treatment with atezolizumab, carboplatin, and/or etoposide (whichever occurs last).

[b] Assessments should be performed before study treatment infusion unless otherwise noted.

[c] Randomized participants will receive their first dose of study treatment the day of randomization into the maintenance phase, if possible. Cycle 1 must be performed within 5 days after randomization. Screening assessments performed ≤ 4 days before Cycle 1, Day 1, do not need to be repeated for Cycle 1, Day 1. Day 1 dose administrations are to be performed within a ±3-day window, unless treatment is delayed or on hold to manage adverse events. If the scheduled dose administration coincides with a weekend or holiday that precludes administration, administration should be performed as soon as possible but within 7 days following the scheduled D1 dose administration. For Arm A, should one study drug be temporarily interrupted because of toxicity caused by lurbinectedin or atezolizumab, treatment will be restarted such that the administration of both study drugs remains synchronized.

[d] The treatment discontinuation visit is to be performed within 30 days of the last study treatment administration or within 30 days from the date the decision was made to permanently discontinue all study treatment.

[e] The follow-up period starts from the day of the treatment discontinuation visit. All participants will enter the follow-up period, regardless of the reason for treatment discontinuation. Participants will remain in follow-up until the end of the study, withdrawal of consent, loss to follow-up, death, or study termination by the Sponsor.

[f] Vital signs include pulse rate, respiratory rate, blood pressure, and temperature. Vital signs should be recorded as described in Section 8.2.2.

[g] Symptom-directed physical examinations; see Section 8.2.1 for details.

[h] May be obtained ≤ 4 days before Day 1 of each cycle.

[i] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils) and platelet count.

Table 2 Schedule of Activities during the Maintenance Phase (cont.)

[j] At screening, the participant must have adequate hematologic and end-organ function defined by laboratory test results obtained within 7 days prior to randomization. See Section 5.1.2 for details.

[k] For participants at participating sites who have signed Informed Consent to take part in mobile nursing visits, this assessment or procedure may be performed by a trained nursing professional at the participant's home or another suitable location.

[l] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide, sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, CPK and LDH. For participants entering the maintenance phase with asymptomatic amylase and/or lipase elevation up to 2.0 × ULN with no abdominal pain and no characteristic CT findings, weekly monitoring of blood amylase and lipase is required until complete or partial resolution (Grade ≤ 1).

[m] Serum pregnancy test within 14 days prior to randomization.

[n] During the maintenance phase of the study, urine pregnancy tests will be performed on Day 1 of every cycle. After study treatment discontinuation, a urine pregnancy test will be performed at either 6 months (+30 days) after the final dose of carboplatin or etoposide or lurbinectedin, or at 5 months (+30 days) after the final dose of atezolizumab, whichever is later. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

Table 2 Schedule of Activities during the Maintenance Phase (cont.)

[o] TSH, free T3 (or total T3 for sites where free T3 is not preferred), and free T4 will be assessed during the maintenance phase on or ≤ 4 days before Day 1 of Cycles 5, 9, 13, and every fourth cycle thereafter.

[p] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. Urinalysis is required at screening and thereafter will be obtained if clinically indicated.

[q] One blood sample for the evaluation of AGP will be collected prior to the start of maintenance treatment on Cycle 1 Day 1; AGP will be collected and analyzed by the central laboratory only for participants randomized to the experimental arm.

[r] Atezolizumab will be administered over 60 (±15) minutes, unless previous infusions during the induction phase have been well-tolerated in which case atezolizumab may be administered over 30 (±10) minutes (see Section 6.1.2.2). Infusions should be given in the following order for the experimental arm: atezolizumab → lurbinectedin. Lurbinectedin will be administered over 1 hour (see Section 6.1.2.1). For treatment continuation criteria for Arm A, please see Table A6-2.

[s] CT scans (with IV contrast unless contraindicated and oral contrast as appropriate per institutional standards) of the chest, abdomen and pelvis. An MRI scan or CT with contrast of the head is required to evaluate CNS metastasis in all participants. For participants for whom imaging of the brain was performed after the end of induction treatment and who subsequently received PCI, brain imaging does not need to be repeated after PCI before randomization. See Section 8.1.1.1 for details. The maintenance baseline tumor scans are to evaluate tumor response per RECIST v1.1 against the induction baseline scans as only participants with complete or partial response, or with stable disease are eligible for maintenance treatment. However, note that the scans performed during maintenance screening will become the new baseline scans to compare against for all subsequent tumor assessments and reassignment of target and non-target lesions is required. See Appendix 8 for more details.

[t] Perform CT scans (with contrast) of the chest and abdomen, and any other known or suspected site of disease. Perform MRI or CT scans of the head as surveillance as per local practice, or as clinically indicated. Perform tumor assessments every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1 of the maintenance phase and every 9 weeks (±7 days) thereafter, regardless of treatment delays, until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Tumor assessments are to be scheduled based on the date of the previously performed tumor assessment. Participants without any radiographic evidence of disease progression 2 years after Cycle 1, Day 1 of the maintenance phase may undergo tumor assessments every 3 months (±7 days) or more frequently if required per local standard of care until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Note that all tumor assessments performed during the maintenance phase are to be compared against the maintenance baseline scans (or nadir) and are not to be compared against the scans performed before or during induction treatment. See Appendix 8 for more details.

[u] If the participant discontinues study treatment for any reason prior to radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration), tumor assessments will continue at the same frequency as would have been followed if the participant had remained on study treatment until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first, even if the participant starts a new anti-cancer therapy after study treatment discontinuation. See Section 7.1 for details.

Table 2 Schedule of Activities during the Maintenance Phase (cont.)

[v] The optional tumor biopsy after induction and prior to maintenance should be collected if clinically feasible after the last cycle of the induction treatment and prior to the start maintenance treatment. Optional tumor biopsy at radiographic disease progression, if clinically feasible, preferably within 40 days after radiographic progression or prior to the start of the next anti-cancer therapy, whichever occurs sooner.

[w] All serious adverse events, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or until initiation of a new systemic anti-cancer therapy, whichever occurs first. Serious adverse events believed to be related to prior exposure to study treatment are to be reported indefinitely. Adverse events of special interest, regardless of relationship to study drug, will continue to be reported until 90 days after the final dose of study treatment or until initiation of a new systemic anti-cancer therapy, whichever occurs first. Adverse events of special interest believed to be related to prior exposure to study treatment are to be reported indefinitely. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or until initiation of a new systemic anti-cancer therapy, whichever occurs first.

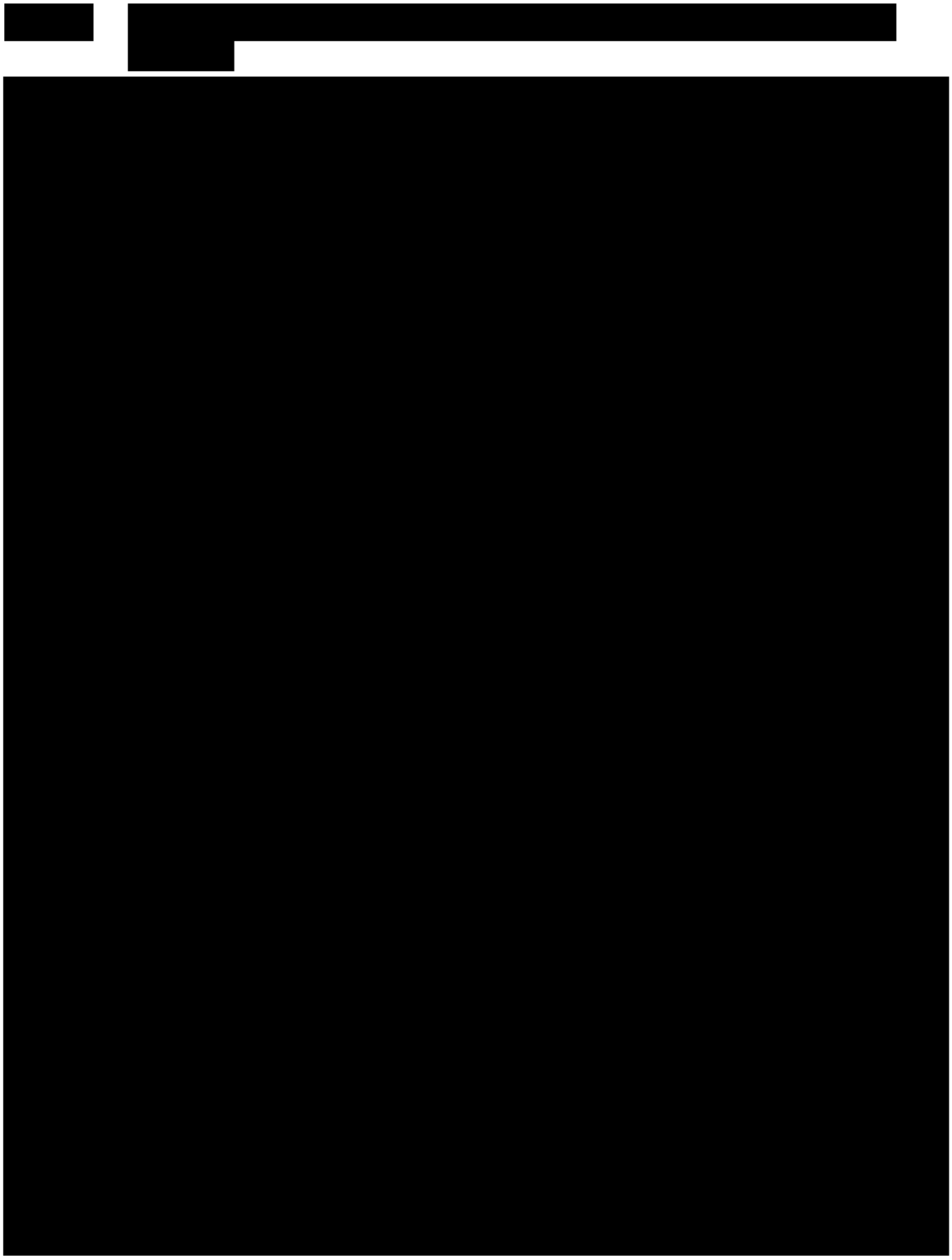
[x] From 7 days prior to the initiation of study treatment until the treatment discontinuation visit. All such medications should be recorded on the Concomitant Medications eCRF.

[y] PRO questionnaires (EORTC QLQ-LC13, EORTC QLQ-C30, EORTC IL46, and EQ-5D-5L) will be completed by the participants at the start of the clinic visit before discussion of the participant's health state, laboratory results, or health record; before administration of study treatment; and/or prior to the performance of any other study assessments that could bias the participant's responses. In scenarios where laboratory assessments (e.g., blood draws) are done in a different clinic than the one providing treatment or when they are done on a different day than study treatment administration, laboratory assessments can be completed before the completion of PROs as long as results have not been discussed with the participant. If the participant comes to the clinic for study drug administration, completes the PRO questionnaires and then does not receive study treatment (i.e., a decision is made that study treatment cannot be administered on that day due to the participant's health status), the collected PROs should be kept and questionnaires for this timepoint should not be re-administered on the day of the delayed study drug administration. The questionnaires will be completed on Cycle 1, Day 1 (baseline); Cycle 2, Day 1; Cycle 3, Day 1; Cycle 4, Day 1, and Cycle 5, Day 1. From Cycle 6 onwards, the questionnaires will be completed at every other study treatment cycle prior to the administration of study drug (i.e., on Cycle 6, Day 1; Cycle 8, Day 1; Cycle 10, Day 1; etc.). PROs will be collected during the treatment period and at the study treatment discontinuation visit. During follow-up, PROs (EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D-5L) will be completed at 3 months (± 30 days) and 6 months (± 30 days). The PRO instruments will be self-administered by the participant via ePRO device or may be collected remotely on non-visiting dates (e.g., during follow-up or in exceptional circumstances).

Table 2 Schedule of Activities during the Maintenance Phase (cont.)

[z] PRO questionnaires (PRO-CTCAE [select items]) will be completed by the participants at the start of the clinic visit before discussion of the participant's health state, laboratory results, or health record; before administration of study treatment; and/or prior to the performance of any other study assessments that could bias the participant's responses. In scenarios where laboratory assessments (e.g., blood draws) are done in a different clinic than the one providing treatment or when they are done on a different day than study treatment administration, laboratory assessments can be completed before the completion of PROs as long as results have not been discussed with the participant. If the participant comes to the clinic for study drug administration, completes the PRO questionnaires and then does not receive study treatment (i.e., a decision is made that study treatment cannot be administered on that day due to the participant's health status), the collected PROs should be kept and questionnaires for this timepoint should not be re-administered on the day of the delayed study drug administration. The questionnaires will be completed on Cycle 1, Day 1 (baseline); Cycle 1, Day 10; Cycle 2, Day 1; Cycle 2, Day 10; Cycle 3, Day 1; Cycle 4, Day 1, and Cycle 5, Day 1. From Cycle 6 onwards, the questionnaires will be completed at every other study treatment cycle prior to the administration of study drug (i.e., on Cycle 6, Day 1; Cycle 8, Day 1; Cycle 10, Day 1; etc.). PROs will be collected during the treatment period and at the study treatment discontinuation visit. The PRO instrument will be self-administered by the participant via ePRO device or may be collected remotely on non-visiting dates (e.g., for Day 10 assessments or in exceptional circumstances).

[aa] After radiographic disease progression per RECIST v1.1 and discontinuation of study treatment, survival follow-up information will be collected by telephone, participant medical records, and/or clinic visits every 3 months or more frequently ($\pm$30 days) until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. All participants will be periodically contacted for survival and new anti-cancer therapy information unless the participant requests to be withdrawn from follow-up (this request must be documented in the source documents and signed by the investigator). If the participant withdraws from the study, study staff may use a public information source (e.g., county records), when permissible, to obtain information about survival status only.



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2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of lurbinectedin, an alkylating drug that binds guanine residues in the minor groove of DNA, in combination with atezolizumab for the maintenance treatment of extensive-stage small-cell lung cancer (ES-SCLC) in participants whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin, and etoposide.

Despite the improved efficacy observed with programmed death-ligand 1 (PD-L1) inhibitors in combination with platinum-based chemotherapy in first-line ES-SCLC, most patients eventually experience disease progression and upon relapse, their prognosis is poor. Therefore, novel combination strategies are needed to deliver better long-term outcomes.

The early introduction of other agents active in small-cell lung cancer (SCLC), and with a complementing pathway to the current treatment approach, is an appealing strategy to further improve the prognosis of patients with advanced SCLC.

2.2 BACKGROUND

2.2.1 Background on Lung Cancer

Lung cancer remains the leading cause of cancer deaths worldwide. In 2020 in the United States, it was estimated that there will be 228,820 new cases of lung cancer (116,300 cases in men and 112,520 cases in women) and 142,670 lung cancer deaths (Siegel et al. 2020). According to the European Cancer Information System (ECIS) 2020, lung cancer is the most common cause of cancer-related deaths in Europe with approximately 384,176 deaths occurring in 2020, accounting for 19.8% of all cancer deaths (ECIS 2020).

Non–small-cell lung cancer (NSCLC) accounts for approximately 85% of all cases of lung cancer (Molina et al. 2008; Howlader et al. 2015). SCLC accounts for approximately 15% of all cases and is distinguished from NSCLC by its rapid growth rate and early development of metastatic disease (Govindan et al. 2006).

Patients with limited-stage SCLC can be treated with chemotherapy and radiation with the potential for long-term survival (Stinchcombe and Gore 2010), though a majority of patients will experience disease relapse. The majority (approximately 70%) of patients with SCLC are diagnosed with ES-SCLC. Chemotherapy alone can palliate symptoms and prolong survival for patients with ES-SCLC; however, long-term survival is rare (Johnson and Jänne 2004; Demedts et al. 2010). SCLC has a very high rate of attrition with fewer patients eligible for therapy in later treatment lines (Armstrong and Liu 2019).

2.2.2 Current Standard Treatment for Extensive-Stage Small-Cell Lung Cancer

SCLC is a very aggressive disease characterized by poor survival, with little progress made in the development of novel treatments for over 2 decades. However, advances with immunotherapies have opened new therapeutic avenues.

Regulatory approval has been granted for atezolizumab in combination with carboplatin and etoposide for the treatment of first-line ES-SCLC in the United States and the European Union based on Study GO30081 (IMpower133). In Study GO30081, 201 participants were randomly assigned to the atezolizumab and carboplatin/etoposide combination therapy group, and 202 participants to the placebo and carboplatin/etoposide combination therapy group. Induction therapy with atezolizumab/placebo and carboplatin and etoposide was given for 4 cycles and followed by maintenance therapy with atezolizumab or placebo until loss of clinical benefit or unacceptable toxicity. At a median follow-up of 13.9 months, the median overall survival (OS) was 12.3 months in the atezolizumab combination therapy group and 10.3 months in the placebo combination therapy group (hazard ratio [HR] for death = 0.70; 95% CI: 0.54 to 0.91; p = 0.007). The median progression-free survival (PFS) was 5.2 months and 4.3 months, respectively (HR for disease progression or death = 0.77; 95% CI: 0.62 to 0.96; p = 0.02). The safety profile of atezolizumab in combination with carboplatin/etoposide followed by atezolizumab monotherapy was consistent with the previously reported safety profile of the individual agents, with no new findings observed (Horn et al. 2018).

In an exploratory analysis of Study GO30081, the benefit of atezolizumab versus placebo in patients who reached the maintenance phase was assessed. About 80% of the intent-to-treat (ITT) population received at least 1 cycle of maintenance treatment with atezolizumab or placebo. The median OS from the start of maintenance treatment observed in this maintenance population was 12.5 months for patients receiving atezolizumab versus 8.4 months in the control arm (HR for OS from start of maintenance = 0.59). Median PFS from the start of maintenance treatment was 2.6 months for the atezolizumab arm versus 1.8 months in the control arm in the maintenance population (HR = 0.64; Reck et al. 2020).

In the United States and the European Union, the currently recommended treatment for first-line ES-SCLC is atezolizumab in combination with carboplatin and etoposide administered as induction therapy, followed by atezolizumab maintenance therapy, or durvalumab in combination with platinum (cisplatin or carboplatin) and etoposide as induction therapy, followed by durvalumab maintenance therapy (National Comprehensive Cancer Network® [NCCN®] 2021a; ESMO 2021).

2.2.3 Background on Lurbinectedin

Lurbinectedin is an alkylating drug that binds guanine residues in the minor groove of DNA, forming adducts and resulting in a bending of the DNA helix towards the major groove. Adduct formation triggers a cascade of events that can affect the subsequent activity of DNA binding proteins, including some transcription factors and DNA repair pathways, resulting in perturbation of the cell cycle and cell death.

In nonclinical studies, lurbinectedin downregulated cytokine production in the tumor microenvironment and inhibited tumor-associated macrophage (TAM) functions and/or reduced the number of TAMs in the tumor microenvironment (Céspedes et al. 2016; Belgiovine et al. 2017). Lurbinectedin has also shown synergy with immune checkpoint inhibitors (Xie et al. 2019).

Lurbinectedin is approved in the United States under accelerated approval for the treatment of patients with metastatic SCLC with disease progression during or after receiving treatment with platinum-based chemotherapy. This accelerated approval is based on the Phase II Study B-005, in which the activity of lurbinectedin monotherapy was studied in different tumor types, including SCLC. In the cohort with SCLC, 105 participants with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0–2, who had received 1 prior line of platinum-based chemotherapy and had no CNS metastases at the time of study entry, were treated with lurbinectedin 3.2 mg/m^2 every 3 weeks (Q3W; Trigo et al. 2020). The results of the objective response rate (ORR) and the duration of response (DOR) by the investigator and blinded Independent Review Committee (IRC) assessments were consistent and clinically meaningful; the high rate of ORR was associated with durable responses and a trend for prolonged OS in responding participants. By investigator assessment, the ORR (all partial responses [PRs]) was 35% with a median duration of 5.3 months. The ORR by IRC assessment was 30% with a median duration of 5.1 months. Participants considered to be platinum-sensitive (chemotherapy-free interval [CTFI] $\geq$90 days) had favorable outcomes compared with participants considered to be platinum-resistant (CTFI $<$90 days). Median PFS by investigator assessment was 3.5 months (95% CI: 2.6 to 4.3 months) in the overall population, and 4.6 months and 2.6 months in the platinum-sensitive and in the platinum-resistant participant populations, respectively. With a median follow-up of 17.1 months, median OS was 9.3 months (95% CI: 6.3 to 11.8 months) in the overall population, 11.9 months in the platinum-sensitive participant population, and 5.0 months in the platinum-resistant participant population. Participants received a median of 4 doses of lurbinectedin at a relative dose intensity of 97%. Fifty-nine percent (59%) of participants experienced Grade$\geq$3 adverse events, 34.3% of participants experienced serious adverse events, and 2 participants (1.9%) died due to an adverse event (dyspnea [due to disease progression]). Discontinuation of treatment with lurbinectedin due to an adverse event occurred in 4.8% of participants, and 24.8% of participants had lurbinectedin dose reductions to manage adverse events. The most common non-hematological treatment-related (or with unknown causality)

adverse events (occurring in >10% of participants) were fatigue (59.0%); gastrointestinal events, including constipation (9.5%); diarrhea (13.3%), nausea (32.4%), and vomiting (18.1%); and decreased appetite (21.0%). The most common treatment-related Grade≥3 adverse events were fatigue (7.6%) and febrile neutropenia (4.8%). Hematologic toxicities included anemia (95.2% all Grades, 9.5% Grade≥3); lymphopenia (85.7% all Grades, 43.8% Grade≥3); leukopenia (79.0% all Grades, 28.6% Grade≥3); neutropenia (71.4% all Grades, 45.7% Grade≥3); and thrombocytopenia (43.8% all Grades, 6.7% Grade≥3). The most common serious adverse events were hematological events: febrile neutropenia (4.8%), neutropenia/decreased ANC (5.7%), thrombocytopenia/platelets decreased (3.8%), and anemia/RBC decreased (3.8%). All events were considered to be treatment-related. Infections occurring in the presence of febrile neutropenia/neutropenic sepsis were analyzed as adverse events of special interest. Infections in the presence of Grade 3 or Grade 4 neutropenia were observed in 8.6% of participants and were mostly respiratory disorders (Preferred Terms that occurred in ≥2 participants were pneumonia [2.9%], upper respiratory tract infection [1.0%], and respiratory tract infection [1.0%]). These infections had a median onset of 10 days after lurbinectedin administration and lasted a median of 6–7 days.

See the Lurbinectedin Investigator's Brochure for details on nonclinical and clinical studies.

2.2.4 Background on Atezolizumab

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells.
Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma, NSCLC, SCLC, triple-negative breast cancer, hepatocellular carcinoma, melanoma, and alveolar soft part sarcoma.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

2.3 BENEFIT–RISK ASSESSMENT

There is a significant unmet need in patients with ES-SCLC. Despite the improved efficacy observed with first-line PD-L1 inhibitors administered in combination with platinum-based chemotherapy, most patients with ES-SCLC experience disease progression, and upon relapse, their prognosis is poor.

The purpose of this study is to assess the efficacy and safety of lurbinectedin in combination with atezolizumab for the maintenance treatment of ES-SCLC in participants whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin, and etoposide. The addition of atezolizumab to carboplatin and etoposide for the first-line treatment of ES-SCLC led to an improvement in PFS and OS, leading to the approval of atezolizumab as part of a first-line therapy for ES-SCLC (Armstrong and Liu 2019). However, as evident from studies with PD-L1 inhibitors and chemotherapy in the first-line treatment ES-SCLC, many patients rapidly progress after the end of 4 cycles of induction therapy (Horn et al. 2018; Paz-Ares et al. 2019; Reck et al. 2020). Given the aggressive nature of SCLC, the combination of an immune-checkpoint inhibitor with a novel transcription inhibitor lurbinectedin, may benefit patients in this setting. Lurbinectedin has shown clinical benefit in participants with SCLC as a single agent in Study B-005. As demonstrated in nonclinical studies, lurbinectedin downregulated cytokine production in the tumor microenvironment and inhibited TAM functions. A combination of lurbinectedin with the PD-L1 inhibitor atezolizumab, could enhance the anti-tumor immune response by reducing the number of TAMs and their immune inhibitory activity. Furthermore, this combination may eliminate the checkpoint signaling that PD-L1 elicits upon binding to PD-1 in cytotoxic T cells, resulting in greater anti-tumor activity than either agent provides alone.

[redacted] primary G-CSF prophylaxis will be implemented for the experimental arm in Study GO43104 to mitigate expected hematological abnormalities. Furthermore, based on the safety profile for lurbinectedin, additional premedication will be implemented to mitigate gastrointestinal toxicities such as nausea and vomiting.

Immune-mediated adverse events observed with atezolizumab are well known, manageable and/or reversible. The Sponsor does not foresee treatment with lurbinectedin to impact immune-mediated adverse events. Currently, considering the different mechanisms of action of lurbinectedin and atezolizumab and the initial safety profile from Study ML40908, overlapping toxicities are expected to be limited, and no exacerbations are anticipated.

Overall, the safety profile of each of the components of the combination is well-defined, generally transient, and manageable. In addition, the preliminary data from the Phase I–II Study ML40908 suggest that the combination of lurbinectedin and atezolizumab has a manageable safety profile at the planned doses for Study GO43104. Thus, the overall benefit–risk assessment is deemed favorable.

See Appendix 6 for information on anticipated risks for lurbinectedin and atezolizumab and risk mitigation measures, including guidelines for managing adverse events associated with lurbinectedin and atezolizumab.

More detailed information about the known and expected risks and reasonably expected adverse events of lurbinectedin and atezolizumab may be found in the lurbinectedin and atezolizumab Investigator's Brochures.

2.3.1 COVID-19 Benefit–Risk Assessment

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, participants with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, it is unclear whether or how systemic cancer therapies, such as chemotherapy, targeted therapy, or immunotherapy, impact the incidence or severity of SARS-CoV-2 infection.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13; Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by cancer immunotherapy.

Severe SARS-CoV-2 infection appears to be associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon (IFN)-γ (Merad and Martin 2020). [redacted] At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from SARS-CoV-2 infection.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for SARS-CoV-2–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in participants receiving atezolizumab in combination with chemotherapy.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy of Cancer [SITC] 2020).

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For participants enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a participant should be made on an individual basis by the investigator in consultation with the participant.

With regards to administering COVID-19 vaccines in participants receiving lurbinectedin, the specific patient population for this trial, mode of action of lurbinectedin and potential risks and benefits to participants have been considered, and no known risks have been identified to date. Standard safety surveillance processes are being followed. No recommendations can be made regarding the optimal sequence of COVID-19 vaccination in participants receiving lurbinectedin. To date, there is no documented risk associated with the combined use of lurbinectedin and COVID-19 vaccination.

For participants enrolling in this study and receiving atezolizumab with or without lurbinectedin treatment, a decision to administer the vaccine to a participant should be made on an individual basis by the investigator in consultation with the participant.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab with or without lurbinectedin treatment to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

The SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 6.8).

3. OBJECTIVES AND ENDPOINTS

This study will evaluate the 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 4 presents the primary objectives for the study expressed using the estimand framework in accordance with the International Council for

Harmonisation (ICH) E9(R1) statistical principles for clinical trials (ICH 2020). Table 5 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., G-CSF, anti-emetics) during the maintenance phase.

Most endpoints described in Table 4 and Table 5 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 4 Primary Objectives and Estimand Definition for Randomized Participants

Primary Objective	Estimand Definition
• To evaluate the efficacy of lurbinectedin in combination with atezolizumab compared with atezolizumab	• Population: individuals with ES-SCLC who have ongoing CR, 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 Sections 5.1.2 and Section 5.2.2, respectively) • Endpoint: IRF-assessed PFS after randomization, defined as the time from randomization to the date of first documented disease progression (as assessed by the IRF according to RECIST v1.1) or death, whichever occurs first • Treatments: – Experimental arm: atezolizumab 1200 mg IV + lurbinectedin 3.2 mg/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 for IRF-assessed PFS
• To evaluate the efficacy of lurbinectedin in combination with atezolizumab compared with atezolizumab	• Population: as defined above • Endpoint: OS after randomization, defined as the time from randomization to the date of death from any cause • Treatments: as defined above • Intercurrent events and handling strategies: as defined above • Population-level summary: hazard ratio for OS

IRF = independent review facility; OS = overall survival; PFS = progression-free survival.

Table 5 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 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 • 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 • PFS rates at 6 months and 12 months, defined as the proportion of participants who have not experienced disease progression or death from any cause at 6 months and 12 months after randomization, as determined by the IRF according to RECIST v1.1 • PFS rates at 6 months and 12 months, defined as the proportion of participants who have not experienced disease progression or death from any cause at 6 months and 12 months after randomization, as determined by the investigator according to RECIST v1.1 • 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 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

Table 5 Secondary and Exploratory Objectives and Endpoints for Randomized Participants (cont.)

• To evaluate the health-related quality of life of participants treated with lurbinectedin in combination with atezolizumab compared with atezolizumab	• TTCD from randomization in patient-reported physical functioning and global health status as measured by the EORTC QLQC30
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
• 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 by 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 functioning and global health status as assessed by the EORTC QLQ-C30 • Change from baseline in lung cancer-related symptoms as assessed by the EORTC QLQLC13
• To characterize the PK profile of lurbinectedin and atezolizumab	• Plasma concentration of lurbinectedin at specified timepoints • Serum concentration of atezolizumab at specified 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; IRF = Independent Review Facility; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PRO = Patient-Reported Outcome; PRO-CTCAE = Patient-Reported Outcome Common Terminology Criteria for Adverse Events; QLQ-C30 = Quality of Life Questionnaire–Core 30; RECIST = Response Evaluation Criteria in Solid Tumor; SD = stable disease; TTCD = time to confirmed deterioration.

4. STUDY DESIGN

4.1 OVERALL 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 Sections 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 (VALG) staging system (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 Sections 5.1.2 and 5.2.2) prior to randomization (maintenance screening). Participants who have received fewer than 4 or more than 4 cycles of carboplatin, etoposide and atezolizumab as induction treatment, 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 NCCN guidelines magnetic resonance imaging (MRI) surveillance can be considered as an alternative option to PCI (NCCN 2021a)

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 OS, crossover will not be allowed from Arm B (atezolizumab) to Arm A (atezolizumab in combination with lurbinectedin).

A study schema is provided in Section 1.2 (see Figure 1). A schedule of activities and a sample collection schedule are provided in Section 1.3 (see Table 1 [induction phase], Table 2 [maintenance phase], and Table 3 [sample collection schedule]).

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. Independent review facility membership and procedures will be detailed in an IRF charter.

4.2 RATIONALE FOR STUDY DESIGN

An open-label design was chosen for this study. Given the known hematological (e.g., neutropenia) and gastrointestinal (e.g., nausea, vomiting) toxicities associated with lurbinectedin therapy, physicians as well as participants assigned to the lurbinectedin-containing arm, may be capable of identifying treatment assignment in a blinded study. In addition, given the safety profile of lurbinectedin, in this study, primary G-CSF use as well as the use of anti-emetics are mandatory for participants assigned to the lurbinectedin-containing arm only, while participants in Arm B (atezolizumab monotherapy) will not require mandatory primary G-CSF prophylaxis or anti-emetic treatment. Thus, the physician must know which arm the participant is randomized to in order to use required prophylactic medication.

A blinded study would require, in addition to the administration of a lurbinectedin placebo, placebos for the mandatory prophylactic medication with G-CSF and anti-emetics (e.g., steroids, serotonin [5-HT_3] receptor antagonist), which would pose a significant burden to participants and site staff.

Adequate steps have been taken to ensure the validity of data in an open-label study design. This includes defining progression with use of the established RECIST v1.1, performing tumor assessments at the same frequency in both arms, assessment of PFS by an IRF, and determining the strategy for the final analysis of the primary endpoint prior to database lock for the primary efficacy analyses, including predefined methods for handling missing data and censoring rules. Efficacy analyses will be performed only at the pre-specified analysis timepoints in the protocol. In addition, primary endpoints of PFS and OS were chosen for this study.

4.2.1 Rationale for Study Population

SCLC is initially highly responsive to chemotherapy with or without cancer immunotherapy, with response rates ranging between 50%−70% (Horn et al. 2018; Paz-Ares et al. 2019). In Study GO30081, around 60% of participants achieved a complete response or PR, and an additional 21% of participants had SD after receiving atezolizumab in combination with chemotherapy (Horn et al. 2018). After induction therapy with carboplatin, etoposide with atezolizumab or placebo, about 80% of participants received at least 1 cycle of maintenance treatment with atezolizumab or placebo (Study GO30081 maintenance population). Participants in the maintenance population had a median OS of 12.5 months from the start of maintenance treatment with atezolizumab versus a median OS of 8.4 months in the control arm (HR for OS from start of maintenance = 0.59). Median PFS from the start of maintenance was 2.6 months for the atezolizumab arm versus 1.8 months in the control arm of the maintenance population (HR = 0.64; Reck et al. 2020).

In Study B-005, lurbinectedin as second-line therapy demonstrated better efficacy in terms of ORR, PFS, and OS in the participants with platinum-sensitive SCLC (CTFI > 90 days) compared with the overall population. Thus, selection of participants with SD or an objective response after induction chemotherapy for maintenance treatment with lurbinectedin added to atezolizumab may enrich the response for participants who could benefit most.

Participants who show disease progression at the last tumor assessment prior to randomization are not considered eligible for Study GO43104, as they progress onto second-line therapy.

Since there is a lack of predictive biomarkers for PD-L1 inhibitors and lurbinectedin in ES-SCLC, the target population will be a biomarker-unselected ES-SCLC population with an ongoing response or SD after completion of 4 cycles of carboplatin, etoposide, and atezolizumab induction treatment.

Controversial results exist regarding the benefit of PCI in patients with ES-SCLC compared with MRI surveillance in the brain, leading to decreased utilization of PCI in clinical practice (Gjyshi et al. 2019). In recent Phase III trials of PD-L1 inhibitors in first-line ES-SCLC, only around 10% of participants received PCI (Horn et al. 2018; Paz-Ares et al. 2019). Study GO43104 permits participants to receive PCI after induction treatment as per the investigator's decision before randomization.

Given the highly aggressive nature of the disease, participants will be randomized within 5 weeks of the last induction therapy administration, or within 9 weeks of the last induction therapy administration, if radiotherapy (e.g., PCI) after induction therapy is used.

Atezolizumab is approved for the first-line treatment of ES-SCLC by the U.S. Food and Drug Administration (FDA) and in the European Union in combination with carboplatin and etoposide. Based on real-world data, the proportion of cisplatin use plus etoposide and atezolizumab is low (2%; McCune et al. 2019) and is only considered in individual cases. Given the lack of regulatory approval for atezolizumab in combination with etoposide and cisplatin, carboplatin may not be replaced by cisplatin in this study.

Participants with a history of CNS metastases are excluded from the study given the current lack of robust data for lurbinectedin in participants with CNS metastases due to their exclusion in the Phase II Study B-005 (Trigo et al. 2020) and overall lack of meaningful CNS penetration by the molecule based on nonclinical data (data on file).

4.2.2 Rationale for Control Group

The current standard treatment for participants with first-line ES-SCLC is atezolizumab in combination with carboplatin and etoposide, as induction therapy, followed by atezolizumab maintenance therapy, or durvalumab in combination with platinum (cisplatin or carboplatin) and etoposide as induction therapy, followed by durvalumab maintenance therapy (NCCN 2021a; ESMO 2021).

Regulatory approval has been granted for atezolizumab in combination with carboplatin and etoposide for the treatment of first-line ES-SCLC in the United States and European Union, based on Study GO30081 results. In Study GO30081, 201 participants were randomly assigned to the atezolizumab and carboplatin/etoposide combination arm and 202 participants to the placebo and carboplatin/etoposide combination arm. At a median follow-up of 13.9 months, the median OS was 12.3 months in the atezolizumab arm and 10.3 months in the placebo arm (OS HR = 0.70; 95% CI: 0.54 to 0.91; p = 0.007). The median PFS was 5.2 months and 4.3 months, respectively (PFS HR = 0.77; 95% CI: 0.62 to 0.96; p = 0.02). The safety profile of atezolizumab in combination with chemotherapy followed by atezolizumab monotherapy was consistent with the previously reported safety profile of the individual agents, with no new findings observed (Horn et al. 2018).

Participants who started maintenance treatment in Study GO30081 (maintenance population) and received at least 1 cycle of atezolizumab had a median OS of 12.5 months from the start of maintenance treatment versus a median OS of 8.4 months in the control arm (OS HR from start of maintenance = 0.59; Reck et al. 2020). PFS was also longer for the atezolizumab arm (median PFS from start of maintenance: 2.6 months vs. 1.8 months; PFS HR = 0.64).

Based on the results of Study GO30081, atezolizumab maintenance therapy was chosen as the comparator in Study GO43104 for participants with non-progressing ES-SCLC after induction therapy with atezolizumab and chemotherapy.

[redacted]

[redacted]

4.2.4 Rationale for the Collection of Tumor Specimens Post-Induction and Prior to Maintenance Therapy and at Radiographic Progression

If clinically feasible, it is recommended that a tumor biopsy be performed post-induction and prior to maintenance therapy and at the time of radiographic disease progression in order to better understand the biological changes with the combination of chemotherapy and atezolizumab during induction therapy and changes that drive the increase in size of the radiographically progressing lesion [redacted]

[redacted]

4.2.5 Rationale for Choice of Stratification Factors

Participants eligible for randomization in this study will be stratified by ECOG PS at maintenance baseline (0 vs. 1), LDH at maintenance baseline (≤ upper limit of normal [ULN] vs. > ULN) via local laboratory test, presence of liver metastases at induction baseline (yes vs. no), and prior receipt of PCI (yes vs. no).

Poor prognostic factors for survival in participants with SCLC include extensive-stage disease, poor ECOG PS, weight loss, and markers associated with excessive bulk of disease such as LDH (Yip et al. 2000; Foster et al. 2009). Among these, disease stage, clinical ECOG PS, and LDH are considered the most important prognostic factors in SCLC (Hermes et al. 2010).

Furthermore, recent Phase III trials investigating cancer immunotherapy have shown the presence of liver metastases to be an additional strong prognostic factor in extensive-stage SCLC (Horn et al. 2018; Owonikoko et al. 2019).

PCI has been reported to decrease the incidence of brain metastases (Slotman et al. 2007), while the evidence regarding the impact of PCI on OS versus MRI surveillance for extensive-stage SCLC is currently inconclusive (Slotman et al. 2007; Takahashi et al. 2017).

4.2.6 Rationale for Primary Endpoint Selection

In Study GO43104, the primary efficacy endpoints are PFS, as assessed by the IRF (per RECIST v1.1), and OS.

Improvement in OS is generally accepted as the best measure of clinical benefit for participants with advanced lung cancer, and is an endpoint that is objective and easily measured. Recent data also suggest that OS may be a sensitive endpoint for cancer immunotherapy (Fehrenbacher et al. 2016). For these reasons, OS is a primary endpoint in this study.

PFS is a commonly used endpoint in oncology trials because it can reflect tumor growth, may correlate with patient symptom control (De Marinis et al. 2008; Griebsch et al. 2014), and may be assessed before the evaluation of a survival benefit. Additionally, its assessment is generally not confounded by subsequent therapies as can be the case for OS. PFS can be considered a good measure of clinical benefit for participants with cancer, especially if the magnitude of effect is large and the treatment has an acceptable benefit–risk profile compared with available therapies (European Medicines Agency Guideline 2012; FDA Guidance for Industry 2018). Furthermore, individual participant data analysis has demonstrated PFS to be a strong surrogate for OS in SCLC (Foster et al. 2015). As such, PFS as a primary endpoint may enable an earlier indication of benefit and may potentially make this new treatment combination available to patients more quickly.

4.2.7 *Rationale for Collection of Information on Race and Ethnicity*

Data pertaining to participant race and ethnicity represents a component of the broad demographic profile of the study population. Collection of demographic data, including information on race and ethnicity, is of importance to the future interpretation of results from the clinical trial, including identification of potential differences in efficacy, safety, and pharmacokinetics among participants. Collection of race and ethnicity data may enable investigation of potential relationships between biomarkers and race or ethnicity, including determination of whether race or ethnicity could be a prognostic factor. Collection of these data may also contribute to a better understanding of the distribution of ES-SCLC according to race or ethnicity.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

4.3.1 Rationale for Lurbinectedin Dose and Schedule

Lurbinectedin has received accelerated approval from the FDA for the treatment of adult patients with metastatic SCLC with disease progression while on or after receiving platinum-based chemotherapy. The approved dosing regimen is 3.2 mg/m^2 Q3W (3.2 mg/m^2 on Day 1 of each 21-day cycle) administered as a 1-hour IV infusion. In an exposure-response analysis for lurbinectedin, the recommended lurbinectedin dosing regimen of 3.2 mg/m² Q3W provided maximum benefit in participants with SCLC who had experienced disease progression while on or after receiving platinum-based chemotherapy with a manageable risk of Grade 4 neutropenia. Lowering the dose resulted in reduced efficacy, whereas increasing it led to a higher incidence of severe hematological toxicity without improvement of efficacy (Fudio et al. 2020).

4.3.2 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab, as outlined in the prescribing information (Tecentriq® U.S. Prescribing Information [USPI]). Anti-tumor activity has been observed across doses ranging from 1–20 mg/kg Q3W.
In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no DLTs were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight-based dose of 15 mg/kg for a person weighing 80 kg) was selected based on both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic (PK), efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details). The 3-week dosing schedule has been chosen as it aligns with the schedule of lurbinectedin administration.

4.3.3 Rationale for Atezolizumab Dose and Schedule in Combination with Carboplatin and Etoposide

An approved dosage regimen for atezolizumab plus carboplatin and etoposide for the first-line treatment of patients with ES-SCLC is 1200 mg Q3W administered IV over 60 (±15) minutes for the first infusion and shortening to 30 [±10] minutes for subsequent infusions (Tecentriq USPI; Tecentriq Summary of Product Characteristics [SmPC]).

4.3.4 Rationale for Lurbinectedin in Combination with Atezolizumab Dose and Schedule

The combination of lurbinectedin and atezolizumab is being investigated in the ongoing investigator-sponsored Phase I/II Study ML40908. Preliminary data from this study suggest that lurbinectedin and atezolizumab can be combined at the doses of 3.2 mg/m^2 Q3W and 1200 mg Q3W, respectively [redacted]

4.3.5 Rationale for Use of Primary Granulocyte Colony–Stimulating Factor Prophylaxis for Lurbinectedin

In clinical studies of 554 participants with advanced solid tumors receiving lurbinectedin, Grade 3 or 4 neutropenia occurred in 41% of participants, with a median time to onset of 15 days and a median duration of 7 days. Febrile neutropenia occurred in 7% of participants (ZEPZELCA® USPI).

In Study B-005, neutropenia was the most common cause of dose administration delays (13 participants [12%]) and dose reductions (17 participants [16%]) for lurbinectedin in participants with SCLC (Trigo et al. 2020).

Dose intensity is an important consideration for treatment effect from lurbinectedin (Fudio et al. 2020). The development of chemotherapy-induced febrile neutropenia or severe neutropenia can lead to dose reductions, delays, or discontinuation of treatment, which may negatively impact patient outcomes (Aapro et al. 2006; Kelly and Wheatley 2009). Primary prophylactic treatment with G-CSFs may prevent febrile neutropenia or reduce the duration of severe neutropenia.

Given the risk factors for participants in Study GO43104 to develop febrile or high-grade neutropenia when receiving lurbinectedin treatment following 4 cycles of myelosuppressive agents (carboplatin and etoposide), together with the expected median age of participants, primary prophylaxis with pegylated G-CSF has been implemented for the experimental arm in this study.

4.4 END OF STUDY DEFINITION

The end of this study is defined as the date of the last participant, last visit (LPLV) or the date at which the last data point required for statistical analysis (i.e., final OS analysis) or safety follow-up is received from the last participant, whichever occurs later. The total length of the study, from screening of the first participant for the induction phase to the end of the study, is expected to be approximately 90 months.

In addition, the Sponsor may decide to terminate the study at any time.

4.5 DURATION OF PARTICIPATION

The total duration of study participation for each individual is expected to range from 1 day to more than 2 years.

Study treatment with induction therapy and maintenance therapy will continue until disease progression per RECIST v1.1, unacceptable toxicity, or a participant's decision to discontinue, whichever occurs first. Randomized participants who discontinue study treatment will enter the study follow-up phase. Participants who are not eligible for the maintenance phase of the study will not enter the study follow-up phase.

5. STUDY POPULATION

Approximately 690 participants are expected to be enrolled into the induction phase of this study. Approximately [redacted] participants with ES-SCLC, who have an ongoing response or SD after completion of 4 cycles of carboplatin, etoposide, and atezolizumab induction treatment, and who meet the eligibility criteria for the maintenance phase, will be randomized into the maintenance phase of this study. The number of participants in the induction phase of the study will be adjusted as necessary based on the actual screen failure rate for entering the maintenance phase to achieve the required number of approximately [redacted] participants in the maintenance phase of the study.

Prospective approval of protocol deviations, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

5.1.1 Inclusion Criteria for the Induction Phase

Potential participants are eligible to be included in the induction phase of the study only if all of the following criteria apply:

- Signed Informed Consent Form
- $\geq$ 18 years at the time of signing the Informed Consent Form
- ECOG PS of 0 or 1
- Histologically or cytologically confirmed ES-SCLC (per the VALG staging system, Appendix 17)
- No prior systemic treatment for ES-SCLC

  For potential participants who have received prior chemoradiotherapy for limited-stage SCLC: must have had treatment with curative intent and a treatment-free interval of at least 6 months between the last dose/cycle of chemotherapy, thoracic radiotherapy, or chemoradiotherapy and the diagnosis of ES-SCLC.
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to enrollment into the induction phase:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL) for participants of non-African descent or ANC $\geq 1.3 \times 10^9$/L (1300/μL) for participants of African descent without G-CSF support
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin $\geq$ 90 g/L (9 g/dL)

    Potential participants may be transfused to meet this criterion.
  - AST, ALT, and ALP $\leq 2.5 \times$ ULN, with the following exceptions:

Potential participants with documented liver metastases: AST and ALT $\leq 5 \times$ ULN.

Potential participants with documented liver or bone metastases: ALP $\leq 5 \times$ ULN.

- Total bilirubin $\leq 1.5 \times$ ULN with the following exception:

  Potential participants with known Gilbert disease: total bilirubin $\leq 3 \times$ ULN.

- Creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 30 mL/min (calculated through use of the Cockcroft-Gault formula)
- Creatine phosphokinase $\leq 2.5 \times$ ULN ($\leq 5.0 \times$ ULN is acceptable if elevation is disease-related)
- Albumin ≥ 30 g/L (3.0 g/dL)

- For potential participants not receiving therapeutic anticoagulation: INR and aPTT $\leq 1.5 \times$ ULN

  For potential participants receiving therapeutic anticoagulation: a stable anticoagulant regimen.

- Measurable disease, as defined by RECIST v1.1

  Previously irradiated lesions can only be considered as measurable disease if
  (1) disease progression has been unequivocally documented at that site since radiation therapy, and
  (2) the previously irradiated lesion is not the only site of measurable disease.

- Submission of pre-induction therapy tumor sample for exploratory biomarker research
  - [redacted]
  - [redacted]
- Negative HIV test at screening, with the following exception: participants with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count $\geq 200/\mu$L, and have an undetectable viral load
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb), or a positive total HBcAb test followed by a negative (per local laboratory definition) hepatitis B virus (HBV) DNA test at screening
  - The HBV DNA test must be performed for individuals who have a negative HBsAg test, and a positive HBcAb test

- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening
  - The HCV RNA test must be performed for participants who have a positive HCV antibody test
- For female participants of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agree to refrain from donating eggs, as defined below:

  Female participants must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 5 months after the final dose of atezolizumab, for 6 months after the final dose of carboplatin or etoposide, and for 7 months after the final dose of lurbinectedin, whichever occurs last.

  Female participants must refrain from donating eggs during this same period.

  A female participant is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a female participant with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
  If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

  - Female participants who would like to become pregnant after study treatment discontinuation should seek advice on oocyte cryopreservation prior to initiation of study treatment because of the possibility of irreversible infertility due to treatment with carboplatin, etoposide and/or lurbinectedin.
- For male participants: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agree to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, male participants must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year

during the treatment period and for 4 months after the final dose of lurbinectedin and for 6 months after the final dose of carboplatin or etoposide, whichever occurs last. Male participants must refrain from donating sperm during this same period.

With a pregnant female partner, male participants must remain abstinent or use a condom during the treatment period and for 4 months after the final dose of lurbinectedin and for 6 months after the final dose of carboplatin or etoposide, whichever occurs last to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

5.1.2 Inclusion Criteria for the Maintenance Phase

Potential participants must meet all of the following criteria to be eligible to be randomized to receive either lurbinectedin in combination with atezolizumab or atezolizumab after completion of the induction phase:

- Able to comply with the requirements and restrictions listed in the Informed Consent Form and the study protocol (there is no separate Informed Consent Form for entering the maintenance phase)
- ECOG PS of 0 or 1
- Have received 4 cycles of first-line treatment with carboplatin, etoposide and atezolizumab and must have an ongoing complete response (CR), partial response (PR), or SD by RECIST v1.1 after completion of the induction therapy
  - Radiographic tumor assessment must have occurred $\leq$28 days prior to randomization into the maintenance phase
  - Participants who have received $<$4 cycles or $>$4 cycles of induction therapy are not eligible
- Randomized within **5 weeks (35 days)**, from the day of the administration of the last dose of atezolizumab, carboplatin or etoposide (whichever occurs last).
  Participants receiving PCI must be randomized within **9 weeks (63 days)** from the last dose of induction treatment.
  - Study treatment during the maintenance phase must not be administered $<$3 weeks (21 days) from Cycle 4, Day 1 of the induction treatment phase
  - Study treatment during the maintenance phase must not be administered $<$2 weeks (14 days) from the last dose of radiotherapy

- Toxicities attributed to prior induction anti-cancer therapy or PCI must have resolved to Grade 1 or better (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0) or baseline other than:
  - Adverse events that are clinically non-significant and/or stable on supportive therapy and are not expected to interfere with treatment in the study such as:

    Grade ≤ 2 alopecia, asthenia, dermatologic events.

    Grade ≤ 2 anemia if hemoglobin ≥ 90 g/L (9 g/dL).

    Asymptomatic amylase and/or lipase elevation up to $2.0 \times$ ULN with no abdominal pain and no characteristic CT findings. However, weekly monitoring of amylase and lipase is required in this case.
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 7 days prior to randomization into the maintenance phase:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL) for participants of non-African descent or ANC $\geq 1.3 \times 10^9$/L (1300/μL) for participants of African descent without G-CSF support
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9 g/dL)

    Participants may be transfused to meet this criterion.
  - AST, ALT, and ALP $\leq 2.5 \times$ ULN, with the following exceptions:

    Potential participants with documented liver metastases: AST and ALT $\leq 5 \times$ ULN.

    Potential participants with documented liver or bone metastases: ALP $\leq 5 \times$ ULN.
  - Total bilirubin $\leq 1.5 \times$ ULN with the following exception:

    Potential participants with known Gilbert disease: total bilirubin $\leq 3 \times$ ULN.
  - Creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 30 mL/min (calculated through use of the Cockcroft-Gault formula)
  - Creatine phosphokinase $\leq 2.5 \times$ ULN ($\leq 5.0 \times$ ULN is acceptable if elevation is disease-related)
  - Albumin ≥ 30 g/L (3.0 g/dL)
- For potential participants not receiving therapeutic anticoagulation: INR and aPTT $\leq 1.5 \times$ ULN

  For potential participants receiving therapeutic anticoagulation: a stable anticoagulant regimen.

5.2 EXCLUSION CRITERIA

5.2.1 Exclusion Criteria for the Induction Phase

Potential participants are excluded from the study if any of the following criteria apply:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 7 months after the final dose of study treatment

  Potential female participants of childbearing potential must have a negative serum pregnancy test result within 14 days prior to enrollment.

- Presence or history of CNS metastases
  - A CT (with contrast) or MRI scan of the head is required at induction screening. A brain MRI scan is the preferred imaging method for evaluating CNS metastases.
- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 1 week prior to enrollment
- Leptomeningeal disease
- Consolidative chest radiation is planned
- Uncontrolled tumor-related pain
  - Potential participants requiring pain medication must be on a stable regimen at study entry to be eligible
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
  - Potential participants with indwelling catheters (e.g., PleurX®) are allowed
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected calcium $>$ ULN)
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease, or current alcohol abuse
- Active or a history of autoimmune disease or immune deficiency (for a full list of excluded conditions see Appendix 15), including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, anti-phospholipid antibody syndrome, granulomatosis with polyangiitis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
  - History of autoimmune-related hypothyroidism who are on thyroid replacement hormone are eligible for the study
  - Controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study

- Eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., participants with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  Rash must cover $<10\%$ of body surface area.

  Disease is well-controlled at baseline and requires only low-potency topical corticosteroids.

  No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
  - History of radiation pneumonitis in the radiation field (fibrosis) is permitted
- Active tuberculosis
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to enrollment, unstable arrhythmia, or unstable angina
  - Known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction $<50\%$ must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the participant at high risk from treatment complications
- Receiving current treatment with anti-viral therapy for HBV or HCV
- Receiving treatment with investigational therapy within 28 days prior to enrollment
- Received prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Received prior treatment with lurbinectedin or trabectedin
- Received treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5 drug-elimination half-lives, whichever is longer, prior to enrollment
- Received treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 1 week prior to enrollment, or

anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

  - Received acute, low-dose systemic immunosuppressant medication, defined as $\leq$10 mg/day prednisone equivalent, or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study
  - Received mineralocorticoids (e.g., fludrocortisone), inhaled or low-dose corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study

- Known allergy or hypersensitivity to any component of the lurbinectedin formulation
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- History of allergic reactions to carboplatin or etoposide
- Received prior allogeneic stem cell or solid organ transplantation
- History of malignancies other than SCLC within 5 years prior to enrollment, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>$90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Received treatment with a live, attenuated vaccine within 4 weeks prior to enrollment, or anticipation of need for such a vaccine during study treatment or within 5 months after the final dose of atezolizumab or within 2 weeks after the final dose of lurbinectedin, whichever is later

5.2.2 Exclusion Criteria for the Maintenance Phase

Potential participants are excluded from randomization in the study if any of the following criteria apply after completion of the induction phase:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 7 months after the final dose of study treatment
- Presence or history of CNS metastases
  - A CT (with contrast) or MRI scan of the head is required at maintenance screening. A brain MRI scan is the preferred imaging method for evaluating CNS metastases.
- Consolidative chest radiation are excluded
- Uncontrolled tumor-related pain
  - Potential participants requiring pain medication must be on a stable regimen at entry of maintenance phase to be eligible

- Lesions (e.g., bone metastases or metastases causing nerve impingement) requiring palliative radiotherapy are not eligible
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
  - Potential participants with indwelling catheters (e.g., PleurX®) are allowed
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected calcium > ULN)
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease, or current alcohol abuse
- Active or a history of autoimmune disease or immune deficiency (for a full list of excluded conditions see Appendix 15), including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, anti-phospholipid antibody syndrome, granulomatosis with polyangiitis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
  - History of autoimmune-related hypothyroidism who are on thyroid replacement hormone are eligible for the study
  - Controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study
  - Eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., participants with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

    Rash must cover < 10% of body surface area.

    Disease is well-controlled at baseline and requires only low-potency topical corticosteroids.

    No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
  - History of radiation pneumonitis in the radiation field (fibrosis) is permitted
- Active tuberculosis
- Undergone a major surgical procedure, other than for diagnosis, within 4 weeks prior to randomization into the maintenance phase, or anticipation of need for a major surgical procedure during the study
- Severe infection within 2 weeks prior to randomization into the maintenance phase, including, but not limited to, hospitalization for complications of infection,

bacteremia, or severe pneumonia, or any active infection that could impact participant safety

- Receive treatment with therapeutic oral or IV antibiotics at the time of randomization
  - Potential participants receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or COPD exacerbation) are eligible for the study
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident), unstable arrhythmia, or unstable angina
  - Potential participants with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction $<50\%$ must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the participant at high risk from treatment complications
- Receiving current treatment with anti-viral therapy for HBV or HCV
- Known allergy or hypersensitivity to any component of the lurbinectedin formulation
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has the following meal and dietary restrictions:

- The lurbinectedin population PK model detected several covariates that affected lurbinectedin pharmacokinetics (refer to the Lurbinectedin Investigator's Brochure). Covariates detected included albumin, α-1 acid glycoprotein, body surface area and the presence of CYP3A inhibitors. Therefore, any food or fruit rich in containing CYP3A inhibitors or inducers (e.g., grapefruit, grapefruit juice, or Seville orange) should be avoided during lurbinectedin treatment.

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of 2 screenings per individual) for the induction phase at the investigator's discretion. Individuals are not required to re-sign the Consent Form if they are re-screened within 28 days after previously signing the Consent Form. There is also 1 re-screening opportunity for the maintenance phase provided randomization occurs within 5 weeks from the last dose of induction therapy (or 9 weeks for participants who received PCI). The investigator will maintain a record of reasons for screen failure (see Section 8). Participants are not required to sign a separate Informed Consent Form to enter the maintenance study phase.

6. STUDY TREATMENTS AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

The investigational medicinal products (IMPs) for this study are lurbinectedin and atezolizumab. Carboplatin and etoposide in the induction phase, and mandatory prophylactic medications (e.g., G-CSF, anti-emetics) in the maintenance phase are considered non-IMPs (NIMPs)/auxiliary medicinal products (AxMPs). Appendix 18 identifies all IMPs, AxMPs, and NIMPs for this study.

6.1 STUDY TREATMENTS ADMINISTERED

Table 6 and Table 7 provide a description of the study treatments for this study.

Table 6 Study Treatment Description during the Induction Phase

Induction Phase (Cycles 1–4)			
	Atezolizumab	**Carboplatin**	**Etoposide**
Use	Standard therapy	Standard therapy	Standard therapy
Type of medicinal product	Test product/Comparator	Background therapy	Background therapy
Drug form	Liquid concentrate	Per local requirements	
Unit dose strength(s)	60 mg/mL	Per local requirements	
Dosage level(s)	1200 mg Q3W on Day 1 over 60 (± 15) minutes (for the first infusion and shortening to 30 [± 10] minutes for subsequent infusions)	Refer to local prescribing information Recommendation: Carboplatin AUC 5 over 30–60 minutes on Day 1 Q3W (after completion of atezolizumab) Carboplatin infusion times and dosing may be adapted in accordance with local standard of care	Refer to local prescribing information Recommendation: Etoposide 100 mg/m^2 IV over 60 minutes on Day 1 (following carboplatin administration), Day 2 and Day 3 Q3W (or oral equivalent) Etoposide infusion times, route of administration and dosing may be adapted in accordance with local standard of care
Packaging	20-cc single-use glass vials	Per local requirements	
Labeling	Per local requirements		
Route of administration	IV infusion	IV infusion	IV infusion (or oral)
Source	Sponsor	Site	Site

AUC = area under the concentration–time curve; Q3W = every 3 weeks.

Table 7 Study Treatment Description during the Maintenance Phase

	Maintenance Phase				
	Lurbinectedin	**Atezolizumab**	**Ondansetron (or equivalent)** [a]	**Corticosteroids** [a, b]	**G-CSF** [a]
Use	Experimental	Standard therapy	Prophylactic medication	Prophylactic medication	Prophylactic medication
Type of medicinal product	Test product	Test product/Comparator	Rescue medication	Rescue medication	Rescue medication
Drug form	Lyophilized powder	Liquid concentrate	Ondansetron 8 mg or equivalent Refer to local prescribing information	Dexamethasone 8 mg IV or equivalent or at institutional doses Refer to local prescribing information	Pegylated G-CSF [c] Refer to local prescribing information or institutional guidelines
Unit Dose Strength(s)	0.5 mg/mL	60 mg/mL			
Dosage Level(s)	3.2 mg/m^2 Q3W	1200 mg Q3W			
Formulation(s)	Refer to pharmacy manual and Investigator's Brochure	Refer to pharmacy manual and Investigator's Brochure			
Packaging	4 mg single-dose vial	20-cc single-use glass vials			
Labeling	Per local requirements				
Route of administration	IV Infusion	IV infusion	IV infusion or oral	IV infusion or oral	Subcutaneous injection
Source	Sponsor	Sponsor	Site	Site	Site

G-CSF = granulocyte colony-stimulating factor.

[a] See Section 6.1.3.

[b] At the first cycle and afterwards per the investigator's decision.

[c] It is strongly recommended to use pegylated instead of non-pegylated G-CSF; however, if pegylated G-CSF cannot be obtained at the site, the use of non-pegylated G-CSF is permitted. Home self-administration of G-CSF is permitted according to institutional standard practice.

The treatment regimens are summarized in Section 4.3.

Guidelines for dose modification (lurbinectedin only) and treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 6.

6.1.1 Study Treatment in the Induction Phase

Once participants are screened for the induction phase and have been determined to be eligible, participants will be enrolled to receive 4 cycles of standard of care treatment with carboplatin, etoposide and atezolizumab unless unacceptable toxicity, disease progression or a participant's decision to discontinue occur, with each cycle being 3 weeks (21 days) in length. All participants will receive a fixed dose of 1200 mg atezolizumab administered by IV infusion on Day 1 of each 21-day cycle. Atezolizumab infusions will be administered per the instructions outlined in Table 8.

The specifics of the chemotherapy regimen (carboplatin and etoposide) and prophylactic medication (e.g., anti-emetics) during the induction phase are at the discretion of the treating physician. Recommendations are provided in Table 6.

6.1.2 Study Treatment in the Maintenance Phase

6.1.2.1 Arm A: Atezolizumab + Lurbinectedin

Atezolizumab and lurbinectedin will be administered in the following order for Arm A:

Atezolizumab → Lurbinectedin

Atezolizumab 1200 mg IV + Lurbinectedin 3.2 mg/m^2 IV on Day 1 of each 21-day cycle

Prophylactic anti-emetic medication and primary prophylaxis with pegylated G-CSF will be administered as described in Section 6.1.3.

All participants will receive atezolizumab administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity, disease progression per RECIST v1.1, or any other criterion as outlined in Section 7.1 have been met. The atezolizumab dose is fixed and is not dependent on body weight or body surface area. There will be no dose modifications such as dose reductions, for atezolizumab. Treatment with atezolizumab may be temporarily suspended as appropriate for management of adverse events.

All participants in Arm A will receive 3.2 mg/m^2 lurbinectedin administered by IV infusion on Day 1 of each 21-day cycle. The lurbinectedin dose is dependent on body surface area (BSA). It is recommended to calculate BSA using the DuBois formula.

The dose of lurbinectedin will be based on the participant's maintenance baseline weight (measured $\leq$28 days prior to randomization into the maintenance phase) and will remain the same throughout the study unless the participant's weight changes by $>$10% relative to the maintenance baseline weight. However, treating physicians may choose to re-calculate the dose of lurbinectedin based on the actual weight assessed prior to each dosing.

Up to 2 lurbinectedin dose reductions will be allowed (first dose reduction: 2.6 mg/m^2 Q3W; second dose reduction: 2 mg/m^2 Q3W). Once the dose has been reduced for an individual participant, it must not be re-escalated again. If the participant receives a lurbinectedin dose of 2 mg/m^2 and experiences a toxicity that would warrant a lurbinectedin dose reduction, treatment with lurbinectedin must be permanently discontinued.

If study treatment has to be temporarily interrupted or permanently discontinued to manage toxicity, atezolizumab and lurbinectedin can be interrupted or discontinued independently from each other (i.e., an interruption or discontinuation of lurbinectedin does not necessarily result in a simultaneous interruption or discontinuation of atezolizumab; an interruption or discontinuation of atezolizumab does not necessarily result in a simultaneous interruption or discontinuation of lurbinectedin), depending on the toxicity and suspected causality (see Appendix 6 for management guidelines). Should one study drug be temporarily interrupted because of toxicity caused by lurbinectedin or atezolizumab, treatment will be restarted such that the administration of both study drugs remains synchronized.

Administration of lurbinectedin and atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Atezolizumab and lurbinectedin infusions and prophylactic medications will be administered per the instructions outlined in Table 8 and Table 9, respectively.

Please see Figure 2 for an overview of the order and timing of administration of study treatment and prophylactic medications for Arm A.

For anaphylaxis precautions, see Appendix 7. Guidelines for medical management of infusion-related reactions are provided in Appendix 6.

Table 8 Administration of First and Subsequent Infusions of Atezolizumab

	First Infusion (Induction Phase)	Subsequent Infusions (Induction and Maintenance Phases)
Atezolizumab infusion	• No premedication is allowed for the first infusion of atezolizumab • Record the participant's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) within 60 minutes prior to starting the infusion • Infuse atezolizumab over 60 (±15) minutes • If clinically indicated, record the participant's vital signs every 15 (± 5) minutes during the infusion	• If the participant experienced an IRR during any previous infusion of atezolizumab, premedication with an antihistamine and/or antipyretic may be administered for subsequent infusions at the discretion of the investigator • Record the participant's vital signs within 60 minutes prior to starting the infusion • If the participant tolerated the previous infusion of atezolizumab well without an IRR, the next infusion of atezolizumab may be infused over 30 (± 10) minutes • If the participant experienced an IRR during the previous infusion, the next infusion of atezolizumab should be administered over 60 (±15) minutes • Continue to record vital signs within 60 minutes prior to the infusion • Record vital signs during the infusion of atezolizumab if clinically indicated
Observation period after infusion of atezolizumab	• After the infusion of atezolizumab, the participant begins a 30-minute observation period • Record the participant's vital signs at 30 (±10) minutes after the end of the infusion of atezolizumab • Participants should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms	• After the infusion of atezolizumab, the participant begins a 30-minute observation period • If the participant experienced an IRR during the (previous) infusion, the observation period should be 60 minutes • If clinically indicated, record the participant's vital signs at 30 (±10) minutes after the end of the infusion

IRR = infusion-related reaction.

Table 9 Administration of First and Subsequent Infusions of Lurbinectedin

	First Infusion	Subsequent Infusions
Lurbinectedin infusion	• Anti-emetic prophylaxis before infusion of lurbinectedin [a]: – Corticosteroids (dexamethasone 8 mg IV or equivalent). – 5-HT$_3$ antagonists (ondansetron 8 mg IV or equivalent), with or without metoclopramide 10 mg IV or equivalent. – Other possible prophylactic medications: Extended oral prednisone not exceeding 10 mg/day and/or oral ondansetron 4–8 mg or equivalent, at the investigator's discretion if required. Additional anti-emetics might be used, if required. • Infuse lurbinectedin over 1 hour • Extended use of anti-emetics is permitted for post-infusion nausea and vomiting • Primary prophylaxis with pegylated G-CSF: A mandatory window of at least 24 hours and up to 48 hours must be allowed from lurbinectedin administration until G-CSF prophylaxis is started	• The requirement for premedication for anti-emetic prophylaxis for the subsequent cycles (i.e., Day 1, Cycle 2 and subsequent cycles) should be evaluated on an individual basis, and its administration left to the investigator's judgment • Infuse lurbinectedin over 1 hour • Extended use of anti-emetics is permitted for post-infusion nausea and vomiting • Primary prophylaxis with pegylated G-CSF: A mandatory window of at least 24 hours and up to 48 hours must be allowed from lurbinectedin administration until G-CSF prophylaxis is started
Management of infusion site reactions	• Infusion site reactions such as phlebitis – Increase the volume of diluent, and extend infusion time by at least 50%	• Infusion site reactions such as phlebitis – Increase the volume of diluent, and extend infusion time by at least 50%

5-HT$_3$ = serotonin; G-CSF = granulocyte colony-stimulating factor.

[a] See Section 6.1.3 for more information on the timing of anti-emetic administration.

6.1.2.2 Arm B: Atezolizumab

Atezolizumab will be administered to participants in Arm B:

Atezolizumab 1200 mg IV on Day 1 of each 21-day cycle

Please follow the instructions for atezolizumab administration as described under Section 6.1.2.1. Prophylactic anti-emetic medication and primary G-CSF prophylaxis is not required for atezolizumab administration alone.

6.1.3 Prophylactic Medications

All participants in the atezolizumab + lurbinectedin arm (Arm A) will receive the following anti-emetic and G-CSF prophylactic medication for lurbinectedin treatment:

- Anti-emetic treatment on Day 1 of the first cycle will be administered as per local standard practice (before or after infusion of atezolizumab, but at least 15–30 minutes before the infusion of lurbinectedin):
  - Corticosteroids (dexamethasone 8 mg IV or equivalent)

    AND
  - 5-HT_3 antagonists (Zofran® [ondansetron hydrochloride] 8 mg IV or equivalent), with or without metoclopramide 10 mg IV or equivalent

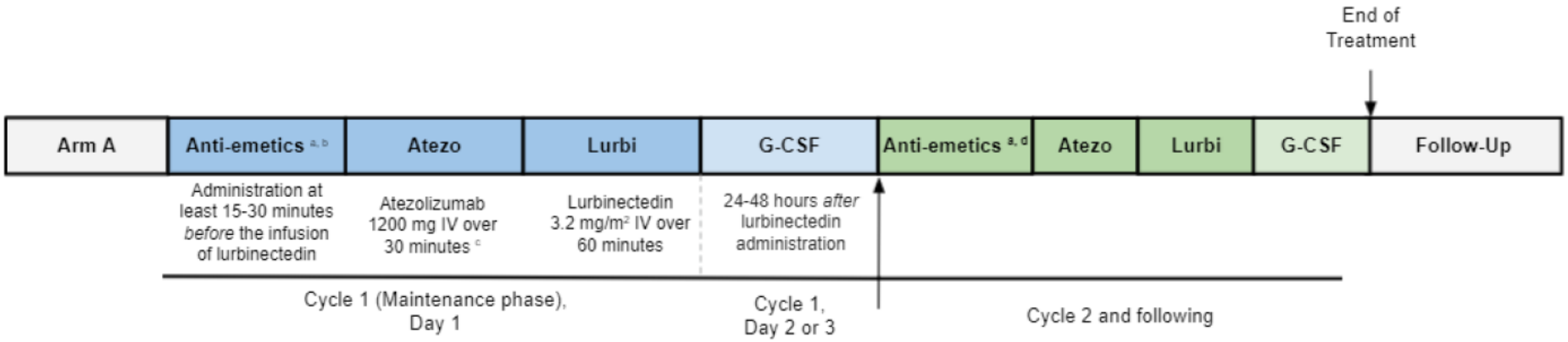
Other possible additional prophylactic medications:

- Extended treatment with oral prednisone not exceeding 10 mg/day or equivalent and/or oral ondansetron 4–8 mg or equivalent, at the investigator's discretion if required
- Additional anti-emetics may be used, if required

Aprepitant and equivalent agents (e.g., fosaprepitant) are not permitted in participants treated with lurbinectedin. The requirement for premedication for anti-emetic prophylaxis for the subsequent cycles (i.e., Day 1, Cycle 2 and subsequent cycles) should be evaluated on an individual basis, and its administration left to the investigator's judgment, taking into account the potential impact of corticosteroids on the immunologic effects of treatment with atezolizumab (see Section 6.8.2.1).

Primary prophylaxis with pegylated G-CSF is mandated in participants receiving lurbinectedin. It is strongly recommended to use pegylated instead of non-pegylated G-CSF; however, if pegylated G-CSF cannot be obtained at the site, the use of non-pegylated G-CSF is permitted. Type, dose, and scheme may vary according to institutional standard practices or guidelines. Home self-administration of G-CSF is permitted according to institutional standard practice. A mandatory window of at least 24 hours to up to 48 hours from lurbinectedin administration must be allowed until G-CSF prophylaxis is started. In circumstances in which participants did not tolerate prior G-CSF use, the investigator may choose not to administer primary G-CSF prophylaxis with close monitoring of hematologic values and any other supportive care according to local standard practice.

Figure 2 Order of Administration of Study Treatment and Prophylactic Medications in Arm A



5-HT3=serotonin; Atezo=atezolizumab; G-CSF=granulocyte colony-stimulating factor; Lurbi=lurbinectedin.

[a] Anti-emetics can be given before or after infusion of atezolizumab, but at least 15–30 minutes before the infusion of lurbinectedin.

[b] For Cycle 1: Corticosteroids and 5-HT3 antagonists, and potential additional medication as described in Section 6.1.3.

[c] 60 minutes if infusion-related reaction occurred during the previous administration.

[d] For Cycle 2 and beyond: Per investigator's judgment as described in Section 6.1.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel, e.g., pharmacist) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP.
The study site will acknowledge receipt of IMPs supplied by the Sponsor, with use of an interactive voice or Web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

Investigational medicinal products will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual, the lurbinectedin and atezolizumab Investigator's Brochures, and/or local prescribing information for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT

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 participant's study identification number from the 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 phase.

Participants will be randomly assigned to one of 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:

- ECOG PS at maintenance baseline (0 vs. 1)
- LDH at maintenance baseline ($\leq$ 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.

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The dose of study treatment and the study participant's identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Appendix 3.

6.5 DOSE MODIFICATION

Up to 2 lurbinectedin dose reductions are allowed (first dose reduction: 2.6 mg/m^2 Q3W; second dose reduction: 2 mg/m^2 Q3W). Once the dose has been reduced for an individual participant, it must not be re-escalated again. If the participant receives a lurbinectedin dose of 2 mg/m^2 and experiences a toxicity that would warrant a lurbinectedin dose reduction, treatment with lurbinectedin must be permanently discontinued (refer to Table A6-1 for more details on dose modification guidelines for lurbinectedin).

Modification of the atezolizumab dose is not permitted.

If study treatment has to be temporarily interrupted or permanently discontinued to manage toxicity, atezolizumab and lurbinectedin can be interrupted or discontinued independently from each other (i.e., an interruption or discontinuation of lurbinectedin does not necessarily result in a simultaneous interruption or discontinuation of atezolizumab; an interruption or discontinuation of atezolizumab does not necessarily result in a simultaneous interruption or discontinuation of lurbinectedin), depending on the toxicity and suspected causality (see Appendix 6 for management guidelines). Should one study drug be temporarily interrupted because of toxicity caused by lurbinectedin or atezolizumab, treatment will be restarted such that the administration of both study drugs remains synchronized.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

The Sponsor will offer continued access to atezolizumab free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below. The Sponsor will evaluate whether to continue providing lurbinectedin in accordance with this policy.

A participant will be eligible to receive atezolizumab and/or lurbinectedin after completing the study if all of the following conditions are met:

- The participant has a life-threatening or severe medical condition and requires continued treatment with atezolizumab and/or lurbinectedin for his or her well-being.
- There are no appropriate alternative treatments available to the participant.
- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A participant will not be eligible to receive atezolizumab and/or lurbinectedin after completing the study if any of the following conditions are met:

- Atezolizumab and/or lurbinectedin are commercially marketed in the participant's country and are reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant).

- The Sponsor has discontinued development of atezolizumab and/or lurbinectedin or data suggest that the treatment is not effective for ES-SCLC.
- The Sponsor has reasonable safety concerns regarding atezolizumab and/or lurbinectedin as a treatment for ES-SCLC.
- Provision of atezolizumab and/or lurbinectedin is not permitted under the laws and regulations of the participant's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

https://assets.roche.com/f/176343/x/1b18e080e0/2025-revision-roche_global_policy_on_continued_access_to_investigational_interventions.pdf

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating an overdose. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 3.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities.

6.8 CONCOMITANT THERAPY

Any medication and/or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements used by a participant in addition to protocol–mandated treatment from 7 days prior to enrollment until the treatment discontinuation visit must be recorded on the Concomitant Medications eCRF along with the following information:

- Reason for use (indication)
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

For participants who discontinue study treatment for any reason other than disease progression, information on the administration of any COVID-19 vaccine will continue to be collected beyond the treatment discontinuation visit until radiographic disease progression per RECIST v1.1 has been confirmed. This is due to the risk of lymphadenopathy as a result of a COVID-19 vaccine (see the respective information in Appendix 8).

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

6.8.1 Permitted Therapy

Participants are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of < 1% per year (see Section 5.1)
- Hormone replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccines (such as influenza, COVID-19)

  Live attenuated vaccines are not permitted (see Section 6.8.3)
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
  - Inhaled or low-dose corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- PCI administered after completion of induction treatment, per local standard of care; requirement to complete PCI before randomization into the maintenance phase
- Palliative radiotherapy (e.g., treatment of known bone metastases or symptomatic relief of pain):
  - Treatment with lurbinectedin must be withheld during palliative radiotherapy and lurbinectedin must not be restarted less than 2 weeks following the last dose of radiotherapy
  - Treatment with atezolizumab may be continued during palliative radiotherapy
- Blood products and transfusions, as clinically indicated
- Bisphosphonates
- Erythropoietin use according to local guidelines
- G-CSF
- In case of nausea or vomiting, prophylaxis and/or symptomatic treatment for emesis according to local guidelines

Premedication with antihistamines, anti-pyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a participant's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Section 6.8.2 and Section 6.8.3) as clinically indicated, per local standard practice. Participants who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea,

hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 6).

6.8.2 Cautionary Therapy

6.8.2.1 Cautionary Therapy for Atezolizumab-Treated Participants Corticosteroids, Immunosuppressive Medications, and TNF-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (see Appendix 6 for details).

6.8.2.2 Medications Given with Precaution due to Effects Related to CYP Enzymes

In vitro studies with human liver microsomes have shown that CYP3A4 is a major metabolic enzyme involved in the metabolism of lurbinectedin, followed by CYP2E1, CYP2D6, and CYP2C9. The contribution of other CYP isoenzymes is negligible. Thus, concomitant medications which induce or inhibit CYP3A4 should be carefully monitored or avoided, whenever possible (see Appendix 16). A significant interaction with aprepitant (CYP3A4 inhibitor) is suggested by Phase II data with lurbinectedin from participants with ovarian cancer and a Phase II Study PM1183-A-008-13 in participants with advanced solid tumors where lurbinectedin clearance was reduced by approximately 42% in the presence of aprepitant and participants experienced unusually long-lasting neutropenia, as well as thrombocytopenia. Although all participants recovered from these events, the use of aprepitant and equivalent agents (e.g., fosaprepitant) is not permitted.

Based on in vitro studies, lurbinectedin was shown to inhibit CYP2C8, CYP3A4 and CYP2B6. However, according to guidelines from the European Medicines Agency and FDA, the calculated in vivo impact of lurbinectedin on those CYP isoenzymes was insignificant. Therefore, no potential drug-drug interaction is expected between lurbinectedin and drugs which are metabolized by CYP3A4, CYP2C8, or CYP2B6 (see Appendix 16).

The investigator should consult the prescribing information and Investigator's Brochures when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

6.8.2.3 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 6.8.3) may be used during the study at the discretion of the investigator.

6.8.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 6.8.2), and during study treatment, until disease progression is documented and the participant has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances
- Cisplatin instead of carboplatin in the induction phase
- Investigational therapy is prohibited within 28 days prior to enrollment and during study treatment
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to enrollment, during study treatment, and for 5 months after the final dose of atezolizumab or for 2 weeks after the final dose of lurbinectedin, whichever is later
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to enrollment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with study treatment
- Systemic immunosuppressive medications other than corticosteroids as described in Section 6.8.2.1 (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of study treatment
- Radiotherapy other than limited-field radiotherapy for pain control
- Aprepitant or other neurokinin-1 receptor (NK-1) antagonists (e.g., fosaprepitant) for participants receiving treatment with lurbinectedin

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will remain in the study follow-up phase. See the schedule of activities (see Section 1.3, Table 2) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

Participants must permanently discontinue study treatment if any of the following criteria are met:

- Any medical condition that the investigator determines may jeopardize the participant's safety if *the participant* continues to receive study treatment
- Investigator determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Disease progression per RECIST v1.1
- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease)
- Use of any anti-cancer therapy not allowed per protocol or use of a prohibited therapy (see Section 6.8.3)
- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual participant's potential response to therapy and severity of the event

The primary reason for study treatment discontinuation must be documented on the appropriate eCRF.

Participants will return to the clinic for a treatment discontinuation visit within 30 days after the final dose of study drug or within 30 days from the date the decision was made to permanently discontinue study treatment.

See the schedule of activities in Section 1.3 (Table 2) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment. If a participant requests to be withdrawn from study treatment and/or follow-up, this request must be documented in the source documents and signed by the investigator.

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study treatment is required by the investigator when a study participant meets abnormal liver tests as outlined in Section A3–7.7, or if the investigator believes that it is in best interest of the participant to discontinue.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

If a participant withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic, and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3 [Table 1 and Table 2]). Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a detailed record of all participants screened to document eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management and obtained before signing of the Informed Consent Form may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the time frame defined in the schedule of activities.

Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse will be recorded at induction baseline. Any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and herbal supplements) used by the participant within 7 days prior to enrollment will be recorded at induction baseline. Demographic data, including age, sex, and self-reported race or ethnicity, will also be recorded. At the time of each physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity prior to each dose; treatment will be administered only if the clinical assessment and local laboratory test values are acceptable. Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

At applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional at the participant's home or another suitable location, such as a local practice, to improve access and convenience for participants in the study. The Sponsor will evaluate and may select a health care company (the MN vendor) to provide MN services for participating sites. The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a participant and the participant gives written informed consent to participate in MN visits, the MN vendor will communicate with the participant and the participant's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Section 1.3 [Table 1, Table 2, and Table 3]) will specify the assessments that may be performed by a MN professional.

8.1 EFFICACY ASSESSMENTS

8.1.1 Tumor and Response Evaluations

A tumor assessment is required at induction screening and at maintenance screening. Participants must have SD or partial or complete response per RECIST v1.1 at maintenance screening in order to be eligible for randomization into the maintenance phase. Tumor assessments are to be performed during the maintenance phase every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1 of the maintenance phase and every 9 weeks (±7 days) thereafter, regardless of treatment delays, until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Participants without any radiographic evidence of disease progression 2 years after Cycle 1, Day 1 of the maintenance phase may undergo tumor assessments every 3 months (±7 days) or more frequently if required per local standard of care until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Thus, tumor assessments are to continue according to schedule in participants who discontinue treatment for reasons other than disease progression per RECIST v1.1, even if they start new non-protocol anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if PD is suspected.

All measurable and/or evaluable lesions should be assessed and documented at screening. Tumor assessments performed as a standard of care prior to obtaining informed consent and within 28 days prior to enrollment do not have to be repeated at screening, so long as they meet criteria as per RECIST v1.1.

Study treatment will be continued until radiographic disease progression according to RECIST v1.1, unacceptable toxicity, or a participant's decision to discontinue, whichever occurs first.

The tumor assessment performed during maintenance screening will serve as the baseline scan (maintenance baseline) for RECIST v1.1 assessment purposes post-randomization.

The potential need for palliative radiotherapy should be considered, if possible, during the selection of target lesions as an irradiated target lesion renders the patient non-evaluable for RECIST v1.1 tumor response with the exception of the assessment of disease progression.

8.1.1.1 Radiographic Assessments

Participants will undergo tumor assessments at induction screening and at maintenance screening. The tumor assessment at induction screening will serve to determine whether participants have SD or partial or complete response following the completion of induction therapy at the time of screening for the maintenance phase. The tumor assessment at maintenance screening will serve as the baseline to determine tumor response per RECIST v1.1 post-randomization.

All participants in the maintenance phase will undergo tumor assessments every 6 weeks (±7 days) for 48 weeks following Day 1 of Cycle 1 of maintenance therapy, regardless of treatment delays. After completion of the Week 48 tumor assessment, tumor assessments are required every 9 weeks (±7 days), regardless of treatment delays. Participants without any radiographic evidence of disease progression 2 years after Cycle 1, Day 1 of the maintenance phase may undergo tumor assessments every 3 months (±7 days) or more frequently if required per local standard of care. Tumor assessments are to be performed until radiographic disease progression per RECIST v1.1 criteria, withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first. Magnetic resonance imaging surveillance of the brain (preferred) or brain CT with contrast every 3–4 months is recommended during Year 1, and every 6 months during Year 2 independent of the use of PCI (NCCN 2021a).

Additional tumor assessments during the induction and maintenance phases will be performed as per local standard of care and as clinically indicated and must also be reported in the study database as unscheduled visits.

Tumor assessments at induction screening, maintenance screening, and subsequent assessments must include computed tomography (CT) scans (with IV contrast, unless contraindicated, and oral contrast as appropriate per institutional standards) of the chest and abdomen. A CT scan, with contrast, of the pelvis is required at induction screening, maintenance screening, and as clinically indicated or as per local standard of care at subsequent response evaluations. Magnetic resonance imaging scans with contrast of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may be used in participants for whom CT scans with IV contrast are contraindicated (i.e., participants with iodine-based contrast allergy or impaired renal clearance).

An MRI scan or CT scan with contrast of the head must be done at induction screening and maintenance screening to evaluate CNS metastases in all participants.
For participants for whom imaging of the brain was performed after induction and who subsequently received PCI, brain imaging does not need to be repeated after PCI before randomization. A brain MRI scan is the preferred imaging method for evaluating CNS metastases as it is more sensitive than CT for identifying brain metastases; however, CT of the brain is acceptable if MRI is contraindicated. If a CT scan with contrast is performed and the presence of brain metastases is considered equivocal, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases. Participants with CNS metastases are not eligible for the study.

All known or suspected sites of disease should be assessed at induction screening and maintenance screening and at subsequent assessments with use of the same imaging method and technique. If more than one method is used at screening, then the most accurate method according to RECIST v1.1 should be used when recording data, and should again be used for all subsequent assessments.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full contrast diagnostic CT scan.

For participants with bone lesions, bone scans, PET scans, and plain films are not considered adequate imaging techniques for measuring bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions. Participants should undergo bone scans if bone disease cannot be assessed by another modality (e.g., CT scan).

Further investigations (e.g., CT scans of the neck) should be performed as clinically indicated.

Randomized participants who discontinue treatment for any reason prior to radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the same frequency as would have been followed if the participant had remained on study treatment, regardless of whether the participant starts a new non-protocol anti-cancer therapy.

Radiographic images will be submitted to an IRF for a quality and completeness check, for independent central review, and for temporary storage prior to transferring images to the Sponsor for the long-term retention and eventual secondary/exploratory use.

Radiographic images, whether reviewed locally or centrally, must be evaluated by a qualified, certified expert.

8.1.1.2 Response Evaluation

Objective response will be determined by the IRF and the investigator at specified timepoints according to RECIST v1.1 (see Appendix 8). Assessments should be performed by the same individual, if possible, to ensure internal consistency across visits.

Endpoints (e.g., confirmed ORR, PFS), will be calculated programmatically by the Sponsor on the basis of the IRF's and investigator's assessments of responses.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at induction baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

8.2.2 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at induction baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

The measurement of vital signs during lurbinectedin infusion should be performed as clinically indicated.

See Table 8 for details on the measurements of vital signs during atezolizumab infusions.

In addition, vital signs should be assessed at other specified timepoints as outlined in the schedule of activities (see Section 1.3).

8.2.3 Electrocardiograms

An ECG is required at screening and when clinically indicated. Electrocardiograms for each participant should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. Electrocardiogram recordings must be performed after the participant has been resting in a supine position for at least 10 minutes.

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

8.2.4 Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and see the schedule of activities (see Section 1.3 [Table 1 and Table 2]) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event Case Report Form (CRF; see Appendix 3).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 months of the final dose of atezolizumab or 30 days after the final dose of lurbinectedin treatment should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event, adverse event or requirement of a dose modification), the results must be recorded on the eCRF.

Sample collection may be performed by a MN professional.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report (CSR).

8.2.5 Pregnancy Testing

The schedule for pregnancy testing for female participants of childbearing potential is outlined in Section 1.3 (Table 1 and Table 2) and will be conducted as outlined in Appendix 2.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported (see Appendix 3). The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. All other medical occurrences that begin before the start of study treatment will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 30 days after the final dose of study treatment or until start of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will be reported from the start of study treatment until 90 days after the final dose of study treatment or until start of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest considered related to prior exposure to study treatment will be reported indefinitely.

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care must be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to the regulatory authority (which include the use of applicable systems, such as EudraVigilance), Institutional Review Boards or Ethics Committees (IRBs/ECs), and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Lurbinectedin	Lurbinectedin Investigator's Brochure
Atezolizumab	Atezolizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Investigator's Brochures and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during study treatment or within 5 months after the final dose of atezolizumab, or within 6 months after the final dose of carboplatin and etoposide, or within 7 months after the final dose of lurbinectedin, whichever is later.

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during their study treatment or within 4 months after the final dose of lurbinectedin, or within 6 months after the final dose of carboplatin or etoposide, whichever is later.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

All pregnancies reported during the study should be followed until pregnancy outcome. The Sponsor or a designee may follow up by telephone, fax, e-mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Cardiovascular and Death Events

Information on cardiovascular events and reporting deaths is provided in Appendix 3.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A3–7.7)
- Suspected transmission of an infectious agent by a study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.
- Hepatitis, including AST or ALT $>$ 10 $\times$ ULN
- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome (CRS), hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade $\geq$2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Myositis
- Myopathies, including rhabdomyolysis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 6.

8.3.9 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

[redacted]

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of lurbinectedin and atezolizumab. Samples collected for analyses of lurbinectedin and atezolizumab plasma and serum concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Participant confidentiality will be maintained. Pharmacokinetic samples will be destroyed no later than 5 years after the final CSR has been completed to allow for assay development and validation (if needed).

8.5 PHARMACODYNAMICS

See Section 8.7 for information on pharmacodynamic biomarkers.

8.6 GENETICS

See Section 8.7 and Appendix 5 for information on genetic biomarkers.

[redacted]

[redacted]

- [redacted]
- [redacted]
  - [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.8 IMMUNOGENICITY ASSESSMENTS

[redacted]

Samples may be stored for a maximum of 5 years (or according to local regulations) after the final CSR has been completed at a facility selected by the Sponsor to enable further analysis of the immunogenicity of atezolizumab.

8.9 HEALTH ECONOMICS

For all participants throughout the study, the investigator and study site personnel will collect data about health care resource utilization associated with medical encounters.

The data collected will include the reasons and duration of hospitalizations and emergency room visits and exclude procedures, tests, and encounters mandated by the protocol.

The Sponsor may use the collected data to conduct economic analyses.

8.10 CLINICAL OUTCOME ASSESSMENTS

Patient-reported outcome (PRO) instruments will be completed to assess the treatment benefit of the lurbinectedin and atezolizumab combination. In addition, PRO instruments will enable the capture of each participant's direct experience with lurbinectedin and atezolizumab.

Patient-reported outcomes data will be collected through use of the following instruments: the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30), EORTC Quality of Life Questionnaire–Lung Cancer Module (QLQ-LC13), EORTC IL46, Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE), and EQ-5D-5L.

8.10.1 Data Collection Methods for Clinical Outcome Assessments

Patient-reported outcomes instruments will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Section 1.3 [Table 1 and Table 2]). At the clinic, instruments will be administered before the participant receives any information on disease status, and prior to the administration of study treatment, unless otherwise specified.

Patient-reported outcomes instruments, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor. The device will be pre-programmed to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic device and instructions for completing the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel only.

Participants should be given the following instructions for completing PRO instruments at home:

- Participants should complete the instruments in a quiet area with minimal distractions and disruptions.
- Participants should answer questions to the best of their ability; there are no right or wrong answers.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

During clinic visits and visits conducted by a MN professional, PRO instruments should be administered as outlined below:

- Participants' health status should not be discussed prior to administration of the instruments

- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for participants to complete the instruments
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions
- Participants should be instructed to answer questions to the best of their ability; there are no right or wrong answers
- Site staff should not interpret or explain questions, but may read questions verbatim upon request
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments

Patient-reported outcomes may be completed remotely during the maintenance phase on Cycle 1, Day 10 and Cycle 2, Day 10. Additionally, remote data collection may occur during follow-up and in exceptional circumstances, if the participant cannot get to the site. Source documentation should be obtained which includes, among other information, that the questionnaires were administered remotely.

8.10.2 Description of Clinical Outcome Assessment Instruments

8.10.2.1 EORTC Quality of Life Questionnaire–Core 30

The QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999; see Appendix 11). It consists of 30 questions that assess five aspects of participant functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), global health status and quality of life (QoL), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week.
Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the global health status and QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent." The QLQ-C30 module takes approximately 10 minutes to complete.

8.10.2.2 EORTC Quality of Life Questionnaire–Lung Cancer Module

The EORTC QLQ-LC13 (Bergman et al. 1994; see Appendix 12) is composed of 13 lung cancer-specific items and includes 11 disease-specific scales and items (dyspnea, coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts, pain medication). The QLQ-LC13 takes approximately 7 minutes to complete.

8.10.2.3 EORTC Item List 46

The single-item EORTC Item List 46 (IL 46) question assesses overall side-effect impact (Appendix 13).

8.10.2.4 EuroQol EQ-5D-5L

The EQ-5D-5L is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013; see Appendix 10). There are two components to the EQ-5D-5L: a 5-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale (VAS) that measures health state. The EQ-5D-5L is designed to capture the participant's current health status. Published weighting systems allow for creation of a single composite score of the participant's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations (see Section 8.9), scored according to its manual, and the results will be reported separately from the CSR.

8.10.2.5 PRO-CTCAE

The PRO-CTCAE is a validated item library that is used to characterize the presence, frequency of occurrence, severity, and/or degree of interference with daily function of 78 patient-reportable symptomatic treatment toxicities (Basch et al. 2014; Dueck et al. 2015). The PRO-CTCAE contains 124 questions that are rated either dichotomously (for determination of presence vs. absence) or on a 5-point Likert scale (for determination of frequency of occurrence, severity, and interference with daily function). Treatment toxicities can occur with observable signs (e.g., vomiting) or non-observable symptoms (e.g., nausea). The standard PRO-CTCAE recall period is the previous 7 days.

A subset of 12 symptoms deemed most applicable to the current study treatments has been selected for this study (see Appendix 14). Symptoms have been selected based on toxicities most commonly associated with lurbinectedin and atezolizumab.

8.11 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

8.11.1 Optional Tumor Biopsies (Participants Providing Separate Consent)

Consenting participants will undergo an optional tumor biopsy (if deemed clinically feasible by the investigator) after the completion of induction treatment and/or at the time of radiographic disease progression (preferably within 40 days after radiographic progression or prior to start of the next anti-cancer treatment, whichever is sooner).

Preferred sample types include FFPE samples prepared from resections, core needle, excisional, incisional, punch, or forceps biopsies. If these sample types are not available, any type of specimen (including fine-needle aspiration, cell pellet specimens [e.g., from pleural effusion and lavage samples], preferably in cell blocks) is acceptable.

The Informed Consent Form will contain a separate section that addresses optional biopsies. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of undergoing optional biopsies. Participants will be told that they are free to choose not to undergo optional biopsies and may withdraw their consent at any time and for any reason. A separate, specific signature will be required to document a participant's agreement to undergo optional biopsies. Participants who choose not to undergo optional biopsies will not provide a separate signature. The investigator should document whether or not the participant has given consent to undergo optional biopsies and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

Samples may be used for exploratory biomarker research as described in Section 8.7. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. [redacted]

8.11.2 Optional Samples for Research Biosample Repository (Participants Providing Separate Consent at Participating Sites)

8.11.2.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents [redacted] which may allow for individualized drug therapy for participants in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- [redacted]

8.11.2.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 8.11.2) will not be applicable at that site.

8.11.2.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on [redacted]

- [redacted]
- [redacted]

[redacted]

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Research Biosample Repository samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

8.11.2.4 Confidentiality

Research Biosample Repository samples and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

8.11.2.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to choose not to provide optional RBR samples and may withdraw their consent at any time and for any reason during the storage period.
A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

8.11.2.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by e-mailing the study number and participant number to the following e-mail address:

global.rcr-withdrawal@roche.com

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

8.11.2.7 Monitoring and Oversight

Research Biosample Repository samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to an individual's participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

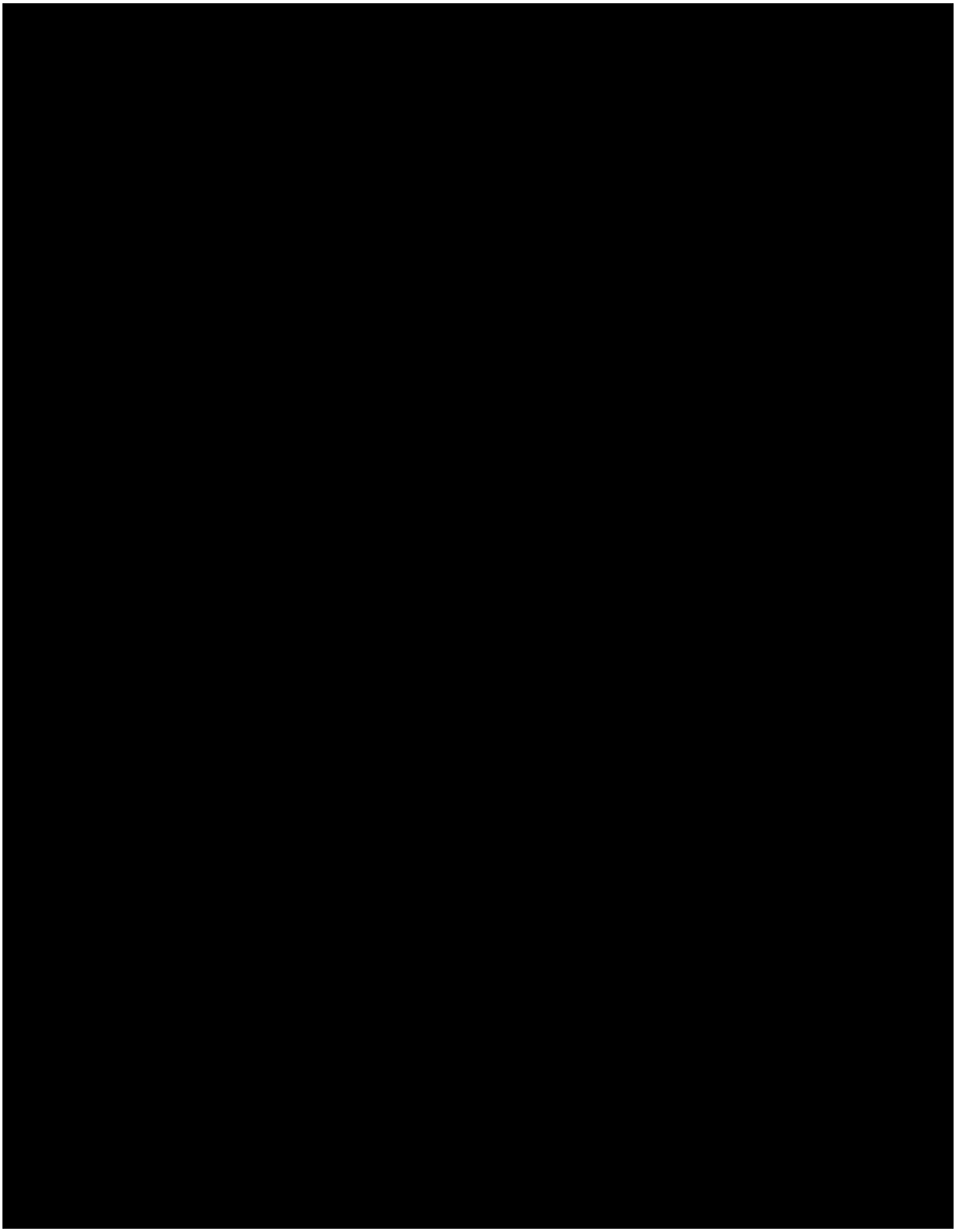
The purpose of this study is hypothesis testing and estimation regarding the effect of lurbinectedin in combination with atezolizumab on the duration of IRF-assessed PFS and/or OS compared with atezolizumab alone. The primary objective of this study is to evaluate the efficacy of lurbinectedin in combination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

[redacted]

9.2 SAMPLE SIZE DETERMINATION

Approximately 920 participants will be screened to achieve the enrollment of 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.

[redacted]



9.3 ANALYSIS SETS

The analysis sets are defined in Table 10.

Table 10 Description of 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; SAS = Safety Analysis Set.

9.4 STATISTICAL ANALYSES

The Statistical Analysis Plan will be finalized before the randomized treatment assignment information is disclosed to the study team for the pre-specified analyses, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.4.1 General Considerations

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

All safety analyses will be performed in the SAS, unless otherwise specified. 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.

Hypothesis tests will be 2-sided unless otherwise indicated.

9.4.2 Estimation Methods for the 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 IRF-assessed PFS according to RECIST v1.1 and OS, as defined in Section 3 (see Table 4).

9.4.2.1 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 with no tumor assessment after baseline 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.

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% CIs. The stratification factors will be those used for randomization. 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.

Further analysis details including sensitivity and supplemental analyses on the primary endpoints will be specified in the Statistical Analysis Plan.

9.4.3 Estimation Methods for the Secondary Endpoints

9.4.3.1 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 9.4.2.1).

9.4.3.2 Confirmed Objective Response Rate

A confirmed objective response is defined as either a CR or a 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.

Confirmed ORR is defined as the proportion of participants who had a confirmed objective response after randomization. The analysis set for confirmed 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.

Confirmed ORR as determined by the investigator according to RECIST v1.1 will also be analyzed through the same methods described above.

9.4.3.3 Duration of Response

Duration of response will be assessed in participants who had a confirmed objective response as determined by IRF with use of 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 that 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 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 patients 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.

9.4.3.4 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 at 24 months after randomization.

9.4.3.5 Incidence and Severity of Adverse Events

The secondary safety objective will be assessed through summaries of the incidence and severity of adverse events in the SAS.

Verbatim description of adverse events will be mapped to the MedDRA thesaurus terms. Severity for all adverse events will be graded by the investigator according to the NCI CTCAE v5.0. Severity for 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, serious adverse events, adverse events leading to death, adverse events of special interest, 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 mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Multiple occurrences of the same event will be counted once at the maximum severity. Deaths and cause of death will be summarized.

9.4.3.6 Time to Confirmed Deterioration

Time to confirmed deterioration (TTCD) for physical functioning and global health status (GHS)/QoL using the EORTC QLQ-C30 is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration.

Confirmed clinically meaningful deterioration for physical functioning and GHS/QoL is defined as a clinically meaningful decrease from baseline in physical functioning or GHS score that must be held for at least two consecutive assessments or an initial clinically meaningful decrease above baseline followed by death.

A score change of $\geq$ 10-point change in GHS/QoL and functional subscale score is perceived by participants as clinically meaningful (Osoba et al. 1998).

For 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. Time to confirmed deterioration using the EORTC scale will be analyzed with use of the same methods as for PFS. Further details regarding the TTCD analysis for the EORTC measures will be described in the Statistical Analysis Plan.

[redacted]

9.4.4 Other Safety Analyses

Drug exposure will be summarized during the maintenance phase in the SAS, including duration, dosage, and dose intensity. Laboratory data with values outside of the normal ranges will be identified. Additionally, selected laboratory data may be summarized by treatment arm and grade. Vital signs may also be summarized by treatment arm and visit.

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

9.4.5 Other Analyses

9.4.5.1 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.

9.4.5.2 Summaries of Demographics and Baseline Characteristics

Demographics (e.g., sex, age) and baseline characteristics (e.g., ECOG PS, 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]

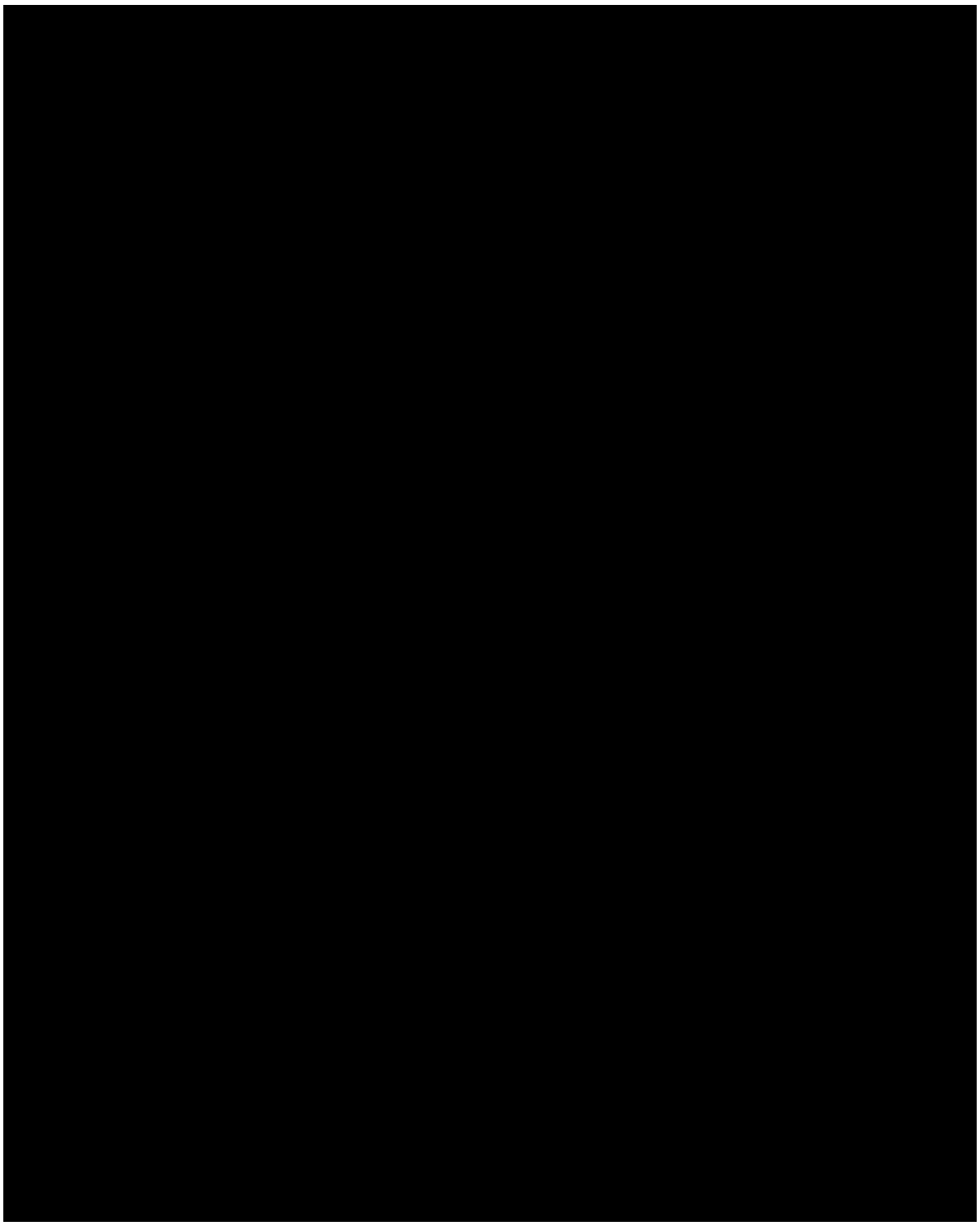
[redacted]

9.4.5.5 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 QLQ-C30 and EORTC QLQ-LC13 (lung cancer-specific subset) questionnaires according to the EORTC scoring manual guidelines.

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 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. 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.

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



9.6 INDEPENDENT DATA MONITORING COMMITTEE

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 IRBs/ECs. A detailed plan will be included in the iDMC Charter.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

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A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Guideline for Good Clinical Practice
- Applicable laws and regulations

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) (EEA sites only), and all other applicable local regulations

A1–2 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or the participant's legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant or the participant's legally authorized representative.

A participant who is re-screened is not required to sign another Informed Consent Form if the re-screening occurs within 28 days from the previous Informed Consent Form signature date.

A1–4 DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 150 sites globally will participate. Approximately 690 participants are expected to be accrued in the induction phase to meet the goal of approximately [redacted] randomized participants total in the maintenance phase. The number of participants in the induction phase of the study will be adjusted as necessary based on the actual screen failure rate for entering the maintenance phase to achieve the required number of approximately [redacted] participants in the maintenance phase of the study. Enrollment will occur through an interactive voice or Web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8 and Appendix 2. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An independent Data Monitoring Committee (iDMC) will be employed to monitor and evaluate participant safety throughout the study. An Independent Review Facility (IRF) will collect, store, and review imaging data.

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

Study data, which may include imaging data, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be provided upon

request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

A1–7 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed CRF or eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data).
The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

A1–8 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1–9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY *AND PROTECTION OF TRADE SECRETS*

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

Appendix 2
Clinical Laboratory Tests

The tests detailed in Table A2-1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A2-1 Protocol-Required Laboratory Assessments

Local Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells) • Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide, sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, CPK and LDH • Coagulation: INR and aPTT • Thyroid function testing: TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 • HIV serology • HBV serology: HBsAg, and total HBcAb for all individuals; HBV DNA for individuals with negative HBsAg test and a positive total HBcAb test • HCV serology: HCV antibody for all individuals; HCV RNA for individuals with a positive HCV antibody test • C-reactive protein • Pregnancy test All female participants of childbearing potential will have a serum pregnancy test at screening (within 14 days prior to enrollment and randomization). Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. • Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood)

HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus.

Investigators must document their review of each laboratory safety report.

Appendix 3
Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can; therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of the underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

  Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- *Is medically significant*:

  Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section A3–3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5 for reporting instructions).

A3–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND/OR SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the eCRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE v5.0 grading scale. The investigator will use the grading scale in Table A3-1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE. In addition to the NCI CTCAE v5.0 grading scale, 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 (Table A3-2; Lee et al. 2019).

Table A3-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v 5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event", it must be reported as a serious adverse event (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2, with the exception of Grade 4 laboratory abnormalities for which the investigator should assess seriousness of the event on an individual basis.

Table A3-2 ASTCT Grading Scale for Cytokine Release Syndrome

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fever [a]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Death
	With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)	
	And/or [b]				
Hypoxia	None	Requiring low-flow nasal cannula [c] or blow-by	Requiring high-flow nasal cannula [c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome.

Note: Organ toxicities associated with CRS may be graded according to NCI CTCAE v5.0 but they do not influence CRS grading.

[a] Fever is defined as temperature ≥38°C not attributable to any other cause.
In participants who have CRS and then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochures and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

For participants receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.

New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, e-mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and e-mailing the form, using the fax number or e-mail address provided to investigators.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the final dose of study treatment or until start of new systemic anti-cancer therapy; whichever occurs first. Serious adverse events or adverse events of special interest believed to be related to prior exposure to study treatment will be reported indefinitely. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and e-mailing the form, using the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 90 days after the final dose of study treatment are provided in Section A3–6.

A3–6 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (see Section 8.3.1), serious adverse events and adverse events of special interest that are believed to be related to prior exposure to study treatment should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and e-mailing the paper Clinical Trial Adverse Event/Special Situations Form, using the fax number or e-mail address provided to investigators.

A3–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and

concepts when recording adverse events on the Adverse Event eCRF.
Avoid colloquialisms and abbreviations. Only 1 adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–7.1 INFUSION-RELATED REACTIONS

Adverse events considered to be IRRs that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion/injection should be captured as a diagnosis (e.g., "infusion-related reaction"/"injection-site reaction"/"anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction/Injection Reaction eCRF. If a participant experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction/Injection Reaction eCRF.

A3–7.2 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by 1 adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

A3–7.3 ADVERSE EVENTS THAT ARE SECONDARY TO OTHER EVENTS

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all 3 events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

A3–7.4 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A3–5 for reporting instructions).
The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.5 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected.
A laboratory value abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.4 for details on recording persistent adverse events).

A3–7.6 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.4 for details on recording persistent adverse events).

A3–7.7 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A3–7.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

A3–7.8 DEATHS

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1) that are attributed by the investigator solely to progression of SCLC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only 1 such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths not related to progression of the underlying cancer and occurring within the adverse event reporting period, must be reported as serious adverse event, regardless of relationship to study treatment. Deaths not related to progression of the underlying cancer and occurring outside the adverse event reporting period should only be reported as serious adverse event if considered related to prior exposure to study treatment. Deaths not related to progression of the underlying cancer and outside the adverse event reporting period and considered unrelated to prior exposure to study treatment should be reported through use of the Long-Term Follow-Up eCRF. Deaths related to the progression of the underlying cancer occurring during the adverse event reporting period should be reported on the Death Attributed to Progressive Disease eCRF. Deaths related to the progression of the underlying cancer occurring outside the adverse event reporting period should be reported on the Long-Term Follow-Up eCRF (for an overview, see Table A3-3).

Table A3-3 Documentation Required for Reporting Deaths

Cause of Death	Timing	
	During Adverse Event Reporting Period [a]	After Adverse Event Reporting Period
SCLC	Death Attributed to Progressive Disease eCRF	Long-Term Follow-Up eCRF
Unrelated Grade 5 Adverse Event	Adverse Event eCRF	Long-Term Follow-Up eCRF [b]
Related Grade 5 Adverse Event	Adverse Event eCRF	Adverse Event eCRF [c]

eCRF = electronic Case Report Form; EDC = electronic data capture; SCLC = small-cell lung cancer.

[a] Up to 90 days after final dose of study treatment or until start of new systemic anti-cancer therapy, whichever occurs first.

[b] Record the primary cause of death as "other", for "other death cause" specify the Adverse Event term.

[c] If the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and e-mailing the paper Clinical Trial Adverse Event/Special Situations Form using the fax number or e-mail address provided to investigators.

A3–7.9 PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study.
When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

A3–7.10 LACK OF EFFICACY OR WORSENING OF SCLC

Medical occurrences or symptoms of deterioration that are anticipated as part of SCLC should not be recorded as adverse events. However, deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event.
When recording an unanticipated worsening of SCLC on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of small-cell carcinoma").

A3–7.11 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section A3–2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of a tumor assessment for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition
  - The participant has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours

A3–7.12 CASES OF ACCIDENTAL OVERDOSE OR MEDICATION ERROR

Accidental overdose and medication error (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). For lurbinectedin and atezolizumab, adverse events associated with special situations should be recorded as described below for each situation:

- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

As an example, an accidental overdose that resulted in a headache would require 2 entries on the Adverse Event eCRF, 1 entry to report the accidental overdose and 1 entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

All special situations associated with lurbinectedin and atezolizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the name of the drug and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the name of the drug and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

A3–7.13 PATIENT-REPORTED OUTCOME DATA

Adverse event reports will not be derived from the Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) or other PRO data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile participant reports of treatment-related symptoms (via the PRO-CTCAE) with investigator reports of adverse events. Sites are not expected to review the PRO-CTCAE or other PRO data for adverse events.

[redacted]

REFERENCES

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625–38.

Appendix 4
Contraceptive and Barrier Guidance

TABLE OF CONTENTS

A4–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during study treatment or within 5 months after the final dose of atezolizumab, 6 months after the final dose of carboplatin, or etoposide, or 7 months after the final dose of lurbinectedin, whichever occurs last. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the pregnancy), either by faxing or by scanning and e-mailing the form, using the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A4–2 PREGNANCIES IN FEMALE PARTNERS OF MALE PARTICIPANTS

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during study treatment or within 4 months after the final dose of lurbinectedin, or within 6 months after the final dose of carboplatin or etoposide, whichever occurs last. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy

Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A4–3 ABORTIONS

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A4–4 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment or the female partner of a male participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

Appendix 5
Genetics: Use and Analysis of DNA

Genetic variation may impact a participant's response to study treatment and susceptibility to, and severity and progression of, disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and the Institutional Review Board or Ethics Committee allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to lurbinectedin, atezolizumab, drug safety, small-cell lung cancer (SCLC) and related disease biology. They may also be used to develop tests or assays, including diagnostic tests related to lurbinectedin, atezolizumab, SCLC and related diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.

DNA samples will be analyzed for whole-genome sequencing (WGS) or [redacted] to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data. The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to lurbinectedin and atezolizumab and treatments of this drug class to understand the study disease or related conditions. The results of genetic analyses may be reported in the Clinical Study Report or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on lurbinectedin and atezolizumab and/or treatments of this drug class or SCLC disease continues but no longer than 15 years or other period as per local requirements.

Appendix 6
Safety Plan: Management of Identified and Potential Risks

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The anticipated important safety risks for lurbinectedin and atezolizumab are outlined below. Please refer to the lurbinectedin and atezolizumab Investigator's Brochures for a complete summary of safety information.

Several measures will be taken to ensure the safety of study participants. Eligibility criteria have been designed to exclude individuals at higher risk for toxicities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

A6–1 RISKS ASSOCIATED WITH STUDY DRUGS

The safety plan for participants in this study is based on clinical experience with lurbinectedin and atezolizumab in completed and/or ongoing studies and the most recent prescribing information for etoposide and carboplatin. The anticipated important safety risks are outlined below. Refer to the current lurbinectedin and atezolizumab Investigator's Brochures for a complete summary of safety information for each respective study drug.

Measures will be taken to ensure the safety of participants in this study, including the use of stringent inclusion and exclusion criteria (see Section 5.1 and Section 5.2, respectively) and close monitoring of participants during the study as indicated below. An independent Data Monitoring Committee (iDMC) will periodically review safety data as outlined in Section 9.6 with more detail provided in the iDMC Charter. Administration of study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for reporting adverse events and for managing participants who experience anticipated adverse events, including criteria for treatment interruption or discontinuation, are provided in Section 8.3.1, Section 8.3.5, Appendix 3, and Appendix 6.

Participants with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS–CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or ESMO).

Severe COVID-19 appears to be associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a participant develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted

through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

A6–1.1 LURBINECTEDIN

Lurbinectedin has been associated with risks such as the following: reversible myelosuppression (including neutropenia, lymphopenia, anemia, and thrombocytopenia), increased liver transaminases, nausea, vomiting, constipation, increased serum creatinine, and increased creatine phosphokinase. See Sections A6–1.1.1 (Hematological Abnormalities), A6–1.1.2 (Liver Abnormalities), A6–1.1.3 (Gastrointestinal Adverse Events), A6–1.1.4 (Renal Abnormalities), A6–1.1.5 (Muscular Adverse Events), and A6–1.1.6 (Infusion Site Events) of the protocol and Section 5 (summary of the data and guidance for the investigator) of the Lurbinectedin Investigator's Brochure for a detailed description of anticipated safety risks for lurbinectedin.

See Section A6–2.4.1 for details on the management guidelines for risks associated with lurbinectedin.

A6–1.1.1 Hematological Abnormalities

Reversible myelosuppression is the most frequent abnormality related to single-agent lurbinectedin at a dose level of 3.2 mg/m^2. Regardless of relationship to lurbinectedin, Grade 3/4 neutropenia was observed in 40.8% of participants treated at this dose level in Phase II and III studies, and it reached Grade 4 in 21.9% of participants. Other Grade 3/4 hematological abnormalities were less common, including lymphopenia (33.4% of participants), leukopenia (29.4% of participants), anemia (17.4% of participants) and thrombocytopenia (9.7% of participants). Treatment-related febrile neutropenia was observed in 6.5% of participants.

A6–1.1.2 Liver Abnormalities

Elevations of aminotransferases (ALT and AST) and bilirubin have been observed during treatment with lurbinectedin. Most transaminase increases observed in Phase II and III studies with single-agent lurbinectedin at 3.2 mg/m^2 every 3 weeks (Q3W) were mild or moderate, transient and asymptomatic. Regardless of relationship to lurbinectedin, Grade 3/4 ALT increases occurred in 6.4% of participants (Grade 4 in 2 participants [0.4%]) and Grade 3/4 AST increase occurred in 3.2% of participants (Grade 4 in 3 participants [0.5%]). In addition, Grade 3/4 bilirubin increases occurred in 2.4% of participants (Grade 4 in 1 participant [0.2%]). No Hy's Law cases, as defined in the U.S. Food and Drug Administration (FDA) guidelines, were observed in these studies.

A6–1.1.3 Gastrointestinal Adverse Events

Despite standard anti-emetic prophylaxis, mild to moderate gastrointestinal toxicity occurred frequently with single-agent lurbinectedin at 3.2 mg/m^2. The most common gastrointestinal adverse events were nausea, vomiting, and constipation.

A6–1.1.4 Renal Abnormalities

In Phase II and III trials with single-agent lurbinectedin administered at 3.2 mg/m^2 Q3W, 84.3% of participants had creatinine increases of any Grade, including 9 participants (1.6%) with Grade 3 events.

Lurbinectedin is not significantly eliminated through the urine, thus participants with limited renal function are not expected to be impacted differently than participants with normal renal function. Nevertheless, no participants with less than 30 mL/min of calculated creatinine clearance have been included in clinical trials with lurbinectedin to date.

A6–1.1.5 Muscular Adverse Events

Regardless of relationship to lurbinectedin, creatine phosphokinase (CPK) increases were reported in 9.4% of participants treated with single-agent lurbinectedin at 3.2 mg/m^2 Q3W in Phase II and III studies. Of these, only 2 participants (0.4%) experienced a Grade 3 CPK increase. Episodes of rhabdomyolysis were reported in 2 clinical trial participants treated with single-agent lurbinectedin at a dose that was higher than 3.2 mg/m^2 Q3W.

A6–1.1.6 Infusion Site Events

Extravasation of lurbinectedin may result in skin and soft tissue injury. This includes rare reports from post-marketing use of lurbinectedin of necrosis requiring debridement.

A6–1.2 ATEZOLIZUMAB

Atezolizumab has been associated with risks such as the following: infusion-related reactions (IRRs), immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). See Section A6–2.4.2 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A6–1.2.1 Pulmonary Events

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Participants will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies, such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease (COPD), or pulmonary hypertension. COVID-19 evaluation should be performed per institutional guidelines where relevant.

Management guidelines for pulmonary events are described in Section A6–2.4.2.

A6–1.2.2 Hepatic Events

Eligible participants must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table A6-5.

Participants with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For participants with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

A6–1.2.3 Gastrointestinal Events

Management guidelines for diarrhea or colitis are provided in Table A6-5.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with 3–5 specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

A6–1.2.4 Endocrine Events

Management guidelines for endocrine events are provided in Table A6-5.

Participants with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The participant should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone and free T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

A6–1.2.5 Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table A6-5.

A6–1.2.6 Immune-Mediated Cardiac Events

Management guidelines for cardiac events are provided in Section A6–2.4.2.

Immune-Mediated Myocarditis

Immune-mediated myocarditis should be suspected in any participant presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on pericardial disorders below) and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a participant who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All participants with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Participants with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-5.

Immune-Mediated Pericardial Disorders

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer-related (metastatic disease or chest radiotherapy), cardiac injury related (post-myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-5. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

A6–1.2.7 Infusion-Related Reactions and Cytokine Release Syndrome

No premedication is indicated for the administration of Cycle 1 (induction phase) of atezolizumab. However, participants who experience an IRR or CRS with atezolizumab may receive premedication with antihistamines, antipyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

Infusion-related reactions are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

Cytokine release syndrome is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be

progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). Cytokine release syndrome has been well-documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for the medical management of IRRs during Cycle 1 are provided in Table A6-5. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a participant develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator's judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

A6–1.2.8 Pancreatic Events

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table A6-5.

A6–1.2.9 Dermatologic Events

The majority of cases of rash reported with the use of atezolizumab were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson Syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table A6-5.

A6–1.2.10 Neurologic Disorders

Participants may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table A6-5.

A6–1.2.11 Immune-Mediated Meningoencephalitis

Immune-mediated meningoencephalitis should be suspected in any participant presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All participants being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Participants with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-5.

A6–1.2.12 Renal Events

Eligible participants must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Participants with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the participant to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Participants with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-5.

A6–1.2.13 Immune-Mediated Myositis

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Participants with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-5.

A6–1.2.14 Hemophagocytic Lymphohistiocytosis

Immune-mediated reactions may involve any organ system and may lead to HLH and macrophage activation syndrome (MAS).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Participants with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A participant should be classified as having HLH if 5 of the following 8 criteria are met:

- Fever $\geq$ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least 2 of the following:
  - Hemoglobin $<$ 90 g/L (9 g/dL)
  - Platelet count $<$ 100 $\times$ 10^9/L (100,000/μL)
  - ANC $<$ 1.0 $\times$ 10^9/L (1000/μL)
- Fasting triglycerides $>$ 2.992 mmol/L (265 mg/dL) and/or fibrinogen $<$ 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin $>$ 500 mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated $\geq$ 2 standard deviations above age-adjusted laboratory-specific norms

Participants with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile participant should be classified as having MAS if the following criteria are met:

- Ferritin $>$ 684 mg/L (684 ng/mL)
- At least 2 of the following:
  - Platelet count $\leq$ 181 $\times$ 109/L (181,000/μL)
  - AST $\geq$ 48 U/L
  - Triglycerides $>$ 1.761 mmol/L (156 mg/dL)
  - Fibrinogen $\leq$ 3.6 g/L (360 mg/dL)

Participants with suspected HLH or MAS should be treated according to the guidelines in Table A6-5.

A6–1.3 RISKS ASSOCIATED WITH COMBINATION USE OF LURBINECTEDIN AND ATEZOLIZUMAB

Lurbinectedin and atezolizumab have anticipated molecule-specific safety profiles based on their mechanism of action and adverse events that may overlap.

- The most frequent adverse events specific to each drug include hematological toxicities for lurbinectedin and immune-mediated adverse events for atezolizumab.
- Atezolizumab treatment is not predicted to further impact hematological abnormalities commonly observed with lurbinectedin treatment in the proposed Phase III Study GO43104. However, given the risk factors of this participant population, primary G-CSF prophylaxis and monitoring via hematological tests have been implemented as risk mitigation measures (see Section 6.1.3 for more information).
- Immune-mediated adverse events observed with atezolizumab treatment are well-known, manageable and/or reversible. The Sponsor does not predict lurbinectedin treatment to impact immune-mediated adverse events.

Overlapping adverse events may include hepatotoxic, gastrointestinal, muscular and renal events, as well as signs and symptoms such as fatigue and decreased appetite that may be related to multiple system organ class events. For the management of such potentially overlapping adverse events in participants treated with lurbinectedin in combination with atezolizumab, adverse events should be managed according to the recommendations in Section A6–2.3.1 (lurbinectedin) and Section A6–2.3.2 (atezolizumab), applied to the component of the study treatment judged to be the primary cause.

The attribution of causality for certain adverse events may be uncertain when the drugs are administrated as a combination treatment and warrants diagnostic investigation. If causality for an adverse event with study treatment cannot be adequately determined, conservative management recommendations should be followed to include dose modification/interruption of both agents.

At present, considering the different mechanisms of action of lurbinectedin and atezolizumab, the initial safety profile from Study ML40908 (lurbinectedin + atezolizumab), and data from molecules with similar mechanisms of action (Chawla et al. 2018; Gordon et al. 2018), overlapping toxicities are expected to be limited and no exacerbations are anticipated.

A6–1.4 ETOPOSIDE

The risk of overlapping toxicities between atezolizumab, carboplatin, and etoposide is thought to be minimal. Etoposide is known to cause bone marrow suppression including myelosuppression, anemia, thrombocytopenia, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea), hepatotoxicity, and alopecia. Etoposide-based chemotherapy is considered to be moderately emetogenic. Etoposide carries a risk of secondary hematologic malignancy. Participants will be monitored for etoposide-related adverse events.

For more details regarding the safety profile of etoposide, refer to the etoposide prescribing information.

A6–1.5 CARBOPLATIN

The risk of overlapping toxicities between atezolizumab, carboplatin, and etoposide is thought to be minimal. Carboplatin is known to cause bone marrow suppression including myelosuppression, anemia, and thrombocytopenia. Carboplatin-based chemotherapy is considered to be moderately emetogenic. Participants will be monitored for carboplatin-related adverse events.

For more details regarding the safety profile of carboplatin, refer to the carboplatin prescribing information.

A6–2 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

A6–2.1 DOSE MODIFICATIONS

Lurbinectedin

Dose modifications for lurbinectedin are as follows:

- Up to 2 individual lurbinectedin dose reductions are allowed (Table A6-1). Once the dose has been reduced for an individual participant, it must not be re-escalated again under any circumstances. Participants who continue to experience treatment-related toxicity and/or frequent dose delays after permitted dose reductions must discontinue treatment with lurbinectedin. They can continue receiving the study medication if objective clinical benefit is adequately documented by the investigator, and upon agreement with the Sponsor. If the participant receives a lurbinectedin dose of 2 mg/m^2 and experiences a toxicity that would warrant a lurbinectedin dose reduction, treatment with lurbinectedin must be permanently discontinued.

- Participants may continue lurbinectedin at a reduced dose after they have adequately recovered from any of the following:
  - Grade ≥ 3 treatment-related non-hematological toxicity
  - Grade 4 thrombocytopenia or Grade 3 thrombocytopenia concomitantly with Grade ≥ 3 bleeding
  - Grade 4 neutropenia, any Grade febrile neutropenia or neutropenia associated with infection/sepsis
  - Frequent or prolonged (> 1 week) dose delay due to treatment-related adverse events

Refer to Table A6-2 for a list of criteria for treatment continuation.

Exceptions: patients experiencing treatment-related Grade ≥ 3 nausea and/or vomiting not optimally treated, Grade 3 asthenia lasting ≤ 3 days, Grade 3 diarrhea lasting ≤ 2 days or not optimally treated, Grade 3 transient ALT/AST elevations which are rapidly reversible and not leading to subsequent delays, and non-clinically relevant biochemical abnormalities, may continue treatment at the same prior dose without any dose reduction being applied, provided optimal concomitant treatment is given for the applicable toxicity.

Participants who experience Grade 3 or Grade 4 hypersensitivity reactions or Grade 3 or Grade 4 rhabdomyolysis will be discontinued from lurbinectedin.

Table A6-1 Lurbinectedin Dose Reduction Levels

Dose Reduction Schedule	Lurbinectedin Dose (mg/m^2) [a]
Starting dose	3.2
First reduction	2.6
Second reduction	2.0

[a] Dose rounded to the first decimal.

In case atezolizumab is discontinued due to immune-related severe adverse events, treatment with lurbinectedin may continue as a single agent. If immune toxicity re-occurs despite discontinuation of atezolizumab, the participant will also discontinue lurbinectedin.

Participants may continue with atezolizumab as a single agent in case of lurbinectedin discontinuation.

Atezolizumab

There will be no dose modifications for atezolizumab in this study.

Carboplatin and Etoposide

Dose modifications for carboplatin and etoposide are permitted for toxicity according to the prescribing information and local standard of care.

A6–2.2 CRITERIA FOR TREATMENT CONTINUATION DURING MAINTENANCE PHASE

If a participant experiences adverse events during the maintenance treatment phase, the criteria outlined in Table A6-2 must be met in order to continue study treatment.

Table A6-2 Criteria for Treatment Continuation in Arm A During the Maintenance Phase

	Lurbinectedin	Atezolizumab
	Day 1	Day 1
ANC	≥ 1.5 × 10^9/L for participants of non-African descent or ≥ 1.3 × 10^9/L for participants of African descent	No defined requirements
Platelets	≥ 100 × 10^9/L	No defined requirements
Hemoglobin [a]	≥ 9 g/dL	
Total bilirubin (or direct bilirubin)	≤ 1.5 × ULN For participants with known Gilbert disease: total bilirubin ≤ 3 × ULN	
AST/ALT	≤ 2.5 × ULN For participants with documented metastatic liver disease, AST and ALT levels ≤ 5 × ULN	
Serum creatinine	≤ 1.5 × ULN or creatinine clearance ≥ 30 mL/min	
TSH [b]	No defined requirements	Within normal range If TSH is above ULN, T4 must be within normal range
Muscular toxicity (myalgia, muscular weakness, CPK increase, rhabdomyolysis)	Grade 1 or better	
Immune-related toxicities (colitis, pneumonitis, endocrinopathies [c] and others)	No defined requirements	Grade 1 or better
Other non-hematological drug-related adverse events (except increased GGT, amylase/lipase, nausea and vomiting, alopecia, asthenia, dermatologic events, and/or neuropathy [d])	Grade 1 or better	

Table A6-2 Criteria for Treatment Continuation in Arm A During the Maintenance Phase

	Lurbinectedin	Atezolizumab
	Day 1	Day 1
Active infection (including sepsis) and/or bleeding (any grade)	Absence	

CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; ULN = upper limit of normal.

[a] Participants may receive packed red blood cells transfusion and/or erythropoietin treatment, if clinically indicated, to increase or maintain adequate hemoglobin levels.

[b] See Section A6–2.4.2 for more information on management guidelines of endocrine event.

[c] For Grade 2 endocrinopathies, please see Table A6-5 for more details.

[d] Any grade is accepted for increased GGT. Amylase and/or lipase increases of up to 2.0 × ULN are allowed. Up to Grade 2 is allowed for alopecia, neuropathy, asthenia, dermatologic events, and nausea or vomiting.

If a participant does not meet the requirements for re-treatment on Day 1 of Cycle 2 or any subsequent cycles, reassessments will be performed at least every 48–72 hours. Treatment with lurbinectedin can be withheld up to a maximum of 3 weeks. Participants not meeting re-treatment criteria after withholding lurbinectedin for a maximum of a 3-week delay should discontinue lurbinectedin treatment. In case of objective clinical benefit, the participant could continue to receive lurbinectedin treatment upon the Sponsor's agreement.

Participants may continue with atezolizumab as a single agent in case lurbinectedin is discontinued.

In case atezolizumab is discontinued due to an immune-related severe adverse event, treatment with lurbinectedin may continue as a single agent. If immune toxicity re-occurs despite discontinuation of atezolizumab, the participant will also discontinue lurbinectedin. Up to 2 dose reductions of lurbinectedin are allowed.

Chemotherapy

Dose modifications for carboplatin and etoposide are permitted for toxicity according to the prescribing information and local standard of care.

A6–2.3 TREATMENT INTERRUPTION

Dose interruptions of study treatment may occur at any time and independently from each other at the discretion of the investigator for management of adverse events.

A6–2.3.1 Lurbinectedin

Lurbinectedin treatment may be temporarily suspended in participants experiencing toxicity considered to be related to lurbinectedin.

The administration of a new cycle of lurbinectedin should be delayed if the re-treatment criteria for adequate organ function are not met on Day 1 of the next scheduled cycle. Parameters will be periodically reevaluated until appropriate recovery. A maximum delay of 21 days will be allowed for recovery from treatment-related adverse events. If recovery has not occurred after a 21-day delay, the participant should discontinue lurbinectedin, except in case of clear evidence of objective benefit per investigator's judgment. The Medical Monitor is available to advise as needed. Participants who remain on lurbinectedin treatment after a 21-day delay because of the reasons described above, will do so after appropriate dose reduction of lurbinectedin.

A6–2.3.2 Atezolizumab

Atezolizumab treatment may be temporarily suspended in participants experiencing toxicity considered to be related to atezolizumab. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. Treatment with atezolizumab may be resumed if the event improves to Grade 1 or better within 12 weeks and if corticosteroids have been reduced to ≤10 mg/day oral prednisone or equivalent within 12 weeks. If atezolizumab is withheld for > 12 weeks (or 4 cycles) of initiating steroids, the participant will be discontinued from atezolizumab.

Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) at the investigator's discretion. The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

For guidelines on treatment interruption to manage specific adverse events associated with atezolizumab and lurbinectedin, see Section A6–2.4.1 for lurbinectedin and Section A6–2.4.2 for atezolizumab.

A6–2.4 MANAGEMENT GUIDELINES

A6–2.4.1 Guidelines for Management of Adverse Events Associated with Lurbinectedin

A6–2.4.1.1 Management of Hematological Abnormalities

Regular monitoring of hematological tests, including differential WBC counts will be performed prior to each dose administration and in addition, on Day 10 of Cycle 1 and Cycle 2 (see the schedule of activities in Section 1.3, Table 2) in order to allow re-treatment of participants with lurbinectedin.

Participants with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines. The administration of a new cycle of lurbinectedin should be delayed until the participant's blood counts have reached adequate levels. Table A6-3 provides treatment guidelines for severe cases of neutropenia and thrombocytopenia deemed related to lurbinectedin.

Dose adjustment, if applicable, should always be considered in participants who experience febrile neutropenia, neutropenic infection, sepsis or Grade 4 neutropenia or thrombocytopenia in prior cycles. Supportive care for thrombocytopenia or anemia, such as transfusions, may be managed according to institutional guidelines.

Extensive early antibiotic coverage and all available supportive measures as indicated should be applied during a febrile neutropenia episode or Grade 4 neutropenia with clinical or epidemiological signs of infection after lurbinectedin treatment. Conversely, the presence of fever or signs of infection during the second week after lurbinectedin treatment start (usually from Days 8–18) must always motivate a thorough clinical examination and complete blood counts, including differential WBC counts.

No increase in opportunistic infections associated with lymphopenia or prolonged Grade 4 neutropenia (more than 2 weeks) has been described in trial participants with solid tumors, although no specific conclusions may be drawn due to the lack of randomized data. Nevertheless, no prophylactic antibiotic coverage is indicated at current available clinical guidelines/recommendations.

Table A6-3 Lurbinectedin Management Guidelines for Hematological Abnormalities

Event	Management
Grade 1, 2 or 3 neutropenia or Grade 1, 2 or 3 thrombocytopenia without bleeding	• Manage according to institutional practice. • Continue lurbinectedin when ANC is $\geq 1.5 \times 10^9$/L for participants of non-African descent or $\geq 1.3 \times 10^9$/L for participants of African descent and when platelets are $\geq 100 \times 10^9$/L.
Neutropenia Grade 4 or any grade of febrile neutropenia	• Interrupt lurbinectedin. • Restart lurbinectedin, at reduced dose, when ANC $\geq 1.5 \times 10^9$/L for non-African descent or ANC $\geq 1.3 \times 10^9$/L for African descent and resolution of any infections.
Thrombocytopenia Grade 3 with bleeding or Grade 4	• Interrupt lurbinectedin until platelet count $\geq 100 \times 10^9$/L (100,000/μL) and resolution of any bleeding. • Restart lurbinectedin at reduced dose.

A6–2.4.1.2 Management of Liver Abnormalities

If Grade 3/4 increases in liver function tests (LFTs) are found, dose reduction and/or delays until resolution to at least Grade 1 are indicated. Re-evaluation before re-treatment is mandatory.

It is recommended that participants with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications should be discontinued in participants who develop increased values of ALT, AST, or bilirubin and other causes (e.g., cancer-related, or infection) should be evaluated.

Management guidelines for hepatotoxicity related to lurbinectedin treatment are provided in Table A6-4.

Table A6-4 Lurbinectedin Management Guidelines for Liver Abnormalities

Severity of Transaminase (ALT or AST) Elevations by NCI CTCAE	Management
Grade 1 or 2	• Dose reduction is usually not required. • Consider discontinuing concomitant hepatotoxic medications and adding supportive care as indicated.
Grade ≥ 3	• Interrupt lurbinectedin and consider more frequent monitoring of ALT and/or AST. • Restart lurbinectedin at a reduced dose when AST and ALT ≤ 2.5 × ULN (or for participants with documented metastatic liver disease, AST and ALT levels ≤ 5 × ULN). • Discontinue if laboratory abnormalities cannot be reversed despite interruption of lurbinectedin.

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

A6–2.4.1.3 Management of Gastrointestinal Adverse Events

Premedication with IV serotonin (5-HT_3) antagonists (ondansetron or equivalent) plus a steroid (dexamethasone or equivalent) will be provided before the first lurbinectedin administration (Cycle 1, Day 1; see Section 6.1.3 for more details on prophylactic medications). The requirement for premedication for anti-emetic prophylaxis for the subsequent cycles (i.e., Day 1, Cycle 2 and subsequent cycles) should be evaluated on an individual basis, and its administration left to investigator judgment. In addition, extended 5-HT_3 antagonists and/or steroids can be administered orally for 3–5 days after drug infusion, if necessary. Prokinetics and additional anti-emetic treatment should be evaluated on an individual basis; however, aprepitant or any other neurokinin-1 (NK-1) antagonist or related Substance P-antagonists (except rolapitant) must NOT be administered with lurbinectedin due to the risk of lurbinectedin overexposure and the resulting severe and prolonged myelosuppression.

A6–2.4.1.4 Management of Renal Abnormalities

Lurbinectedin may cause dehydration due to nausea/vomiting, as well as other toxicities such as diarrhea, or even sepsis, which may lead to secondary renal impairment (pre-renal causes). Hence, a normal blood pressure and adequate participant hydration are required before treatment with lurbinectedin.

Regular monitoring of plasma creatinine levels before each new cycle, as well as electrolytes will be performed.

A renal function with creatinine clearance of at least 30 mL/min is required at baseline, as well as re-treatment criterion. Assessment of creatinine clearance before the administration of each new cycle will be performed.

A6–2.4.1.5 Management of Muscular Adverse Events

Level of CPK enzyme will be monitored before each new cycle as specified in the schedule of activities in Section 1.3 (Table 2). Participants are required to have ≤Grade 1 elevations at baseline or before re-treatment in order to be eligible to receive lurbinectedin infusions. Grade 3 or higher CPK levels will require lurbinectedin dose interruption followed by dose reduction once the adverse event resolves to Grade 1 or better.

Permanently discontinue lurbinectedin treatment if the participant experiences Grade 3 or 4 rhabdomyolysis.

A6–2.4.1.6 Management of Infusion Site Reactions

Careful handling of lurbinectedin is advised. Although short infusion times (one hour) make extravasation unlikely, episodes of extravasation were reported in three participants (0.5%) treated with single-agent lurbinectedin at 3.2 mg/m^2 in Phase II and III studies.

Extravasation of lurbinectedin may result in skin and soft tissue injury, including necrosis requiring debridement. Use of a central venous catheter is suggested to reduce the risk of extravasation, particularly in participants with limited venous access. Participants must be monitored for signs and symptoms of extravasation during lurbinectedin infusions. In the event of extravasation, the infusion must be discontinued immediately, the infusion catheter must be removed, and the participant must be monitored for signs and symptoms of tissue necrosis. The time to onset of necrosis after extravasation may vary.

A6–2.4.2 Guidelines for Management of Adverse Events Associated with Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology, when clinically indicated.

Although toxicities observed with atezolizumab have been mild and self-limiting, they should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

Management guidelines for patients who experience adverse events associated with atezolizumab are provided in Table A6-5.

Table A6-5 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab

GENERAL GUIDANCE

Early Recognition and Close Monitoring:

Timely and up-to-date information about the risks associated with atezolizumab should be shared with patients and family caregivers prior to initiating atezolizumab and throughout treatment and survival follow-up. Patients and caregivers should be instructed to have a high level of suspicion that new symptoms are treatment-related. *Patients should be assessed for signs and symptoms of organ dysfunctions throughout the study, including monitoring of results of thyroid function, liver function, and other laboratory tests as appropriate (e.g., blood glucose, creatinine, amylase, lipase, urine protein).* Patients presenting with adverse events of any severity grade should be monitored closely and referred promptly to specialists for evaluation. Treatment and supportive care measures should be initiated as per institutional guidelines.

Monitoring of high-risk cardiac patients:

In high-risk cardiac patients (including those with abnormal baseline cardiac troponin levels, when available), TTE monitoring should be *performed on a regular basis*, if clinically indicated and considered appropriate per institutional practice.

Monitoring for Myocarditis, Myositis, and Myasthenia Gravis:

Myocarditis symptoms are nonspecific and may occur as early as days or weeks after the first or second dose of atezolizumab. Although myocarditis events are rare, myocarditis is often severe and associated with myositis or myasthenia gravis. All patients with possible myocarditis should be urgently evaluated by performing a cardiac enzyme assessment, an ECG, a chest X-ray, a TTE for evaluation of left ventricular ejection fraction and global longitudinal strain, and a cardiac MRI as appropriate per institutional practice. A cardiologist should be consulted. An endomyocardial biopsy may be *performed* to enable a definitive diagnosis and appropriate treatment, if clinically indicated. *For suspicion of myositis, myocarditis, and/or myasthenia gravis, there is a possibility of overlapping symptoms, and patients should therefore be evaluated with a shared set of diagnostics, including erythrocyte sedimentation rate, C-reactive protein, creatine kinase, antibody tests (acetylcholine, muscle-specific kinase, striational), aldolase, troponin, ECG, nerve conduction, and electromyography). Such patients should undergo frequent pulmonary evaluations.*

Use of Corticosteroids and Immunosuppressants for Managing Adverse Events:

In the guidance for specific events below, treatment with high-dose corticosteroids refers to 1–2 mg/kg/day oral prednisone (or equivalent) or IV methylprednisolone (or equivalent), and an additional immunosuppressive agent can be added if symptoms do not improve within 48 hours after initiating high-dose corticosteroids. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day of oral prednisone before atezolizumab can be resumed.

Action to be Taken with Atezolizumab:
Treatment with atezolizumab may be withheld or permanently discontinued because of toxicities, as specified below. If atezolizumab is withheld, treatment can be resumed if the event resolves to Grade 1 or better, or when symptoms improve as specified below. As a general rule, atezolizumab can be withheld for up to 12 weeks after event onset. *Treatment with atezolizumab may be resumed if the event improves to Grade ≤1 within 12 weeks and if corticosteroids have been reduced to ≤10 mg/day oral prednisone or equivalent within 12 weeks. If atezolizumab is withheld for >12 weeks (or 4 cycles) of initiating steroids, the participant will be discontinued from atezolizumab.*
If an event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from an immune-mediated event, except when resumption of atezolizumab is expressly prohibited as described below. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and should be documented by the investigator. The Medical Monitor is available to advise as needed.

Event	Symptoms or CTCAE Severity Grade	Action to be Taken with Atezolizumab	Adverse Event Management [To Be Implemented in Combination with Above General Guidance]
Pulmonary event	Grade 1	• Continue with one exception: For pneumonitis, consider withholding and resuming on radiographic evidence of improvement.	• Re-evaluate on serial imaging. • *Closely monitor patients, including asymptomatic patients.*
	Grade 2	• Withhold.	• Consider bronchoscopy or BAL with or without transbronchial biopsy. • Initiate treatment with high-dose oral corticosteroids.
	Recurrent Grade 2 **or** Grade 2 event not improving after 48–72 hours of corticosteroids **or** Grade 3 or 4	• Permanently discontinue. • In case of pneumonitis, atezolizumab should not be resumed under any circumstances.	• Bronchoscopy or BAL with or without transbronchial biopsy is recommended. • Initiate treatment with oral or IV broad-spectrum antibiotics and high-dose IV corticosteroids. • If event does not improve, consider adding an immunosuppressive agent.

Hepatic event	Guidelines for patients **<u>without</u>** hepatocellular carcinoma		
	Grade 1	• Continue.	• Closely monitor patient.
	Grade 2	**Events of > 5 days' duration:** • Withhold.	**All events:** • Monitor liver function tests more frequently until return to baseline values. **Events of > 5 days' duration:** • Initiate treatment with high-dose oral corticosteroids.
	Grade 3 or 4	• Permanently discontinue.	• Consider liver biopsy to establish etiology of hepatic injury. • Initiate treatment with high-dose oral corticosteroids. • If event does not improve, consider adding an immunosuppressive agent.
	Guidelines for patients **<u>with</u>** hepatocellular carcinoma		
	AST/ALT is within normal limits at baseline and increases to > 3 × ULN to ≤ 10 × ULN **<u>or</u>** AST/ALT is > ULN to ≤ 3 × ULN at baseline and increases to > 5 × ULN to ≤ 10 × ULN **<u>or</u>** AST/ALT is > 3 × ULN to ≤ 5 × ULN at baseline and increases to > 8 × ULN to ≤ 10 × ULN	• Withhold.	• Monitor liver function tests more frequently until return to baseline values. • For events of > 5 days' duration, consider initiating treatment with high-dose oral corticosteroids.

	AST or ALT increases to $> 10 \times$ ULN or total bilirubin increases to $> 3 \times$ ULN	• Permanently discontinue.	• Consider liver biopsy to establish etiology of hepatic injury. • Initiate treatment with high-dose oral corticosteroids. • If event does not improve, consider adding an immunosuppressive agent.
Diarrhea or colitis	Grade 1	• Continue.	• Closely monitor patient. • For events of $>$ 7 days' duration, endoscopy is recommended.
	Grade 2	• Withhold.	• Endoscopy is recommended. • If strong clinical suspicion for immune-mediated colitis, initiate empiric IV *corticosteroids* while waiting for definitive diagnosis. • For recurrent events or events that persist $>$ 5 days, initiate treatment with high-dose oral corticosteroids. • If event does not improve, consider adding an immunosuppressive agent.
	Grade 3	• Withhold.	• Order confirmatory biopsy. • Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement. • If event does not improve *or patient is unable to transition to oral corticosteroids*, consider adding an immunosuppressive agent.
	Grade 4	• Permanently discontinue.	

Hypothyroidism	Grade 1	• Continue.	• Closely monitor patient.
	Grade 2	• Consider withholding. • If withheld, resume when symptoms are controlled and thyroid function is improving.	• Initiate treatment with thyroid replacement hormone.
	Grade 3 or 4	• Withhold. • Resume when symptoms are controlled and thyroid function is improving. • Permanently discontinue and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism.	• Initiate treatment with thyroid replacement hormone. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status).
Hyperthyroidism	Grade 1, TSH ≥ 0.1 mU/L and < 0.5 mU/L	• Continue.	• *Monitor TSH every 4 weeks.*
	Grade 1, TSH < 0.1 mU/L **or** Grade 2	• Consider withholding. • Resume when symptoms are controlled and thyroid function is improving.	• Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed.
	Grade 3 or 4	• Withhold. • Resume when symptoms are controlled and thyroid function is improving. • Permanently discontinue for life-threatening immune-mediated hyperthyroidism.	

Symptomatic adrenal insufficiency	Grade 2, 3, or 4	• Withhold. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume. • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding, permanently discontinue.	• Perform appropriate imaging. • Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper. • *Monitor for signs of adrenal crisis, such as hemodynamic instability.*
Hyperglycemia	Grade 1 or 2 without Type I diabetes	• Continue.	• Closely monitor patient.
	Grade 3 or 4 **or** Type 1 diabetes	• Withhold. • Resume when symptoms resolve and glucose levels are stable.	• Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis.
Hypophysitis (pan-hypopituitarism)	Grade 1	• Continue.	• Closely monitor patient.
	Grade 2 or 3	• Withhold.	• Perform brain MRI (pituitary protocol). • Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper. • Initiate other hormone replacement if clinically indicated, *only after corticosteroid replacement to avoid adrenal crisis*.
	Recurrent hypophysitis Grade 2 or 3 **or** Grade 4	• Permanently discontinue.	

Ocular event	Grade 1	• Continue.	• Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.
	Persistent Grade 1 despite treatment **or** Grade 2	• Withhold.	
	Grade 3 or 4	• Permanently discontinue.	• Initiate treatment with high-dose oral corticosteroids.
Myocarditis or pericardial disorders	*Grade 1*	• *Withhold*	• *Conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.*
	Grade 2, 3, or 4	• Permanently discontinue. • Atezolizumab should not be resumed under any circumstances.	• Consider anti-arrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. • Initiate treatment with higher-dose IV corticosteroids equivalent to 1 g/day IV methylprednisolone for 3–5 days and convert to high-dose oral corticosteroids upon improvement. • If event does not improve within *24* hours after initiating corticosteroids, consider adding an immunosuppressive agent.
Amylase and/or lipase elevation	Grade 1	• Continue.	• Closely monitor patient.
	Grade 2, amylase and/or lipase > 1.5–2.0 × ULN	• Continue.	• For prolonged elevation (e.g., > 3 weeks), consider treatment with oral corticosteroids equivalent to 10 mg/day prednisone.
	Grade 2, asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN **or** Grade 3 or 4	• Withhold. • For recurrent events, permanently discontinue.	• Consider treatment with high-dose oral corticosteroids.

Pancreatitis	Grade 1	• Continue.	• Closely monitor patient.
	Grade 2 or 3	• Withhold. • For recurrent events, permanently discontinue.	• Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement.
	Grade 4	• Permanently discontinue.	• Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement. • If event does not improve, consider adding an immunosuppressive agent.
Dermatologic event	Grade 1	• Continue.	• Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
	Grade 2	• Continue.	• Consider biopsy, if indicated. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if the event does not improve. • If unresponsive to topical corticosteroids, consider oral *corticosteroids equivalent to* 0.5 mg/kg/day prednisone.
	Grade 3	• Withhold.	• Order a biopsy, if indicated. • Initiate treatment with oral corticosteroids equivalent to 10 mg/day prednisone, increasing to high-dose oral corticosteroids if event does not improve within 48–72 hours.
	Grade 4	• Permanently discontinue.	
Stevens-Johnson syndrome or toxic epidermal necrolysis	Suspected event, any grade	• Withhold.	• Order a biopsy, if indicated. • Follow the applicable treatment/management guidelines for dermatologic events above.
	Confirmed event, any grade	• Permanently discontinue. • Atezolizumab should not be resumed under any circumstances.	

Myasthenia gravis and Guillain-Barré syndrome	Any grade	• Permanently discontinue. • Atezolizumab should not be resumed after permanent discontinuation.	• Consider initiation of high-dose oral or IV corticosteroids. • Consider IVIG or plasmapheresis in patients with rapid progression with development of bulbar and/or respiratory symptoms. • In life-threatening cases, consider higher-dose IV methylprednisolone 1 g/day for 3–5 days and other immunosuppressive agents.
Facial paresis	Grade 1 or 2	• Withhold. • If event resolves fully, resume. • If event does not resolve fully while withholding, permanently discontinue.	• Investigate etiology. • Closely monitor patient **or** initiate high-dose oral corticosteroids (if progressing from mild). • Initiate non-opioid treatment (e.g., gabapentin, pregabalin, duloxetine) for pain.
	Grade 3 or 4	• Permanently discontinue.	• Follow guidelines for management of myasthenia gravis and Guillain-Barré syndrome.
Other cranial nerve disorder (excluding facial paresis)	*Grade 1 or 2*	• *Withhold.*	• *Investigate etiology.*
	Grade 3 or 4	• *Permanently discontinue.*	• *Follow guidelines for management of myasthenia gravis and Guillain-Barré syndrome.*
Other neuropathy (excluding myasthenia gravis, Guillain-Barré syndrome, facial paresis, and other cranial nerve disorders)	Grade 1	• Continue.	• Closely monitor patient.
	Grade 2	• Withhold.	• Investigate etiology.
	Grade 3 or 4	• Permanently discontinue.	• Follow guidelines for management of myasthenia gravis and Guillain-Barré syndrome.

Myelitis	Grade 1	• Continue unless symptoms worsen or do not improve.	• Investigate etiology.
	Grade 2	• Permanently discontinue. • *Atezolizumab should not be resumed under any circumstances.*	• Investigate etiology and rule out infection. • Initiate treatment with high-dose oral corticosteroids.
	Grade 3 or 4	• Permanently discontinue. • Atezolizumab should not be resumed under any circumstances.	• Initiate non-opioid treatment (e.g., gabapentin, pregabalin, duloxetine) for pain. • Hospitalize patient. • Initiate treatment with IV corticosteroids equivalent to 1 g/day methylprednisolone. • If event does not improve or there is worsening of symptoms within *48 hours*, consider IVIG or plasmapheresis and manage as per institutional practice.
Meningoencephalitis	Any grade	• Permanently discontinue. • Atezolizumab should not be resumed under any circumstances.	• Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement. • If event does not improve, consider adding an immunosuppressive agent.
Renal event	Grade 1	• Continue.	• Closely monitor patient.
	Grade 2	• Withhold.	• Initiate treatment with high-dose oral corticosteroids.
	Grade 3 or 4	• Permanently discontinue.	• Consider renal biopsy. • Initiate treatment with high-dose oral corticosteroids. • If event does not improve, consider adding an immunosuppressive agent.

Myositis	Grade 1	• Continue.	• Closely monitor patient.
	Grade 2	• Withhold.	• Consider treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement. • If the event does not improve, consider adding an immunosuppressive agent.
	Grade 3	• Withhold. • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and atezolizumab should not be resumed under any circumstances.*	• Initiate treatment with high-dose IV corticosteroids, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to oral corticosteroids upon improvement. • If event does not improve within 24–48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • Consider IVIG or plasmapheresis.
	Recurrent Grade 3 **or** Grade 4	• Permanently discontinue. • Atezolizumab should not be resumed under any circumstances.	
Suspected HLH [a]	Any grade	• Permanently discontinue. • Atezolizumab should not be resumed under any circumstances.	• Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If the event does not respond to treatment within 24 hours, contact the Medical Monitor and initiate treatment as appropriate according to published guidelines. [b]

IRR and CRS	Grade 1 [c]: Fever [d] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose.	• In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS.
	Grade 2 [c]: Fever [d] with hypotension not requiring vasopressors **and/or** hypoxia requiring low-flow oxygen [e] by nasal cannula or blow-by	• *If event occurs during infusion, immediately discontinue. Do not restart infusion.* • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. • *Permanently discontinue atezolizumab for patients with Grade ≥3 wheezing, bronchospasm, or urticaria.* • *If event occurs during or within 24 hours after infusion, administer next*	• For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy *if the patient is not responding as expected after initiating corticosteroids.* • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the

		dose at ≤50% of initial infusion rate.	ICU is recommended), permanently discontinue atezolizumab, and contact the Medical Monitor. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Medical Monitor.
	Grade 3 [c]: Fever [d] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** hypoxia requiring high-flow oxygen [e] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue [f].	• For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Administer an anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.

	Grade 4 [c] Fever [d] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue [f].	• Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Administer an anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [g] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.
Atezolizumab-related event not described above	Grade 1	• Continue.	• Closely monitor patient.
	Grade 2	• Consider withholding and resuming when event resolves to Grade 1 or better.	• Refer to current standard guidelines for management of immune checkpoint inhibitor-related toxicities, such as those provided by a professional society (e.g., NCCN, ESMO, SITC, ASCO).
	Grade 3	• Withold.	
	Grade 4	• Permanently discontinue.	

ASCO = American Society of Clinical Oncology; ASTCT = American Society for Transplantation and Cellular Therapy; BAL = bronchoscopic alveolar lavage; BiPAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; ECMO = extracorporeal membrane oxygenation; eCRF = electronic Case Report Form; ESMO = European Society for Medical Oncology; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; IVIG = intravenous immunoglobulin; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network;

NCI = National Cancer Institute; SITC = Society for Immunotherapy of Cancer; TTE = transthoracic echocardiogram; VAD = ventricular assist device; ULN = upper limit of normal.

[a] Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014).

[b] Refer to La Rosée (2015); Schram and Berliner (2015); La Rosée et al. (2019).

[c] Grading system for these management guidelines is based on ASTCT Consensus Grading Scale for CRS. NCI CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[d] Fever is defined as temperature $\geq 38°C$ not attributable to any other cause. In patients who develop CRS and then receive antipyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[e] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at >6 L/min.

[f] For subsequent infusions, administer oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit-risk ratio.

[g] Refer to Riegler et al. (2019).

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Appendix 7
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), SC, IV, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

1. Stop the study treatment administration, if possible.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by participant status and as directed by the physician in charge.
6. Continue to observe the participant and document observations.

Appendix 8
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

Note: This study requires a tumor assessment at induction screening with the assignment of target and non-target lesions per RECIST v1.1. This is required so that investigators can assess tumor response at the time of maintenance screening given that only participants with partial response (PR), complete response (CR), or stable disease (SD) are eligible for the maintenance phase of the study. However, in order to assess the treatment effect of the experimental treatment in this study, lurbinectedin, all subsequent tumor assessments performed during the maintenance phase (and follow-up phase if applicable) must be compared against the scans done at maintenance screening (or nadir achieved at or after maintenance screening) and NOT against the scan performed at induction screening.

The potential need for palliative radiotherapy should be considered, if possible, during the selection of target lesions as an irradiated target lesion renders the patient non-evaluable for RECIST v1.1 tumor response with the exception of the assessment of disease progression.

For participants who achieve a CR in target lesions following the completion of induction therapy, but with residual disease in other lesions, new target and non-target lesions must be assigned at maintenance screening. For other participants, the investigator should carefully assess the maintenance screening scans and consider whether a reassignment of target and non-target lesions is warranted. For participants with an overall response of CR after the completion of induction therapy (i.e., participants with no radiographic evidence of disease at maintenance baseline), the guidance in Table A8-1 should be followed for the assessment of overall response at a single timepoint post-maintenance baseline. In those participants, the recurrence of disease (to be reported as new lesion[s]) or the appearance of a new lesion results in an overall response assessment of progressive disease (PD).

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

Table A8-1 Participants with No Radiographic Evidence of Disease at Maintenance Baseline: Criteria for Overall Response at a Single Timepoint

Target Lesions	Non-Target Lesions	New Lesion	Overall Timepoint Response
NA	NA	No	NED
NA	NA	Yes	PD

NA = not applicable; NED = no evidence of disease; PD = progressive disease.

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, with use of calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed with use of calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

Computed tomography is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Magnetic resonance imaging is also acceptable.

If prior to enrollment it is known that a participant is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the participant at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For participants who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the participant should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of

non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which participants have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm

but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF; e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non-lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely completely disappeared, the measurement should be recorded as 0 mm
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- CR: Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- SD: Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

NO RADIOGRAPHIC EVIDENCE OF DISEASE AT MAINTENANCE BASELINE

Participants with no radiographic evidence of disease at maintenance baseline will be assigned the response below at subsequent overall response timepoint(s):

- NED: Absence of new lesions or recurrence
- PD: Recurrence of disease or the appearance of a new lesion

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Participants with Measurable and Non-Measurable Disease

For participants with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will; therefore, be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the participant's baseline lesions show PR

or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table A8-2 provides a summary of the overall response status calculation at each response assessment timepoint for participants who have measurable disease at baseline.

Table A8-2 Criteria for Overall Response at a Single Timepoint: Participants with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

In order to meet eligibility for enrollment in the induction phase, participants are required to present with measurable disease as defined per RECIST v1.1 at induction screening. Due to response to induction treatment, participants may no longer present with measurable disease at the time of maintenance screening. They may have an overall response of "complete response," that is, no evidence of disease (refer to Table A8-1, which provides a summary of the overall timepoint response assessment for participants with no evidence of disease at maintenance screening) or they may present with

non-measurable disease only at the time of maintenance screening. Table A8-3 provides a summary of the overall response status calculation at each response assessment timepoint during the maintenance phase for participants who have only non-measurable disease at maintenance screening.

Table A8-3 Timepoint Response: Participants with Non-Target Disease Only at Maintenance Screening

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

MISSING ASSESSMENTS AND NOT EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the participant is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a participant had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the participant will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Participants with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to continue radiographic tumor response assessments even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such participants is to be determined by evaluation of target and non-target lesions as shown in Table A8-2.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

POTENTIAL LYMPHADENOPATHY AFTER COVID-19 VACCINATION

Vaccination is an established but uncommon cause of ipsilateral transient lymphadenopathy. Lymphadenopathy has been described as an uncommon adverse reaction with COVID-19 vaccines with a reported incidence of 0.3% for Pfizer/BioNTech, which generally resolved within 10 days, and as 'uncommon' (i.e., less than 1%) for AstraZeneca as per respective product information (Polack et al. 2020; Pfizer–BioNTech 2021; AstraZeneca 2021). Axillary swelling or tenderness has been reported with an overall incidence of 8.5% with the COVID-19 vaccine from Moderna (Baden et al. 2021; Moderna 2021), with an incidence of 16% in the younger age group (18–64 years; Centers for Disease Control 2020).

Lymphadenopathy, particularly in the ipsilateral axilla, in people who have received a COVID-19 vaccination may appear similar to malignant nodal involvement and; hence, could impact image interpretation. This is of particular importance for clinical studies with tumor response as primary or secondary endpoint and with progressive disease triggering study treatment discontinuation. We would therefore like to draw your attention to the potential lymphadenopathy as a consequence of a COVID-19 vaccination and recommend the following:

- Participants on clinical trials should receive their COVID-19 vaccine based on an individual benefit–risk assessment and local availability. The schedule of tumor response assessments should not be a consideration when scheduling the vaccination.
- The per protocol schedule for tumor response assessments must continue to be followed, regardless of when the COVID-19 vaccine was administered. When interpreting tumor response on imaging, take the timing of the vaccination and the side of the vaccination into consideration. Consider performing follow-up assessments as per your clinical judgment and published guidance to discern lymphadenopathy resulting from malignancy from swollen lymph nodes related to the vaccine (Edmonds et al. 2021; Lehman et al. 2021; McIntosh et al. 2021; Tu et al. 2021).
- Please note that vaccines are considered concomitant medication and must be reported on the Concomitant Medication eCRF according to the protocol instructions for concomitant medications.

Should you have any questions or require additional information, please do not hesitate to contact your study Monitor.

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Appendix 9
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active; able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours
3	Capable of only limited self-care; confined to a bed or chair >50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix 10
EuroQol EQ-5D-5L

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

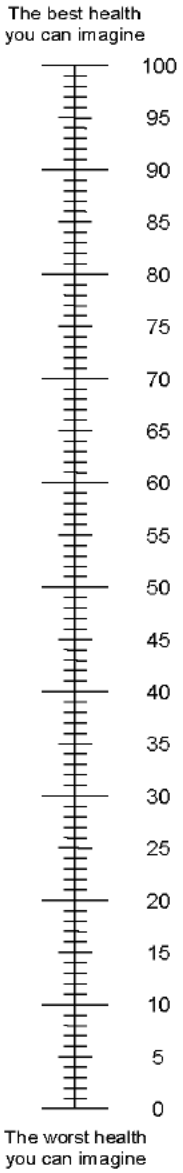
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 11
European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire (EORTC QLQ–C30)

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ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _ _ _ _

Your birthdate (Day, Month, Year): _ _ _ _ _ _

Today's date (Day, Month, Year): 31 _ _ _ _ _ _

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 12
European Organisation for Research and Treatment of Cancer Quality of Life–Lung Cancer Module (EORTC QLQ–LC13)

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ENGLISH

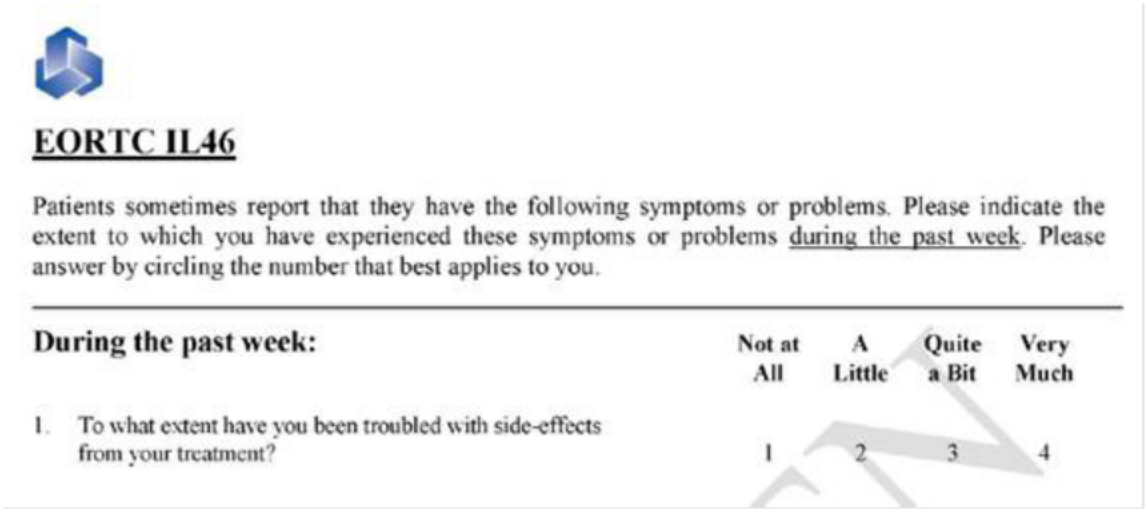
EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Appendix 13
European Organisation for Research and Treatment of Cancer — Item List 46

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.



EORTC IL46

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
1. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4

Appendix 14
Patient-Reported Outcome Common Terminology Criteria for Adverse Events

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NCI PRO-CTCAE ™ ITEMS

Item Library Version 1.0

English

Form Created on 19 March 2021

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1a. In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
1b. In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

2a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
2b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

3a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost con-stantly
3b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

4a. In the last 7 days, how OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
4b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

5a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

6a. In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
6b. In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
6c. In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

7a. In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
7b. In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

8a. In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
8b. In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

9a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
9b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

10a. In the last 7 days, did you BRUISE EASILY (BLACK AND BLUE MARKS)?	
O Yes	O No

11a. In the last 7 days, how OFTEN did you have SHIVERING OR SHAKING CHILLS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
11b. In the last 7 days, what was the SEVERITY of your SHIVERING OR SHAKING CHILLS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

12a. In the last 7 days, how OFTEN did you have NOSEBLEEDS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
12b. In the last 7 days, what was the SEVERITY of your NOSEBLEEDS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

Appendix 15
Preexisting Autoimmune Diseases and Immune Deficiencies

Participants should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. **Participants with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study**. Possible exceptions to this exclusion could be participants with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Participants with a history of autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for participants who have previously experienced a severe or life–threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Anti-phospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune myelitis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Granulomatosis with polyangiitis • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cholangitis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease

Appendix 16
Cytochrome P450 3A Inhibitors and Inducers

Table A16-1 Examples of Clinical Inhibitors for CYP450-Mediated Metabolism (for Concomitant Use Clinical DDI Studies and/or Drug Labeling; 6 March 2020)

	Strongest Inhibitors (≥10-Fold Increase)	Strong Inhibitors (<10–≥5-Fold Increase)	Moderate Inhibitors (≤2–<5-Fold Increase)	Weak Inhibitors (≥1.25–<2-Fold Increase)
Inhibitors				
CYP3A4	boceprevir, cobicistat[1], danoprevir and ritonavir[2], elvitegravir and ritonavir[2], grapefruit juice[3], indinavir and ritonavir[2], itraconazole[1], ketoconazole, lopinavir and ritonavir[1,2], paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[2], posaconazole, ritonavir[1,2], saquinavir and ritonavir[1,2], telaprevir[1], tipranavir and ritonavir([1,2], telithromycin, troleandomycin, voriconazole	Clarithromycin[2], idelalisib, nefazodone, nelfinavir[1]	aprepitant, ciprofloxacin, conivaptan[4], crizotinib, cyclosporine, diltiazem[5], dronedarone[1], erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil[1], Seville orange	chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor[1], lomitapide, ranitidine, ranolazine[1], ticagrelor[1]
Inducers				
CYP3A	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort[6]		bosentan, efavirenz, etravirine, phenobarbital, primidone	armodafinil, modafinil[7], rufinamide

Source: FDA Drug Development and Drug Interactions: Table of Substrates Inhibitors and Inducers 2020.

AUC = area under the concentration–time curve; DDI = drug-drug interaction; FDA = U.S. Food and Drug Administration; HCV = hepatitis C virus; P-gp = P-glycoprotein.

This table is prepared to provide examples of clinical inhibitors and inducers and is not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61].

[1] Inhibitor of P-gp (defined as those increasing AUC of digoxin to ≥ 1.25-fold).

[2] Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.

[3] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low-dose, single strength).

[4] The classification is based on studies conducted with intravenously administered conivaptan.

[5] Diltiazem increased AUC of certain sensitive CYP3A substrates (e.g., buspirone) more than 5-fold.

[6] The effect of St. John's wort varies widely and is preparation-dependent.

[7] Based on effect of 200 mg/day modafinil. A higher-dose (400 mg/day) modafinil had larger induction effect on CYP3A.

Appendix 17
Veterans Administration Lung Study Group Staging System for Small-cell Lung Cancer

Stage	Characteristics
Limited SCLC	• Disease confined to one hemithorax, although local extensions may be present • No extrathoracic metastases except for possible ipsilateral, supraclavicular nodes if they can be included in the same portal as the primary tumor; and • Primary tumor and regional nodes that can be adequately treated and totally encompassed in every portal
Extensive SCLC	• Inoperable patients who cannot be classified as having limited disease

SCLC = small-cell lung cancer.

Note: Adapted from Micke et al. (2002).

REFERENCES

Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: veterans administration lung study group versus international association for the study of lung cancer—what limits limited disease? Lung Cancer 2002;37:271–6.

Appendix 18
Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table A18-1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product) [a]	Authorized	No [b]
Lurbinectedin (PM01183/JZP712)	IMP (test product)	Unauthorized	Not applicable
Carboplatin	AxMP (background treatment)	Authorized	Yes
Etoposide	AxMP (background treatment)	Authorized	Yes
Ondansetron (or equivalent)	AxMP (rescue medication)	Authorized	Yes
Metoclopramide (or equivalent)	AxMP (rescue medication)	Authorized	Yes
Dexamethasone (or equivalent)	AxMP (rescue medication)	Authorized	Yes
Pegylated G-CSF	AxMP (rescue medication)	Not applicable [c]	Not applicable [c]
Prednisone	AxMP (rescue medication)	Authorized	Yes
Methylprednisolone	AxMP (rescue medication)	Authorized	Yes
Thyroid replacement hormone	AxMP (rescue medicine)	Authorized	Yes
Methimazole/ Carbimazole	AxMP (rescue medicine)	Authorized	Yes

AxMP = auxiliary medicinal product; EEA = European Economic Area; ES-SCLC = extensive-stage small-cell lung cancer; G-CSF = granulocyte colony-stimulating factor; IMP = investigational medicinal product.

[a] Atezolizumab is considered to be an IMP test product as well as an IMP comparator.

[b] Atezolizumab, in combination with carboplatin and etoposide, is approved for the first-line treatment of adult patients with ES-SCLC, but not in combination with lurbinectedin.

[c] G-CSF is a class of medicine and not an individual product. Therefore, this field is not applicable. The Sponsor expects that appropriate G-CSF is given as standard treatment per local practice.

Table A18-2 Investigational and Non-Investigational Medicinal Product Designations for the United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in UK	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product) [a]	Authorized	No [b]
Lurbinectedin (PM01183/JZP712)	IMP (test product)	Unauthorized	Not applicable
Carboplatin	NIMP (background treatment)	Authorized	Yes
Etoposide	NIMP (background treatment)	Authorized	Yes
Ondansetron (or equivalent)	NIMP (rescue medication)	Authorized	Yes
Metoclopramide (or equivalent)	NIMP (rescue medication)	Authorized	Yes
Dexamethasone (or equivalent)	NIMP (rescue medication)	Authorized	Yes
Pegylated G-CSF	NIMP (rescue medication)	Not applicable [c]	Not applicable [c]
Prednisone	NIMP (rescue medication)	Authorized	Yes
Methylprednisolone	NIMP (rescue medication)	Authorized	Yes
Thyroid replacement hormone	NIMP (rescue medicine)	Authorized	Yes
Methimazole/ Carbimazole	NIMP (rescue medicine)	Authorized	Yes

ES-SCLC = extensive-stage small-cell lung cancer; G-CSF = granulocyte colony-stimulating factor; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; UK = United Kingdom.

[a] Atezolizumab is considered to be an IMP test product as well as an IMP comparator.

[b] Atezolizumab, in combination with carboplatin and etoposide, is approved for the first-line treatment of adult patients with ES-SCLC, but not in combination with lurbinectedin.

[c] G-CSF is a class of medicine and not an individual product. Therefore, this field is not applicable. The Sponsor expects that appropriate G-CSF is given as standard treatment per local practice.

Appendix 19
Protocol Amendment History

A rationale for the current amendment precedes the Table of Contents.

PROTOCOL AMENDMENT, VERSION 7: 27 NOVEMBER 2023

Protocol GO43104 has been amended to align the risks and management guidelines with Atezolizumab Investigator's Brochure Version 20. In addition, the alpha spending function for the primary endpoint of overall survival was changed from O'Brien-Fleming to Hwang-Shih-DeCani with the gamma parameter of −1.5. Further, the protocol has been updated to express the primary study objectives and the analyses sets using the estimand framework in accordance with the ICH E9(R1) statistical principles for clinical trials (ICH 2020).

Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- [redacted]
- [redacted]
- [redacted]
- The list of approved indications for atezolizumab has been updated to include alveolar soft part sarcoma (Section 2.2.4).
- The primary objectives are expressed using the estimand framework. Applicable changes have been made to Table 4 in Section 3 and duplicative language has been removed from Section 9.4.2.1. In addition, the description of the analysis sets has been amended in accordance with the estimand framework (Section 9.3).
- The definition of the analysis populations was removed from Table 5 for consistency as the analysis sets per estimand framework are defined in Section 9.
- The EQ-5D-5L analysis was removed as an endpoint because only summaries of responses are needed. Additional minor changes to the PRO endpoints were made in Section 9.4.5.5 to improve clarity.
- Based on the observed participant recruitment, the length of the study has been updated in Section 4.4 from approximately 52 months to approximately 60 months [redacted]

- [redacted], the contraception period for women has been extended to 7 months after the last dose of lurbinectedin (Section 5.1.1, Section 5.2.1, Section 5.2.2 and Appendix 4 A4-1).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 8.3.4).
- [redacted] the statistical testing boundary has been changed from O'Brien-Fleming to Hwang-Shih-DeCani with the gamma parameter of −1.5 (Section 9).
- [redacted]
- [redacted]
- Previous sections under statistical considerations on sensitivity analyses, supplementary analyses and subgroup analyses have been removed from the study protocol because details of these exploratory analyses will be outlined in the Statistical Analysis Plan.
- A footnote has been added to Table A6-2 to align the treatment continuation guidance for atezolizumab for endocrinopathies with that in Table A6-8 (Section A6-2.2).
- Lurbinectedin management guidelines for hematological abnormalities have been updated to allow management according to institutional practice of Grade 3 thrombocytopenia without bleeding (Table A6-2.4.1.1, Appendix 6).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure Version 20 (Section A6-2.4.2).

[redacted]

[redacted]

Appendix 19: Protocol Amendment History

[redacted]

- [redacted]

[redacted]

- [redacted]

Appendix 19: Protocol Amendment History

- [redacted]

Appendix 19: Protocol Amendment History

[redacted]

- [redacted]

Appendix 19: Protocol Amendment History

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

Appendix 19: Protocol Amendment History

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Appendix 20
Abbreviations

Abbreviation or Term	Definition
1L	first-line
5-HT_3	serotonin
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
AGP	α-1-acid glycoprotein
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the concentration–time curve
AxMP	auxiliary medicinal product
BSA	body surface area
COPD	chronic obstructive pulmonary disease
CR	complete response
CRF	Case Report Form
CRS	cytokine release syndrome
CSR	Clinical Study Report
CT	computed tomography
CTFI	chemotherapy-free interval
CTR	Clinical Trial Regulation
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECIS	European Cancer Information System
ECOG	Eastern Cooperative Oncology Group
ECHO	echocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EEA	European Economic Area
EORTC	European Organisation for Research and Treatment of Cancer
ES-SCLC	extensive-stage small-cell lung cancer
FA	final analysis
FAS	full analysis set
Fc	fragment crystallizable
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FPI	first participant in the maintenance phase
G-CSF	granulocyte colony-stimulating factor

Appendix 20: Abbreviations

Abbreviation or Term	Definition
GHS	global health status
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQoL	health related quality of life
[redacted]	
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IL	interleukin
IL46	Item List 46
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRC	Independent Review Committee
IRF	Independent Review Facility
IRR	infusion-related reaction
ITT	intent-to-treat
IxRS	interactive voice or Web-based response system
LDH	lactate dehydrogenase
LPLV	last participant last visit
MAS	macrophage activation syndrome
MN	mobile nurse
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NIMP	non-investigational medicinal product
NK-1	neurokinin-1 receptor
NSCLC	non–small-cell lung cancer
ORR	objective response rate

Appendix 20: Abbreviations

Abbreviation or Term	Definition
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCI	prophylactic cranial irradiation
PD	progressive disease
PD-L1	programmed death-ligand 1
PET	positron emission tomography
P-gp	P-glycoprotein
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PRO-CTCAE	*Patient*-Reported Outcomes Common Terminology Criteria for Adverse Events
PS	performance status
Q3W	every 3 weeks
QLQ-C30	Quality of Life Questionnaire–Core 30
QLQ-LC13	Quality of Life Questionnaire–Lung Cancer Module
QoL	quality of life
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCLC	small-cell lung cancer
SD	stable disease
SITC	Society for Immunotherapy of Cancer
TAM	tumor-associated macrophage
TTCD	time to confirmed deterioration
TTE	transthoracic echocardiogram
ULN	upper limit of normal
USPI	United States Prescribing Information
VALG	Veterans Administration Lung Study Group
[redacted]	[redacted]
WGS	whole-genome sequencing

Signature Page for Protocol - GO43104 - TECENTRIQ - v8 - Global/Core - Published
System identifier: RIM-CLIN-989061

Approval Task	[redacted] Company Signatory 05-Mar-2025 15:16:48 GMT+0000