Official Title: A Phase I/III, Randomized, Double-Blind, Placebo-Controlled Study of Carboplatin Plus Etoposide With or Without Atezolizumab (Anti-PD-L1 Antibody) in Patients With Untreated Extensive-Stage Small Cell Lung Cancer

NCT Number: NCT02763579

Document Dates: Protocol Amendment Version 7 : 06 March 2019

SAP Amendment Version 3: 14 May 2018

PROTOCOL

TITLE:	**A PHASE I/III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF CARBOPLATIN PLUS ETOPOSIDE WITH OR WITHOUT ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) IN PATIENTS WITH UNTREATED EXTENSIVE-STAGE SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO30081/NCT02763579
VERSION NUMBER:	7
EUDRACT NUMBER:	2015-004861-97
IND NUMBER:	117296
TEST PRODUCT:	Atezolizumab (MPDL3280A, RO5541267)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	8 December 2015
DATE(S) AMENDED:	Version 2 (VHP Only): 8 June 2016 Version 3: 25 August 2016 Version 4: 29 August 2017 Version 5 (Spain): 27 February 2018 Version 5 (China): 28 October 2018 Version 6 (Spain): 28 October 2018 Version 7: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	06-Mar-2019 17:25:16

PROTOCOL AMENDMENT, VERSION 7: RATIONALE

Protocol GO30081 was previously amended locally (Spain and China). The changes in these amendments have been incorporated into this global amendment. In addition, there are several changes that are completely new (not previously in local amendments). Cumulative changes from the local amendments, as well as the new changes, include the following:

- Language has been added to the end of study definition to clarify that if the Sponsor decides to terminate the study, patients who are still receiving study treatment or are in survival follow-up may be enrolled into an extension study or a non-interventional study (Section 3.2).
- Language has been added to clarify use of samples after withdrawal of patient consent (Section 4.5.6).
- Language has been added to clarify that, after withdrawal of consent for participation in the Roche Clinical Repository (RCR), remaining RCR samples will be destroyed or will no longer linked to the patient. Furthermore, instructions about patient withdrawal from the RCR after site closure have been modified to indicate that the investigator must inform the Sponsor of patient withdrawal by emailing the study number and patient number to [redacted] (Section 4.5.11.6).
- Changes have been added to align the protocol with the statistical analysis plan (Version 2 and Version 3) for the global cohort:
  - The Study GO30081 Statistical Analysis Plan (SAP) Version 1 was amended to reflect the final statistical analysis timeline prior to the study database lock and unblinding. In SAP Version 1, the interim and final analysis of overall survival (OS) were planned to be conducted at 220 and 280 death events, i.e., when 55% and 70% patients have events, respectively. Recent data from Study GO29436 that are external to Study GO30081 suggest that the treatment effect on OS may be delayed and an accurate assessment of the magnitude of the treatment effect will take longer than initially expected. Thus the interim and final analysis of this study are planned to be conducted at more mature time points, i.e., when death event to patient ratio reaches 60% and 77%, respectively, which corresponds to 240 events for the OS interim analysis, and 306 events for the OS final analysis. Progression-free survival (PFS) analysis timing is adjusted accordingly to be conducted at the same time as OS interim analysis and 295 PFS events are expected by that time (Sections 3.2, 6.1, and 6.8.1).
  - The Study GO30081 Statistical Analysis Plan (SAP) Version 2 was amended prior to the study database lock and unblinding, due to the potential risk of over-stratification (Akazawa et al. 1997). If at least one stratum (i.e., a combination of stratification factor levels across sex [male vs female], Eastern Cooperative Oncology Group [ECOG] performance status [0 vs 1], and brain metastasis [Yes vs No] per interactive voice/Web response system [IxRS]) has less than 10 events (progression-free survival [PFS] or overall survival [OS] events), the stratification factor (one of 3 stratification factors: sex, ECOG performance

status, and brain metastasis per IxRS) which contains the level with the smallest number of patients will be removed from the stratified analyses. The removal of the stratification factor will continue until there is no stratum with less than 10 events (PFS or OS events). The final set of stratification factors used in stratified analyses will be applied to all endpoints where stratified analyses are planned (Section 6.4 and 6.4.1).

- The statistical analysis plan and [redacted] (Section 6.1.1). [redacted]
- Section 5.1.1 has been amended to align with current atezolizumab risk language and information regarding the management of atezolizumab-specific adverse events has been included in a new Appendix (Appendix 12). Included in this appendix are new guidelines for the management of myositis and language regarding the fact that systemic immune activation is a potential risk with atezolizumab, regardless of whether atezolizumab is given alone or in combination with other immunomodulating agents. Sections 5.1.1, 5.1.5, 5.1.6.1 and 5.1.8 have been updated (and Section 5.1.6.1 was moved to Appendix 12) to reflect the addition of Appendix 12.
- [redacted]
- The Appendix 10 (Anaphylaxis Precautions) has been modified to remove the requirement for use of a tourniquet. The application of a tourniquet is no longer recommended due to the limited therapeutic benefit and risk of losing time for more important measures (Ring J, Beyer K, Biedermann T, et al. Allergo J Int. 2014;23(3):96–112).
- Language has been added for consistency with Roche's current data retention policy and to accommodate more stringent local requirements (if applicable) (Section 7.6).
- Language has been added to indicate that the study will comply with applicable local, regional, and national laws (Section 8.1).

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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE I/III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF CARBOPLATIN PLUS ETOPOSIDE WITH OR WITHOUT ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) IN PATIENTS WITH UNTREATED EXTENSIVE-STAGE SMALL CELL LUNG CANCER**
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MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	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 to the Sponsor or their designee. Contact details will be provided to the investigator prior to study start.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE I/III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF CARBOPLATIN PLUS ETOPOSIDE WITH OR WITHOUT ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) IN PATIENTS WITH UNTREATED EXTENSIVE-STAGE SMALL CELL LUNG CANCER**
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PHASE:	I/III
INDICATION:	Small cell lung cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

The following objective statements apply to the global enrollment phase, [redacted]

Efficacy Objectives

Primary Efficacy Objectives

The co-primary objectives of this study are the following:

- To evaluate the efficacy of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the intent-to-treat (ITT) population as measured by investigator-assessed progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)
- To evaluate the efficacy of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the ITT population as measured by overall survival (OS)

Secondary Efficacy Objectives

The secondary efficacy objectives for this study are:

- To evaluate the efficacy of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the ITT population as measured by investigator-assessed objective response rate (ORR) according to RECIST v1.1
- To evaluate the efficacy of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the ITT population as measured by investigator-assessed duration of response (DOR) according to RECIST v1.1
- To evaluate the PFS rate at 6 months and at 1 year in each treatment arm for the ITT population
- To evaluate the OS rate at 1 and 2 years in each treatment arm for the ITT population

- To determine the impact of atezolizumab as measured by time to deterioration (TTD) in patient-reported lung cancer symptoms of cough, dyspnea (single item and multi-item subscales), chest pain, arm/shoulder pain, or fatigue using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13) in patients treated with atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the ITT population

Safety Objectives

The safety objectives for this study are:

- To evaluate the safety and tolerability of atezolizumab in combination with carboplatin + etoposide compared with carboplatin + etoposide
- To evaluate the incidence and titers of anti-therapeutic antibodies (ATAs) against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the pharmacokinetics of atezolizumab, carboplatin, and etoposide in chemotherapy-naive patients with extensive-stage small cell lung cancer (ES-SCLC).

Exploratory Objectives

The exploratory objectives for this study are:

- To evaluate investigator-assessed PFS, ORR, DCR, DOR, TIR, and TTR according to modified RECIST for the atezolizumab-containing treatment arm in the ITT population
- To evaluate the relationship between tumor biomarkers (including but not limited to PD-L1, programmed death-1 (PD-1), somatic mutations, and others), as defined by immunohistochemistry (IHC) or quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR), next generation sequencing (NGS), and/or other methods and measures of efficacy
- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue, blood, plasma and serum and their association with disease status, mechanisms of resistance, and/or response to study treatment
- To evaluate and compare patient's health status as assessed by the EuroQoL 5 Dimensions 5-Level (EQ-5D-5L) questionnaire to generate utility scores for use in economic models for reimbursement
- To determine the impact of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide as measured by change from baseline in patient-reported outcomes (PRO) of health-related quality of life, lung cancer–related symptoms, physical functioning, and health status as assessed by the EORTC QLQ-C30 and LC13
- To evaluate the impact of chemotherapy (both carboplatin and etoposide) on peripheral and tumor-specific T-cell populations during and after induction therapy and its relationship to efficacy and safety outcomes

Study Design

Description of Study

This is a randomized, Phase I/III, multicenter, double-blinded, placebo-controlled study designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin + etoposide compared with treatment with placebo + carboplatin + etoposide in patients who have ES-SCLC and are chemotherapy-naive for their extensive-stage disease.

Eligible patients will be stratified by sex (male vs. female), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1), and presence of brain metastases (yes vs. no) and randomized 1:1 to receive one of the following treatment regimens: A) atezolizumab + carboplatin ± etoposide or B) placebo + carboplatin + etoposide.

Induction treatment will be administered on a 21-day cycle for four cycles.

Following the induction phase, patients will continue maintenance therapy with either atezolizumab or placebo. During the maintenance phase, prophylactic cranial irradiation is permitted as per local standard-of-care and will be reported on the Prophylactic Cranial Irradiation electronic Case Report Form (eCRF). Thoracic radiation with curative intent or the intent to eliminate residual disease is not permitted. Palliative thoracic radiation is allowed.

Treatment should be discontinued in all patients (in both treatment arms) who exhibit evidence of disease progression per RECIST v1.1. However, to better accommodate standard clinical practice which is guided by the fact that patients with ES-SCLC whose disease progresses after first-line treatment have limited treatment options and such options have limited efficacy and significant toxicity, patients may be considered for treatment beyond radiographic disease progression per RECIST v1.1, at the discretion of the investigator and after appropriate discussion with the patient and obtaining informed consent, only if all of the following criteria are met:

- Evidence of clinical benefit as assessed by the investigator
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial progression

Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 should be closely monitored clinically and with a follow-up scan in 6 weeks or sooner if symptomatic deterioration occurs. Treatment should be discontinued if clinical deterioration due to disease progression occurs at any time, or if persistent disease growth is confirmed in a follow-up scan. In addition, patients should be discontinued for unacceptable toxicity or for any other signs or symptoms of deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status.

If clinically feasible, it is recommended that the patient undergo a tumor biopsy sample collection at the time of radiographic disease progression. These data will be used to explore whether radiographic findings are consistent with the presence of a tumor. Additionally, these data will be analyzed to evaluate the association between changes in tumor tissue and clinical outcome and to further understand the potential mechanisms of progression and resistance to atezolizumab as compared with such mechanisms after treatment with chemotherapy alone. This exploratory biomarker evaluation will not be used for any treatment-related decisions.

Patients will undergo tumor assessments at baseline and every 6 weeks (± 7 days) for 48 weeks following Cycle 1, Day 1, regardless of treatment dose delays. After completion of the Week 48 tumor assessment, tumor assessments will be required every 9 weeks (± 7 days) thereafter, regardless of treatment dose delays. Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first.

Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will continue to undergo tumor assessments every 6 weeks (±7 days), or sooner if symptomatic deterioration occurs. For these patients, tumor assessments will continue every 6 weeks (±7 days), regardless of time in the study, until study treatment is discontinued.

Patients who discontinue treatment for reasons other than 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 patient had remained on study treatment (i.e., every 6 weeks [±7 days] for 48 weeks following Cycle 1, Day 1 and then every 9 weeks [±7 days] thereafter, regardless of treatment dose delays) until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.

In case of an early termination of the study, patients who are deriving clinical benefit from treatment with atezolizumab will be permitted to continue treatment with atezolizumab at the discretion of the investigator.

[redacted]

Number of Patients

Approximately 400 patients will be randomized into the global enrollment phase of this study.

[redacted]

Target Population

Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry:

- Signed Informed Consent Form
- Male or female, 18 years of age or older
- ECOG performance status of 0 or 1
- Histologically or cytologically confirmed ES-SCLC (per the Veterans Administration Lung Study Group (VALG) staging system
- No prior systemic treatment for ES-SCLC
- Patients who have received prior chemoradiotherapy for limited-stage SCLC must have been treated with curative intent and experienced a treatment-free interval of at least 6 months since last chemotherapy, radiotherapy, or chemoradiotherapy cycle from diagnosis of extensive-stage SCLC
- Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:

    Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)

    No ongoing requirement for corticosteroids as therapy for CNS disease

    No evidence of interim progression between the completion of CNS-directed therapy and randomization

    Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to randomization, if all other criteria are met.
- Measurable disease, as defined by RECIST v1.1

    Previously irradiated lesions can only be considered as measurable disease if disease progression has been unequivocally documented at that site since radiation and the previously irradiated lesion is not the only site of disease.
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to randomization:

    ANC $\geq$ 1500 cells/μL without granulocyte colony-stimulating factor support

    Lymphocyte count $\geq$ 500/μL

    Platelet count $\geq$ 100,000/μL without transfusion

    Hemoglobin $\geq$ 9.0 g/dL

        Patients may be transfused to meet this criterion.

    INR or aPTT $\leq$ 1.5 $\times$ upper limit of normal (ULN)

This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.

AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ ULN, with the following exceptions:

Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN

Patients with documented liver or bone metastases: alkaline phosphatase $\leq 5 \times$ ULN.

Serum bilirubin $\leq 1.25 \times$ ULN

Patients with known Gilbert disease who have serum bilirubin level $\leq 3 \times$ ULN may be enrolled.

Serum creatinine $\leq 1.5 \times$ ULN

- Patients must submit a pre-treatment tumor tissue sample. Any available tumor tissue sample can be submitted. The tissue sample should be submitted before or within 4 weeks after randomization; however, patients may be enrolled into the study before the pre-treatment tumor tissue sample is submitted.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 5 months after the last dose of study treatment.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of 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 patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during treatment with chemotherapy (i.e., carboplatin and etoposide) and for at least 6 months after the last dose of chemotherapy to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- [redacted]

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments
- 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 randomization
- Leptomeningeal disease

- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed regardless of drainage frequency.
- Uncontrolled or symptomatic hypercalcemia

  Patients who are receiving denosumab prior to randomization must be willing and eligible to discontinue its use and replace it with a bisphosphonate while in the study.
- Malignancies other than SCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS $>$ 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous-cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
- Women who are pregnant, lactating, or intending to become pregnant during the study
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

  Patients with a history of autoimmune-related hypothyroidism on thyroid replacement hormone therapy are eligible.

  Patients with controlled Type I diabetes mellitus on an insulin regimen are eligible.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are eligible for the study provided that they meet the following conditions:

  - Rash must cover less than 10% of body surface area
  - Disease is well controlled at baseline and only requires low potency topical steroids
  - No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency, or oral steroids)
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive test result for HIV

  All patients must be tested for HIV; patients who test positive for HIV will be excluded.
- Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test result at screening) or hepatitis C virus (HCV)

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible. HBV DNA should be obtained in these patients prior to randomization.

  Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
- Active tuberculosis
- Severe infections at the time of randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to randomization, unstable arrhythmias, or unstable angina

  Patients 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.

- Major surgical procedure other than for diagnosis within 28 days prior to randomization or anticipation of need for a major surgical procedure during the course of the study
- Prior allogeneic bone marrow transplantation or solid organ transplant
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk for treatment complications
- Patients with illnesses or conditions that interfere with their capacity to understand, follow, and/or comply with study procedures
- Treatment with any other investigational agent with therapeutic intent within 28 days prior to randomization
- Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation that such a live attenuated vaccine will be required during the study

  Patients must not receive live, attenuated influenza vaccines (e.g., FluMist®) within 4 weeks prior to randomization, during treatment, and for 5 months following the last dose of atezolizumab/placebo.
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunosuppressive medications (including, but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 1 week prior to randomization

  Patients who have received acute systemic immunosuppressant medications (e.g., use of corticosteroids for nausea, vomiting, or management of or premedication for allergic reactions) may be enrolled in the study after discussion with and approval by the Medical Monitor. In those patients, the need and length of the washout period prior to randomization will also be established in conjunction with the Medical Monitor.

  The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of allergic reactions to carboplatin or etoposide

End of Study

The end of study is will occur when all of the following criteria have been met:

- The last patient last visit (LPLV) has occurred (i.e., last patient in the global [redacted]).
- Approximately *306* deaths have been observed among the randomized patients in the global enrollment phase.
- [redacted]

Additionally, the Sponsor may decide to terminate the study at any time. *If the Sponsor decides to terminate the study, patients who are still receiving study treatment or undergoing survival follow-up may be enrolled in an extension study or a non-interventional study.*

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 31 months.

Outcome Measures

Efficacy Outcome Measures

Primary Efficacy Outcome Measures

The primary efficacy outcome measures for this study are:

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first.
- OS, defined as the time from randomization to death from any cause.

Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are:

- Objective response, defined as PR or CR as determined by the investigator according to RECIST v1.1
- DOR, defined as the time interval from first occurrence of a documented objective response to the time of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever comes first
- PFS rates at 6 months and at 1 year
- OS rates at 1 and 2 years
- TTD in patient-reported lung cancer symptoms, defined as time from randomization to deterioration (10-point change) on each of the EORTC QLQ-C30 and EORTC QLQ-LC13 symptom subscales maintained for two assessments or one assessment followed by death from any cause within 3 weeks

Safety Outcome Measures

The safety outcome measures for this study are:

- Incidence, nature, and severity of adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0
- Changes in vital signs, physical findings, and clinical laboratory results during and following study treatment administration
- Incidence of ATA response to atezolizumab and potential correlation with PK, pharmacodynamic, safety, and efficacy parameters

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are:

- Maximum observed serum atezolizumab concentration (C_{max}) after infusion
- Minimum observed serum atezolizumab concentration (C_{min}) prior to infusion at selected cycles, at treatment discontinuation, and at 120 days ($\pm$30 days) after the last dose of atezolizumab
- Plasma concentrations for carboplatin
- Plasma concentrations for etoposide

Exploratory Outcome Measures

The exploratory outcome measures for this study are:

- Objective response, PFS and DOR as determined by the investigator according to modified RECIST
- Status of PD-L1–, immune-, and SCLC-related and other exploratory biomarkers in archival and/or freshly obtained tumor tissues, and blood (or blood derivatives) collected before, during, or after treatment with atezolizumab or at progression and association with disease status and/or response to atezolizumab
- Utility scores of the EQ-5D-5L

- Change from baseline in PROs of health-related quality of life, lung cancer–related symptoms, physical functioning, and health status as assessed by the EORTC QLQ-C30 and QLQ-LC13
- Changes in levels and type of peripheral and tumor-specific T-cell populations during and after induction therapy and its relationship to efficacy and safety outcomes

Investigational Medicinal Products

The induction phase of the study will consist of four cycles of atezolizumab/placebo plus chemotherapy, with each cycle being 21 days in duration. On Day 1 of each cycle, all eligible patients will receive drug infusions in the following order:

Arm A: atezolizumab → carboplatin → etoposide

Arm B: placebo → carboplatin → etoposide

On Days 2 and 3, patients will receive etoposide alone.

After the induction phase, patients will begin maintenance therapy with atezolizumab/placebo every 3 weeks.

Test Product (Investigational Drug)

The test products in this study are atezolizumab and atezolizumab placebo. Patients will receive atezolizumab/placebo 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered by IV infusion every 21 [±2] days in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. For information on the formulation, packaging, and handling of atezolizumab and atezolizumab placebo refer to the atezolizumab Pharmacy Manual and Investigator's Brochure. Atezolizumab and atezolizumab placebo will be supplied by the Sponsor.

Non-Investigational Medicinal Products

Carboplatin and etoposide are background treatment and are considered non-investigational medicinal products (NIMPs). For information on the formulation, packaging, and handling of carboplatin and etoposide see the prescribing information for each drug.

Carboplatin should be administered after completion of atezolizumab/placebo by IV infusion over 30–60 minutes to achieve an initial target area under the concentration-time curve (AUC) of 5 mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines.

During the induction phase (Cycles 1–4), on Day 1 of each cycle, etoposide (100 mg/m^2) should be administered intravenously over 60 minutes following carboplatin administration. On Days 2 and 3 of each cycle, etoposide (100 mg/m^2) should be administered intravenously over 60 minutes. Premedication should be administered according to local standard-of-care.

Because the effects of corticosteroids on T-cell proliferation have the potential to attenuate atezolizumab-mediated anti-tumor immune activity, premedication with corticosteroids should be minimized to the extent that is clinically feasible.

Statistical Methods

All analyses will be restricted to the patients enrolled in the global enrollment phase only ([redacted]), unless otherwise noted. The analysis populations used in this section, such as the ITT (i.e., all randomized patients) and the PD-L1–selected populations will not [redacted], unless otherwise noted.

The analyses of PFS and OS will be performed on all randomized patients (ITT), with patients grouped according to the treatment assigned at randomization, regardless of whether they receive any assigned study drug. ORR will be analyzed using all randomized patients who have measurable disease at baseline. DOR will be assessed in patients who have an objective response. TTD analyses will be conducted on all patients with a non-missing baseline PRO assessment. Change from baseline analysis on PROs will be performed using patients who have both a non-missing baseline assessment and at least one post-baseline assessment with patients grouped according to the treatment assigned at randomization.

Primary Analysis

To adjust for multiplicity due to having two co-primary endpoints, a group sequential Holm's procedure will be implemented: initially the hypothesis test for PFS will be conducted at a two-sided alpha of 0.005 and OS will be tested at a two-sided alpha of 0.045. Once a null hypothesis is rejected, the test mass predefined for that endpoint becomes available and can be recycled to the other unrejected test.

The null and alternative hypotheses regarding PFS or OS in the ITT population can be phrased in terms of the PFS or OS survival functions $S_A(t)$ and $S_B(t)$ for Arm A (atezolizumab + carboplatin + etoposide) and Arm B (placebo + carboplatin + etoposide), respectively:

$$H0: S_A(t) = S_B(t) \text{ versus } H1: S_A(t) \neq S_B(t)$$

One of the co-primary efficacy endpoints is PFS as assessed by the investigator using RECIST v1.1. PFS is defined as the time between the date of randomization and the date of first documented disease progression or death, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

The $stratified$ log-rank test, will be used as the primary analysis to compare PFS between the two treatment arms. The results from the unstratified log-rank will also be provided.

The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm. Cox proportional-hazards models will be used to estimate the $stratified$ HR and its 95% CI. The unstratified HR will also be presented.

OS, the other co-primary efficacy endpoint, is defined as the time from the date of randomization to the date of death from any cause. Patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Patients with no post-baseline information will be censored at the date of randomization plus 1 day. Methods for OS analyses are similar to those described for the PFS endpoint.

Determination of Sample Size

Approximately 400 patients will be randomized into the global enrollment phase of this study to the atezolizumab + carboplatin + etoposide arm and the placebo + carboplatin + etoposide arm in a 1:1 ratio.

There are two co-primary efficacy endpoints: PFS and OS. To control the overall two-sided Type I error rate at 0.05, the two-sided significance levels of 0.005 and 0.045 are allocated to the primary comparisons for PFS and OS, respectively.

The following sample size calculation applies to the global enrollment phase, [redacted] unless otherwise noted.

The sample size of the study is determined by the analysis of OS. To detect an improvement of HR = 0.68 in OS using a log-rank test, approximately 306 deaths in the ITT population will be required to achieve 91% power at a two-sided significance level of 0.045. One OS interim analysis will be performed when approximately 240 OS events in the ITT population are observed, which by estimation will occur at approximately 25 months after the first patient is randomized.

The primary analysis of PFS is planned to be conducted at the time of the OS interim analysis, and is estimated to be when approximately 295 PFS events in the ITT population have occurred, which is expected at approximately 25 months after the first patient is randomized. This provides 99% power to detect an improvement of HR = 0.55 in PFS at a two-sided significance level of 0.005. There will be no interim analysis for PFS.

By a group sequential Holm procedure, if the primary analysis of PFS is significant, then the two-sided 0.005 alpha will be recycled to OS. Otherwise, iIf the OS analysis at either interim or final is significant, the allocated test mass of two-sided 0.045 alpha can be returned to PFS so PFS primary analysis can be tested at a two-sided 0.05 level. Additional details will be provided in the SAP.

The final analysis of OS will be performed when approximately *306* OS events in the ITT population have been observed, which is expected at approximately *36* months after the first patient is randomized.

The calculation of sample size and estimates of the analysis timelines are based on the following assumptions:

- PFS and OS are exponentially distributed.
- The median duration of PFS in the control arm is 6 months.
- The median duration of OS in the control arm is 10 months.
- The two interim and final analyses of OS use the Lan-DeMets alpha spending function to approximate the O'Brien-Fleming boundary.
- The dropout rate is 5% over 12 months for PFS and OS.

The sample size of the [redacted]

Interim Analyses

There will be no interim analyses planned for PFS in this study. An external independent Data Monitoring Committee (iDMC) will be set up to evaluate safety data on an ongoing basis. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an independent Data Coordinating Center (iDCC). Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRBs/ECs. A detailed plan will be included in the iDMC Charter.

One interim efficacy analysis of OS is planned when approximately *240* OS events have been observed. The primary analysis of PFS will be conducted at the same time of the interim OS analysis *and is estimated to occur when approximately 295 PFS events in the ITT population have occurred, which is expected at approximately 25 months after the first patient is randomized*.

The final OS analysis will be conducted when approximately *306* OS events in the ITT population have been observed. This is expected to occur approximately *36* months after the first patient is randomized, but the exact timing of this analysis will depend on the actual number of OS events.

To control the type I error for OS, the stopping boundaries for OS interim and final analyses are to be computed with use of the Lan-DeMets approximation to the O'Brien-Fleming boundary.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ASCO	American Society of Clinical Oncology
ATA	anti-therapeutic antibody
AUC	area under the concentration–time curve
C_{max}	maximum observed serum concentration
C_{min}	minimum observed serum concentration
CAV	cyclophosphamide, doxorubicin, and vincristine
CR	complete response
CRCL	creatinine clearance
CT	computed tomography
C_{trough}	trough concentration
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
ePRO	electronic PRO
EQ-5D-5L	EuroQoL 5 Dimensions 5-Level Version
ES-SCLC	extensive-stage small cell lung cancer
ESMO	European Society for Medical Oncology
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GFR	glomerular filtration rate
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
HRQoL	health-related quality of life
IC	tumor-infiltrating immune cell
ICH	International Conference on Harmonisation
iDCC	independent Data Coordinating Center

Abbreviation	Definition
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
imAE	immune-modulated adverse event
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
IxRS	interactive voice/Web response system
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PUVA	psoralen plus ultraviolet A radiation
q3w	every 3 weeks
QLQ-C30	Quality-of-Life Questionnaire Core 30
QLQ-LC13	Quality-of-Life Questionnaire Lung Cancer Module
qRT-PCR	quantitative reverse transcriptase–polymerase chain reaction
RCC	renal cell carcinoma
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SCLC	small cell lung cancer
SIRS	systemic inflammatory response syndrome
TC	tumor cell

Abbreviation	Definition
TIR	time in response
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
TTD	time to deterioration
TTR	time to response
UBC	urothelial bladder cancer
ULN	upper limit of normal
VALG	Veterans Administration Lung Study Group

1. BACKGROUND

1.1 BACKGROUND ON LUNG CANCER

Lung cancer remains the leading cause of cancer deaths worldwide; it is the most common cancer in men and accounted for approximately 13% of all new cancers in 2008 (Jemal et al. 2011). In 2012, it was estimated that there were 313,000 new cases of lung cancer and 268,000 lung cancer deaths in Europe (GLOBOCAN 2012). Similar data from the United States estimated that there would be 221,200 new cases of lung cancer and 158,040 lung cancer deaths in 2015 (Siegel et al. 2015).

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases of lung cancer (Molina et al. 2008; Howlader et al. 2014). Small cell lung cancer (SCLC) accounts for approximately 13% of all cases, and is distinguished from NSCLC by its rapid growth time and early development of metastatic disease (Govindan et al. 2006). Nearly all cases of SCLC are attributable to cigarette smoking (Pesch et al. 2012). Poor prognostic factors for survival in patients with SCLC include extensive-stage disease, poor performance status, weight loss, and markers associated with excessive bulk of disease (e.g., lactate dehydrogenase) (Yip et al. 2000; Foster et al. 2009).

Patients with limited-stage SCLC can be treated with chemotherapy and radiation with the potential for long-term survival (Stinchcombe et al. 2010). However, the majority (approximately 70%) of patients with SCLC are diagnosed with extensive-stage disease (ES-SCLC), which has poor survival prospects (median overall survival [OS] approximately 10 months) (Socinsk et al. 2009). Chest pain, dyspnea, and cough are among the most frequent disease-related symptoms experienced by patients with lung cancer. Chemotherapy alone can palliate symptoms and prolong survival for patients with ES-SCLC, however long-term survival is rare (Johnson et al. 2004; Demedts et al. 2010).

1.1.1 Treatment for Extensive-Stage Small Cell Lung Cancer

The current standard first-line treatment for patients with ES-SCLC is platinum-based chemotherapy with etoposide, a topoisomerase II inhibitor (NCCN 2015, Fruh et al. 2013). In the mid-1980s, clinical studies with the combination of cisplatin and etoposide as first-line treatment in patients with ES-SCLC showed complete response (CR) rates $>$40% and median survival time of approximately 9 months (Evans et al. 1985). Subsequently, small randomized studies have suggested similar efficacy of cisplatin and carboplatin in patients with SCLC (Skarlos et al. 1994; Okamoto et al. 2007). A meta-analysis of four randomized studies compared cisplatin-based versus carboplatin-based regimens in patients with SCLC (Rossi et al. 2012). Of the 663 patients included in this meta-analysis, 68% had extensive-stage disease. In patients receiving cisplatin- versus carboplatin-containing regimens, there was no significant difference observed in response rate (67% vs. 66%), progression-free survival (PFS) (5.5 vs. 5.3 months; hazard ratio [HR]: 1.10; 95% CI: 0.94, 1.29) or OS (9.6 vs. 9.4 months; HR: 1.08; 95% CI: 0.92, 1.27), suggesting

equivalent efficacy in patients with SCLC. Several studies using cisplatin or carboplatin with etoposide (at various doses) have shown consistent outcomes (see Table 1).

Table 1 Results from Randomized Studies using Platinum-Based Chemotherapy for ES-SCLC

	Platinum Dosing	Etoposide Dosing	ORR (%)	Median PFS (months)	Median OS (months)
Roth et al. 1992	Cisplatin 20 mg/m^2 Days 1–5	80 mg/m^2 Days 1–5	61%	4.3	8.6
Pujol et al. 2001	Cisplatin 100 mg/m^2 Day 2	100 mg/m^2 Days 1–3	61%	6.3	9.3
Noda et al. 2002	Cisplatin 80 mg/m^2 Day 1	100 mg/m^2 Days 1–3	68%	4.8	9.4
Eckardt et al. 2006	Cisplatin 80 mg/m^2 Day 1	100 mg/m^2 Days 1–3	69%	6.3	10.1
Hanna et al. 2006	Cisplatin 60 mg/m^2 Day 1	120 mg/m^2 Days 1–3	44%	4.6	10.2
Okamoto et al. 2007	Cisplatin 25 mg/m^2 Days 1–3	80 mg/m^2 Days 1–3	73%	4.7	9.9
Okamoto et al. 2007	Carboplatin AUC 5 Day 1	80 mg/m^2 Days 1–3	73%	5.2	10.6
Rudin et al. 2008	Carboplatin AUC 5 Day 1	100 mg/m^2 Days 1–3	52%	5.4	10.6
Socinski et al. 2009	Carboplatin AUC 5 Day 1	80 mg/m^2 Days 1–3	60%	7.6	10.6
Nagel et al. 2011	Carboplatin AUC 6 Day 1	120 mg/m^2 Days 1–3	67%	7.0	11.0
Schmittel et al. 2011	Carboplatin AUC 5 Day 1	140 mg/m^2 Days 1–3	52%	6.0	9.0

AUC = area under the concentration-time curve; ES-SCLC = extensive-stage small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

In the second-line setting, single-agent topotecan is approved by the U.S. Food and Drug Administration (FDA) as subsequent therapy for patients with SCLC who initially respond to chemotherapy but then progress after 2–3 months. This is based on a Phase III study in which intravenous topotecan was compared with the combination regimen CAV (cyclophosphamide, doxorubicin, and vincristine). Both arms had similar response rates and survival; however, the proportion of patients who experienced symptom improvement was greater in the topotecan group than in the CAV group for 4 of 8 symptoms evaluated, including dyspnea, anorexia, hoarseness, and fatigue, as well as interference with daily activity (von Pawel et al. 1999). Subsequently, a Phase III study also showed the superiority of oral topotecan versus best supportive care for patients with relapsed SCLC not considered candidates for standard intravenous therapy (O'Brien et al. 2006).

Despite the impressive initial response rates observed with first-line chemotherapy regimens, most patients with ES-SCLC develop chemotherapy resistant disease and their prognosis is poor. PFS is approximately 6 months and median survival remains under a year. Therefore, there is a significant need for improved novel treatment options for patients with ES-SCLC. Against this background, immunotherapeutic agents, including antibodies that modulate immune cell activity, offer an alternative treatment approach that could potentially improve the prognosis of patients with this disease.

1.2 BACKGROUND ON ATEZOLIZUMAB (MPDL3280A)

Programmed death–ligand 1 (PD-L1) is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors programmed death–1 (PD-1) and B7.1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer (Blank et al. 2005; Keir et al. 2008). Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen-presenting cells can mediate downregulation of immune responses, including inhibition of T-cell activation and cytokine production (Butte et al. 2007; Yang et al. 2011).

Overexpression of PD-L1 on tumor cells (TCs) has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

Atezolizumab (MPDL3280A; anti–PD-L1 antibody) is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids), and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has

minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human PD-L1 and inhibits its interaction with its receptors, PD-1 and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells.

Atezolizumab is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans. Atezolizumab is approved for the treatment of patients with metastatic NSCLC after prior chemotherapy and for the treatment of patients with locally advanced or metastatic urothelial cancer after prior chemotherapy.

1.2.1 Summary of Nonclinical Studies

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were thus undertaken with atezolizumab.

The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support IV administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway and supported entry into clinical studies in patients.

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

1.3 CLINICAL EXPERIENCE WITH ATEZOLIZUMAB

1.3.1 Ongoing Clinical Studies

Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as monotherapy and in combination with several anti-cancer therapies (refer to the Atezolizumab Investigator's Brochure for study descriptions).

Single-agent safety and efficacy data in patients with lung cancer are presented below from the following two studies:

- Study PCD4989g: a Phase Ia, multicenter, first-in-human, open label, dose escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion given

every 3 weeks (Q3W) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.

- Study GO28753 (POPLAR): a randomized, Phase II, open-label study assessing the clinical benefit of atezolizumab as a single agent versus docetaxel in patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen.

In addition, the safety and efficacy data of atezolizumab in combination with platinum-based chemotherapy are also summarized below from the Phase Ib Study GP28328 that is investigating the safety and efficacy of atezolizumab in combination with chemotherapy in patients with advanced solid tumors.

1.3.2 Clinical Safety

1.3.2.1 Single-Agent Clinical Safety in Patients with Lung Cancer

Study PCD4989g is a Phase Ia dose escalation and expansion study in which atezolizumab is being used as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies, and provides the majority of data (with 558 safety-evaluable patients as of the data cutoff date of 11 May 2015) for the safety profile of atezolizumab as monotherapy.

Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of adverse events have been determined.

The safety profile of atezolizumab as a single agent is observed to be consistent across different indications, including SCLC, NSCLC, urothelial bladder cancer (UBC), renal cell carcinoma (RCC), melanoma, gastric cancer, colorectal cancer, head and neck cancer, breast cancer, and sarcoma.

Single-Agent Clinical Safety in Patients in Study PCD4989g

Of the 558 patients in Study PCD4989g, 520 patients (93.2%) experienced at least one adverse event, including 376 patients (67.4%) who experienced one treatment-related adverse event. Commonly reported events (reported in $\geq$10% of all patients) included fatigue, decreased appetite, nausea, pyrexia, constipation, and cough (see Table 2).

Table 2 Study PCD4989g: Adverse Events with Frequency ≥10% of Patients for All Grades

Preferred Term	All Grades n (%)	All Grades Related n (%)	Grade 3–4 n (%)	Grades 3–4 Related n (%)
Any adverse event	520 (93.2)	376 (67.4)	239 (42.8)	66 (11.8)
Fatigue	192 (34.4)	115 (20.6)	13 (2.3)	6 (1.1)
Decreased Appetite	142 (25.4)	62 (11.1)	4 (0.7)	0 (0.0)
Nausea	136 (24.4)	65 (11.6)	5 (0.9)	2 (0.4)
Pyrexia	117 (21.0)	63 (11.3)	2 (0.4)	0 (0.0)
Constipation	116 (20.8)	8 (1.4)	2 (0.4)	0 (0.0)
Cough	113 (20.3)	11 (2.0)	1 (0.2)	1 (0.2)
Dyspnea	112 (20.1)	18 (3.2)	18 (3.2)	4 (0.7)
Diarrhea	110 (19.7)	53 (9.5)	2 (0.4)	1 (0.2)
Anemia	104 (18.6)	26 (4.7)	23 (4.1)	5 (0.9)
Vomiting	96 (17.2)	28 (5.0)	3 (0.5)	2 (0.4)
Asthenia	88 (15.8)	53 (9.5)	8 (1.4)	4 (0.7)
Back Pain	85 (15.2)	9 (1.6)	8 (1.4)	1 (0.2)
Headache	83 (14.9)	32 (5.7)	2 (0.4)	1 (0.2)
Arthralgia	79 (14.2)	35 (6.3)	2 (0.4)	0 (0.0)
Pruritus	75 (13.4)	55 (9.9)	0 (0.0)	0 (0.0)
Rash	73 (13.1)	53 (9.5)	0 (0.0)	0 (0.0)
Abdominal Pain	63 (11.3)	12 (2.2)	8 (1.4)	0 (0.0)
Insomnia	62 (11.1)	7 (1.3)	1 (0.2)	0 (0.0)
Peripheral edema	59 (10.6)	7 (1.3)	—	—
Chills	57 (10.2)	31 (5.6)	0 (0.0)	0 (0.0)

Note: "—" refers to missing Common Terminology Criteria grade.
'Related' refers to investigator designation of causality to atezolizumab.

Single-Agent Clinical Safety in Patients with SCLC in Study PCD4989g

Seventeen patients with SCLC in Study PCD4989g had received at least one dose of atezolizumab as of 15 December 2015. Of these 17 patients, 16 patients experienced at least one adverse event. Sixty-five percent of patients experienced treatment-related adverse events, with the most frequently reported adverse event being fatigue (24%). There were eight treatment-related, Grade 3-5, adverse events reported in 3 patients, including one Grade 3 pneumonitis leading to treatment discontinuation and one Grade 5 hepatic failure. Although the patient numbers are limited, the adverse events reported in the SCLC cohort in Study PCD4989g are consistent with the safety profile of atezolizumab observed in the entire study.

Refer to the Atezolizumab Investigator's Brochure for details on adverse events observed in patients treated with atezolizumab.

Single-Agent Clinical Safety in Patients with NSCLC in POPLAR Study GO28753

As of the 8 May 2015 data cutoff date, the Phase II POPLAR study (GO28753) included data from 142 patients with NSCLC treated with atezolizumab as a fixed dose of 1200 mg IV every 3 weeks and 135 patients treated with 75 mg/m^2 IV docetaxel every 3 weeks. The frequency of patients who reported any adverse event regardless of attribution was 96.3% for the atezolizumab arm and 95.8% for the docetaxel arm. A higher number of Grade $\geq$3 adverse events were observed in the docetaxel arm (56.3% vs. 44.4%), explained primarily by the difference in adverse events due to bone marrow suppression. Adverse events reported in at least 10% of patients in either treatment arm are listed in Table 3.

Table 3 Adverse Events Reported in at Least 10% of Patients in the POPLAR Study GO28753

MedDRA Preferred Term	No. of Patients (%)	
	Atezolizumab (n = 142)	Docetaxel (n = 135)
Fatigue	55 (38.7)	54 (40.0)
Decreased appetite	49 (34.5)	28 (20.7)
Dyspnoea	38 (26.8)	27 (20.0)
Cough	38 (26.8)	33 (24.4)
Nausea	31 (21.8)	45 (33.3)
Constipation	29 (20.4)	32 (23.7)
Pyrexia	24 (16.9)	16 (11.9)
Diarrhoea	24 (16.9)	38 (28.1)
Arthralgia	22 (15.5)	12 (8.9)
Anaemia	23 (16.2)	26 (19.3)
Insomnia	19 (13.4)	11 (8.1)
Musculoskeletal pain	19 (13.4)	7 (5.2)
Vomiting	18 (12.7)	18 (13.3)
Back Pain	16 (11.3)	11 (8.1)
Asthenia	14 (9.9)	22 (16.3)
Pneumonia	15 (10.6)	4 (3.0)
Rash	15 (10.6)	16 (11.9)
Myalgia	8 (5.6)	18 (13.3)
Alopecia	3 (2.1)	52 (38.5)
Neuropathy peripheral	2 (1.4)	16 (11.9)
Neutropenia	2 (1.4)	17 (12.6)

MedDRA = Medical Dictionary for Regulatory Activities.

For additional information, refer to the Atezolizumab Investigator's Brochure.

1.3.2.2 Clinical Safety in Combination with Platinum-Based Doublet Chemotherapy

Study GP28328 is a Phase 1b study investigating atezolizumab in combination with chemotherapy in patients with multiple tumor types including NSCLC, triple-negative breast cancer, RCC, and colorectal cancer. Patients with NSCLC were enrolled in Arms C, D, and E of the study and received atezolizumab in combination with carboplatin-based doublet chemotherapy. As of 1 September 2015, 25 patients were enrolled in Arm C (atezolizumab + carboplatin and paclitaxel), 25 patients in Arm D (atezolizumab + carboplatin and pemetrexed), and 26 patients in Arm E (atezolizumab + carboplatin and nab-paclitaxel). The treatment combinations have been

generally well tolerated. No DLTs have been reported during the dose-escalation stage in any study arm.

All patients enrolled in Arms C and D experienced an adverse event and 95% of patients enrolled in Arm E experienced an adverse event (see Table 4). The adverse events commonly reported in 2 or more patients across these study arms included anemia, decreased appetite, hypomagnesemia, nausea, neutropenia, constipation, vomiting, fatigue, rash, cough, and diarrhea. The adverse events were consistent with the known safety profile of each agent (atezolizumab monotherapy and chemotherapy). No additive effects were observed when atezolizumab was administered with chemotherapy.

Table 4 Study GP28328: All Reported Adverse Events

Parameter	Arm C Atezolizumab + carboplatin + paclitaxel (n = 25) No. (%)	Arm D Atezolizumab + carboplatin + pemetrexed (n = 25) No. (%)	Arm E Atezolizumab + carboplatin nab-paclitaxel (n = 26) No. (%)
Any AEs	25 (100)	25 (100)	25 (96.2)
Related AEs	24 (96)	25 (100)	25 (96.2)
Grade 3–5 AEs	19 (76.0)	19 (76.0	24 (92.3)
Related Grade 3–5 AEs	18 (72.0)	13 (52.0)	23 (88.5)
Serious AEs	11 (44.0	11 (44.0)	11 (42.3
AEs leading to discontinuation of atezolizumab	1 (4.0)	1 (4.0)	1 (3.8)
AEs leading to death (Grade 5)	1 (4.0)	1 (4.0)	1 (3.8)
Related AEs leading to death (Grade 5)	1 (4.0)	1 (4.0)	0 (0)
Immune-mediated AEs	17 (68.0	13 (52.0)	14 (53.8)

AE = adverse event.

1.3.2.3 Immune-Mediated Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated adverse events have been closely monitored during the atezolizumab clinical program. These include potential dermatologic, hepatic, endocrine, gastrointestinal, and respiratory events.

Refer to the Atezolizumab Investigator's Brochure for details on immune-mediated adverse events observed in patients treated with atezolizumab.

1.3.3 Clinical Activity

Anti-tumor activity, including Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1-based responses (RECIST v1.1 responses), have been observed in patients with different tumor types treated with atezolizumab monotherapy in Study PCD4989g.

Refer to the Atezolizumab Investigator's Brochure for details on clinical activity in all patients treated to date, regardless of tumor type.

Single-agent data are summarized below from Study PCD4989g for the SCLC and NSCLC cohorts. In addition, data from the randomized Study GO28753 (POPLAR) in patients with advanced NSCLC and from the Phase Ib Study GP28328 evaluating atezolizumab plus carboplatin-based chemotherapy in patients with NSCLC, are also provided.

1.3.3.1 Single-Agent Clinical Activity in Patients with SCLC in Study PCD4989g

As of the clinical data cutoff date of 15 December 2015, 17 patients in the SCLC cohort of Study PCD4989g with a minimum follow-up of 6.7 months were evaluable for efficacy. Sixty-five percent of patients were male and 88% of the patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 1. The median age was 63 years (range 44−80 years) and patients were heavily pre-treated (65% of patients had received ≥ 3 prior therapies).

The confirmed objective response rate (ORR) by RECIST v1.1 was 6% (1 partial response [PR], with a duration of response [DOR] of 7 months). The ORR by immune-related response criteria (irRC) was 24%. Four of 17 patients received atezolizumab for ≥ 6 months (2 of these patients for ≥ 12 months). One patient with irPR stopped atezolizumab treatment per protocol after 1 year and remained in PR by immune-related response criteria for an additional 1 year until progression of disease. After retreatment, the patient again derived benefit and was still receiving atezolizumab treatment as of the data cutoff (i.e., 2.6 years after receiving the first treatment dose). Median PFS by RECIST v1.1 was 1.5 months (95% CI: 1.2, 2.7), and median OS was 5.9 months (95% CI: 4.3, 20.1). PD-L1 expression was low overall, consistent with published data.

Although the patient numbers are limited, the preliminary safety and efficacy results provide evidence of an acceptable safety profile and encouraging single-agent activity of atezolizumab in patients with SCLC based on the irRC response rate and the prolonged duration of treatment and clinical benefit experienced by a subset of patients. Furthermore, a Phase I study investigating atezolizumab in combination with carboplatin and etoposide in patients with ES-SCLC is ongoing and will also provide additional efficacy and safety data.

1.3.3.2 Single-Agent Clinical Activity in Patients with NSCLC in Study PCD4989g

As of the 2 December 2014 cutoff date, 88 patients with NSCLC in Study PCD4989g who received their first dose of atezolizumab by 21 October 2013 were evaluable for efficacy. The median age was 60.5 years; the group represented a heavily pre-treated patient population. RECIST v1.1 responses (confirmed) were observed in a total of

20 patients (20 of 88 patients; 22.7%), inclusive of squamous and non-squamous histologies and across all treatment cohorts (treatment dose levels: 1–20 mg/kg). A total of 8 of 20 responding patients have continued to respond at the time of the clinical data cutoff.

1.3.3.3 Single-Agent Clinical Activity in Patients with NSCLC in the POPLAR Study

The primary OS analysis in Study GO28753 (POPLAR) was conducted when 173 deaths had occurred (clinical cutoff: 8 May 2015). Demographic characteristics were comparable between the atezolizumab and docetaxel treatment arms in the intent-to-treat (ITT) population. The median age was 62 years in both treatment arms, and the majority of patients had one prior therapy (64.6% for atezolizumab and 67.1% for docetaxel), non-squamous histology (66.0% for atezolizumab and 66.4% for docetaxel), and ECOG performance status of 1 (67.6% for atezolizumab and 68.3% for docetaxel). More females were enrolled in the docetaxel arm (46.9% vs. 35.4%).

Atezolizumab showed significant improvement in OS compared with docetaxel in patients with advanced, previously treated NSCLC unselected for PD-L1 expression. OS in the ITT population was 12.6 months (95% CI: 9.7, 16.4) for atezolizumab versus 9.7 months (95% CI: 8.6, 12.0) for docetaxel (HR 0.73; 95% CI: 0.53, 0.99; p = 0.04). PFS was similar between groups (2.7 months with atezolizumab vs. 3.0 months with docetaxel). Objective responses with atezolizumab were durable, with a median duration of 14.3 months (95% CI: 11.6, not estimable) compared with 7.2 months (95% CI: 5.6, 12.5) for docetaxel (Fehrenbacher et al. 2016).

1.3.3.4 Clinical Efficacy in Combination with Carboplatin-Based Doublet Chemotherapy in Patients with NSCLC

As of the 10 February 2015 data cutoff, 58 patients with NSCLC were enrolled into Arm C (atezolizumab + carboplatin and paclitaxel), Arm D (atezolizumab + carboplatin and pemetrexed), and Arm E (atezolizumab + carboplatin and nab-paclitaxel) of Study GP28328. Patients who had received their first dose of atezolizumab by 10 November 2014 were evaluable for efficacy (n = 41). All patients had histologically or cytologically documented Stage IIIB, Stage IV, or recurrent NSCLC and had not received prior chemotherapy for advanced disease. For safety evaluable patients who received any amount of atezolizumab by the cutoff date, the median age was 65 years and 79% (46 of 58) of patients had non-squamous histology. The overall confirmed objective response rate per RECIST v1.1 in all three arms combined was 63% (26 of 41 patients).

Within each cohort, the ORR was 50% (95% CI: 16%, 84%) in Arm C (four PRs among 8 patients), 77% (95% CI: 50%, 93%) in Arm D (13 PRs among 17 patients), and 56% (95% CI: 30%, 80%) in Arm E (five PRs and four CRs among 16 patients). Patients with high levels of PD-L1 expression appeared to have higher response rates, but responses were also seen in patients with lower PD-L1 expression levels (Liu et al. 2015).

1.3.4 Clinical Pharmacokinetics and Immunogenicity

On the basis of available preliminary PK data (0.03–20 mg/kg) in Study PCD4989g, atezolizumab appeared to show linear pharmacokinetics at doses ≥ 1 mg/kg. For the 1-mg/kg and 20-mg/kg dose groups, the mean apparent clearance and the mean volume of distribution under steady-state conditions had a range of 3.11–4.14 mL/kg and 48.1–67.0 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

The development of anti-therapeutic antibodies (ATAs) has been observed in patients in all dose cohorts and was associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses from 10–20 mg/kg. Patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between the detection of ATAs and adverse events, infusion reactions, or efficacy has been observed.

1.3.5 Rationale for Atezolizumab Dosage

The fixed dose of 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g as described below.

The target exposure for atezolizumab was projected on the basis of nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, the observed atezolizumab interim pharmacokinetics in humans, and other factors. The target trough concentration (C_{trough}) was projected to be 6 μg/mL on the basis of several assumptions, including the following: 1) 95% tumor-receptor saturation is needed for efficacy and 2) the tumor-interstitial concentration to plasma ratio is 0.30 based on tissue distribution data in tumor-bearing mice.

The atezolizumab dose is also informed by available clinical activity, safety, pharmacokinetics, and immunogenicity data. Anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg. The MTD of atezolizumab was not reached, and no DLTs have been observed at any dose in Study PCD4989g. Currently available PK and ATA data suggest that the 15-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent) for Phase II and Phase III studies would be sufficient to both maintain $C_{trough} \geq 6$ μg/mL and further safeguard against both interpatient variability and the potential effect of ATAs that could lead to subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent). From inspection of available observed C_{trough} data, moving further to the 20-mg/kg atezolizumab q3w regimen does not appear to be warranted to maintain targeted C_{trough} levels relative to the proposed 15-mg/kg atezolizumab q3w level.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight. Therefore, a fixed dose of 1200 mg has been selected (equivalent to an average body weight–based dose of 15 mg/kg). Selection of an every-21-day dosing interval is supported by this preliminary pharmacokinetics evaluation.

Refer to the Atezolizumab Investigator's Brochure for details regarding nonclinical and clinical pharmacology of atezolizumab.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with Stage IV cancer (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

PD-L1 is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors PD-1 and B7.1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer (Blank et al. 2005; Keir et al. 2008). Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen-presenting cells can mediate downregulation of immune responses, including inhibition of T-cell activation and cytokine production (Butte et al. 2007; Yang et al. 2011).

Overexpression of PD-L1 on TCs has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

1.4.1 Rationale for Testing Atezolizumab in Combination with Carboplatin and Etoposide in ES-SCLC

Platinum-based regimens remain the standard first-line option for patients with ES-SCLC. The combination of cisplatin or carboplatin with etoposide has shown response rates ranging from 50%–70% in patients with ES-SCLC. Studies using cisplatin or carboplatin with etoposide (at various doses) have shown consistent outcomes, suggesting their efficacy is equivalent in patients with ES-SCLC, and in clinical practice, carboplatin is frequently substituted for cisplatin to reduce the risk of emesis, neuropathy, and nephropathy. The combination of carboplatin and etoposide is included in the National Cancer Comprehensive Network (NCCN) and the European Society of Medical Oncology (ESMO) guidelines (NCCN 2015; Fruh et al. 2013).

Despite the initial response rates observed with first-line chemotherapy regimens, median survival remains under a year, leaving considerable room for improvement in outcomes. TC killing by cytotoxic chemotherapy can reasonably be expected to expose the immune system to high levels of tumor antigens. Therefore, invigorating tumor-specific T-cell immunity by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007). Evaluating the safety and efficacy of these treatment combinations in patients with SCLC will enable future tests of this hypothesis.

Whole exome sequencing studies have shown that SCLC exhibits a high mutation rate (7.4 mut/Mb) compared with other tumor types, and therefore may be a highly immunogenic tumor that may potentially benefit from treatment with immune checkpoint inhibitors (Rudin et al. 2012). In addition, nearly all cases of SCLC are attributable to cigarette smoking, which has been shown to be associated with benefit from anti–PD-L1/anti–PD-1 antibodies (Borghaei et al. 2015; Garon et al. 2015).

The preliminary safety and efficacy results for atezolizumab given as monotherapy in patients with SCLC in the Phase Ia Study PCD4989g provide evidence of an acceptable safety profile and clinical activity of atezolizumab, although the patient numbers are limited. Furthermore, a Phase I/II study investigating atezolizumab in combination with carboplatin and etoposide in patients with ES-SCLC is ongoing and will provide efficacy and safety data for the combination treatment in this patient population.

Efficacy results from the POPLAR (GO28753) study demonstrated an OS benefit of single-agent atezolizumab compared to docetaxel in patients with advanced NSCLC, which is a disease that is similar to SCLC in its high mutational load, anatomical location, and association with smoking. In addition, the preliminary efficacy and safety results from the Phase Ib Study GP28328 evaluating atezolizumab in combination with platinum-based chemotherapy demonstrate an acceptable safety profile when combining atezolizumab with platinum-based doublet chemotherapy in a non–PD-L1–selected population. In this study, ORRs ranging from 50%–75% were observed in patients with NSCLC (see Section 1.3.3.4). Objective responses were seen at all levels of PD-L1 expression. No additive adverse effects were observed when atezolizumab was administered with carboplatin-based chemotherapy.

Other checkpoint inhibitors targeting the PD-L1/PD-1 pathway have shown clinical activity in patients with recurrent SCLC. In the Phase I/II CheckMate 032 study, the PD-1 inhibitor nivolumab given as monotherapy in unselected patients with SCLC whose disease progressed after at least one line of therapy, including a first-line platinum-based regimen, demonstrated an ORR (by blinded independent central review) of 10% and a median OS of 4.4 months (95% CI: 3.0, 9.3) (Antonia et al. 2016). In the Phase Ib KEYNOTE-028 study, the PD-1 inhibitor pembrolizumab showed an ORR of 35% (95% CI: 15%, 59%) in heavily pre-treated patients with ES-SCLC whose disease was PD-L1 positive (Ott et al. 2015).

In light of these observations, this study (Study GO30081; IMpower133) is designed to evaluate whether the anti-tumor effect seen in atezolizumab-treated patients would translate into statistically significant and clinically relevant improvement in PFS and OS when used in combination with carboplatin and etoposide compared with placebo, carboplatin, and etoposide in patients with chemotherapy-naive ES-SCLC. This study will allow for the evaluation of efficacy of atezolizumab in the ITT population and for the evaluation of exploratory immune endpoints such as, but not limited to a retrospective evaluation by PD-L1 expression and their association with patient outcomes.

Patients with SCLC frequently present with symptoms of widespread metastatic disease and may experience fast clinical deterioration; therefore, there is a need for rapid treatment initiation for these patients. In addition, tissue sample collection for investigational biomarker testing may be difficult in this patient population because the amount of tissue available in many cases is limited. As demonstrated in Study GP28328, objective responses were observed at all levels of PD-L1 expression when atezolizumab was added to cytotoxic chemotherapy. This study will therefore enroll patients with ES-SCLC whose disease is unselected for PD-L1 expression. Pre-treatment tumor tissue samples will be collected to allow for the analysis of immune endpoints such as, but not limited to PD-L1 expression, and patient outcomes.

This study will enroll patients with ES-SCLC who are chemotherapy-naive for their extensive-stage disease, and for whom the experimental arm can represent a valuable treatment option and a reasonable benefit-risk balance.

In order to account for the possibility of pseudoprogression/tumor-immune infiltration (i.e., radiographic increase in tumor volume due to the influx of immune cells) (Hales et al. 2010) and the potential for delayed anti-tumor activity, this study will allow patients to receive treatment beyond the initial apparent radiographic progression per RECIST v1.1 (see Section 3.3.4 and Section 4.6) and will use modified RECIST criteria (in addition to RECIST v1.1) to evaluate clinical benefit (Appendix 5).

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 should be closely monitored clinically and with a follow-up scan in 6 weeks, or sooner if symptomatic deterioration occurs. Treatment should be discontinued if clinical deterioration as a result of disease progression occurs at any time or if persistent disease growth is confirmed in a follow-up scan. In addition, patients should be discontinued for unacceptable toxicity, or for any other signs or symptoms of deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status (see Section 3.1).

Because it is not yet possible to reliably differentiate pseudoprogression/tumor-immune infiltration from true tumor progression, the risk exists that some patients who are not responding to treatment but continue to receive treatment may experience further progression of SCLC and delay treatment with subsequent therapies for which they are eligible. Patients will be fully informed of the risk of continuing study treatment in spite of apparent radiographic progression, and consent must be documented appropriately before treatment may continue. Investigators should make a careful assessment of the potential benefit of continuing study treatment beyond radiographic disease progression, considering radiographic data and the clinical status of the patient.

Atezolizumab has been generally well tolerated as a single agent and in combination with cytotoxic chemotherapy (see Section 1.3.2). Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, hypothyroidism, hyperthyroidism, adrenal insufficiency, Type 1 diabetes mellitus, pancreatitis, hepatitis, pneumonitis, colitis, meningoencephalitis, myasthenia gravis/myasthenic syndrome, and Guillain-Barré syndrome have been observed in clinical studies with atezolizumab. To date, these events have been manageable with treatment.

In summary, treatment with atezolizumab in combination with carboplatin + etoposide offers the potential for clinical benefit in patients with ES-SCLC.

1.4.2 [redacted]

[redacted]

2. OBJECTIVES

The following objective statements apply to the global enrollment phase, [redacted]

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objectives

The co-primary objectives of this study are the following:

- To evaluate the efficacy of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the ITT population as measured by investigator-assessed PFS according to RECIST v1.1
- To evaluate the efficacy of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the ITT population as measured by OS

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives for this study are:

- To evaluate the efficacy of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the ITT population as measured by investigator-assessed ORR according to RECIST v1.1
- To evaluate the efficacy of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the ITT population as measured by investigator-assessed duration of response (DOR) according to RECIST v1.1
- To evaluate the PFS rate at 6 months and at 1 year in each treatment arm for the ITT population
- To evaluate the OS rate at 1 and 2 years in each treatment arm for the ITT population
- To determine the impact of atezolizumab as measured by time to deterioration (TTD) in patient-reported lung cancer symptoms of cough, dyspnea (single-item and multi-item subscales), chest pain, arm/shoulder pain, or fatigue using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13) in patients treated with atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the ITT population

2.2 SAFETY OBJECTIVES

The safety objectives for this study are:

- To evaluate the safety and tolerability of atezolizumab in combination with carboplatin + etoposide compared with carboplatin + etoposide
- To evaluate the incidence and titers of ATAs against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the pharmacokinetics of atezolizumab, carboplatin, and etoposide in chemotherapy-naive patients with ES-SCLC.

2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are:

- To evaluate investigator-assessed PFS, ORR, and DOR modified RECIST for the atezolizumab-containing treatment arm in the ITT population
- To evaluate the relationship between tumor biomarkers (including but not limited to PD-L1, PD-1, somatic mutations, and others), as defined by immunohistochemistry (IHC) or quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR), next generation sequencing (NGS), and/or other methods and measures of efficacy
- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue, blood, plasma and serum and their association with disease status, mechanisms of resistance, and/or response to study treatment
- To evaluate and compare patient's health status as assessed by the EuroQoL 5 Dimensions 5-Level (EQ-5D-5L) questionnaire to generate utility scores for use in economic models for reimbursement
- To determine the impact of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide as measured by change from baseline in patient-reported outcomes (PRO) of health-related quality of life, lung cancer–related symptoms, physical functioning, and health status as assessed by the EORTC QLQ-C30 and LC13
- To evaluate the impact of chemotherapy (both carboplatin and etoposide) on peripheral and tumor-specific T-cell populations during and after induction therapy and its relationship to efficacy and safety outcomes

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a randomized, Phase I/III, multicenter, double-blinded, placebo-controlled study designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin + etoposide compared with treatment with placebo + carboplatin + etoposide in patients who have ES-SCLC and are chemotherapy-naive for their extensive-stage disease. Figure 1 illustrates the study design. Schedules of assessments are provided in Appendix 1 and Appendix 2.

Eligible patients will be stratified by sex (male vs. female), ECOG performance status (0 vs. 1), and presence of brain metastases (yes vs. no) and randomized 1:1 to receive one of the following treatment regimens as shown in Table 5.

Table 5 Study GO30081 Treatment Arms

Treatment Arm	Induction (Four 21-Day Cycles)	Maintenance (21-Day Cycles)
A	atezolizumab + carboplatin + etoposide	atezolizumab
B	placebo + carboplatin + etoposide	placebo

Induction treatment will be administered on a 21-day cycle for four cycles.

Following the induction phase, patients will continue maintenance therapy with either atezolizumab or placebo. During the maintenance phase, prophylactic cranial irradiation is permitted as per local standard-of-care and will be reported on the Prophylactic Cranial Irradiation electronic Case Report Form (eCRF). Thoracic radiation with curative intent or the intent to eliminate residual disease is not permitted. Palliative thoracic radiation is allowed.

Treatment should be discontinued in all patients (in both treatment arms) who exhibit evidence of disease progression per RECIST v1.1. However, to better accommodate standard clinical practice which is guided by the fact that patients with ES-SCLC whose disease progresses after first-line treatment have limited treatment options and such options have limited efficacy and significant toxicity, patients may be considered for treatment beyond radiographic disease progression per RECIST v1.1, at the discretion of the investigator and after appropriate discussion with the patient and obtaining informed consent, only if all of the following criteria are met:

- Evidence of clinical benefit as assessed by the investigator
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial progression

Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 should be closely monitored clinically and with a follow-up scan in 6 weeks or sooner if symptomatic deterioration occurs. Treatment should be discontinued if clinical deterioration due to disease progression occurs at any time, or if persistent disease growth is confirmed in a follow-up scan. In addition, patients should be discontinued for unacceptable toxicity or for any other signs or symptoms of deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status.

If clinically feasible, it is recommended that the patient undergo a tumor biopsy sample collection at the time of radiographic disease progression. These data will be used to explore whether radiographic findings are consistent with the presence of a tumor. Additionally, these data will be analyzed to evaluate the association between changes in tumor tissue and clinical outcome and to further understand the potential mechanisms of progression and resistance to atezolizumab as compared with such mechanisms after treatment with chemotherapy alone. This exploratory biomarker evaluation will not be used for any treatment-related decisions.

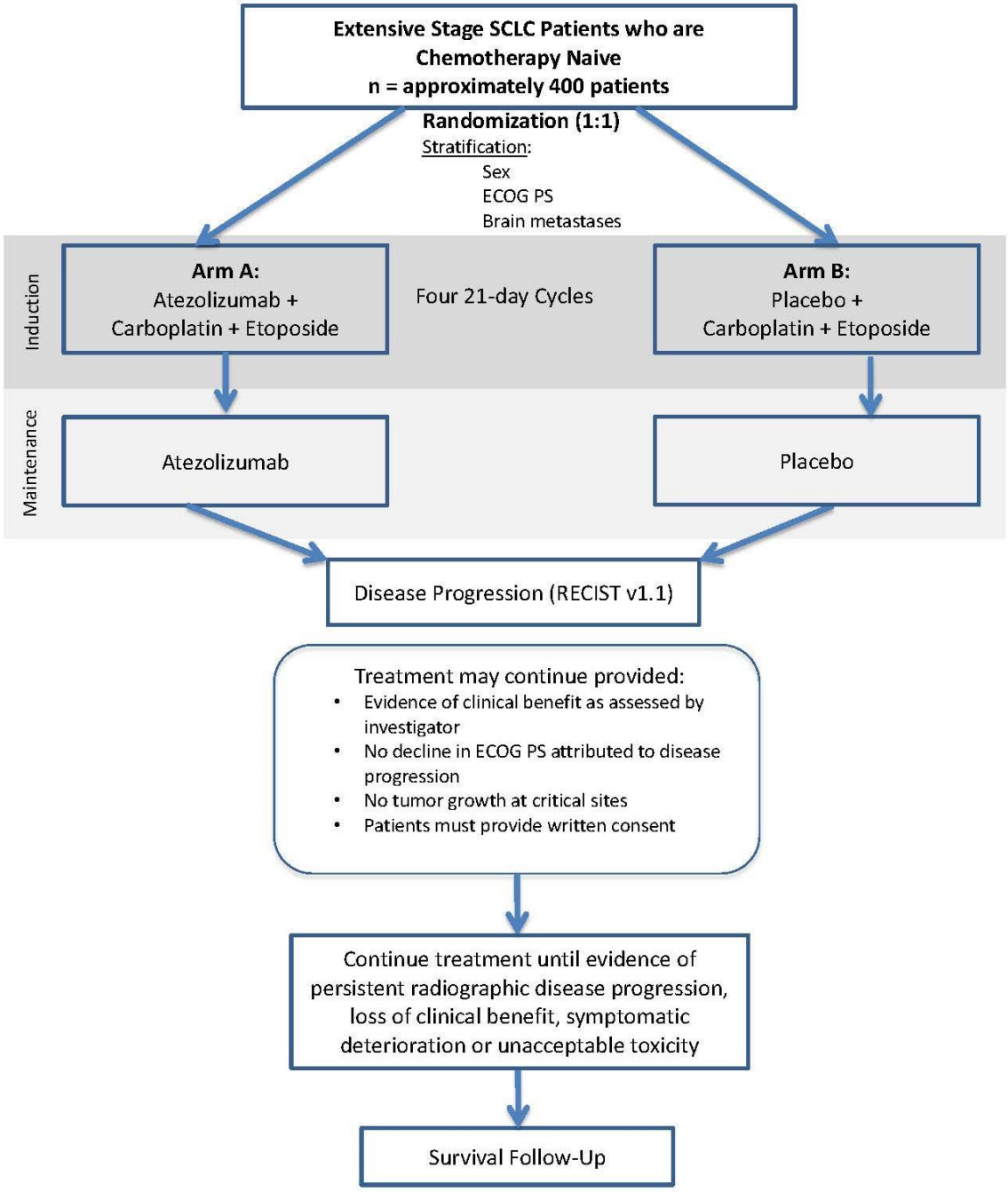
Patients will undergo tumor assessments at baseline and every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1, regardless of treatment dose delays. After completion of the Week 48 tumor assessment, tumor assessments will be required every 9 weeks (±7 days) thereafter, regardless of treatment dose delays. Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first.

Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will continue to undergo tumor assessments every 6 weeks (±7 days), or sooner if symptomatic deterioration occurs. For these patients, tumor assessments will continue every 6 weeks (±7 days), regardless of time in the study, until study treatment is discontinued.

Patients who discontinue treatment for reasons other than 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 patient had remained on study treatment (i.e., every 6 weeks [±7 days] for 48 weeks following Cycle 1, Day 1 and then every 9 weeks [± 7 days] thereafter, regardless of treatment dose delays) until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.

In case of an early termination of the study, patients who are deriving clinical benefit from treatment with atezolizumab will be permitted to continue treatment with atezolizumab at the discretion of the investigator.

Figure 1 Study Schema



ECOG PS = Eastern Cooperative Oncology Group performance status; SCLC = small cell lung cancer; RECIST = Response Evaluation Criteria in Solid Tumors.

3.1.1 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will be used to evaluate safety during the study. Unblinded safety data will be reviewed by the iDMC after a minimum of 12 patients have been enrolled into each treatment arm and have received treatment

for two cycles. Subsequently, the iDMC will review safety data approximately every 6 months.

The safety data will include disposition, demographic data, adverse events, serious adverse events, and relevant laboratory data.

The Sponsor will remain blinded to the efficacy results until the primary PFS analysis. All summaries and analyses by treatment arm for the iDMC review will be prepared by an external independent Data Coordinating Center (iDCC). Following the data review, the iDMC will provide a recommendation as to whether the study may continue, whether amendment(s) to the protocol should be implemented, or whether the study should be stopped. The final decision will rest with the Sponsor.

Members of the iDMC will be external to the Sponsor and will follow a separate iDMC Charter that outlines their roles and responsibilities, as well as a detailed monitoring plan.

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

3.2 END OF STUDY AND LENGTH OF STUDY

The end of study will occur when all of the following criteria have been met:

- The last patient last visit (LPLV) has occurred (i.e., last patient in the global [redacted]).
- Approximately *306* deaths have been observed among the randomized patients in the global enrollment phase.
- [redacted] (see Section 6.1.1).

Additionally, the Sponsor may decide to terminate the study at any time. *If the Sponsor decides to terminate the study, patients who are still receiving study treatment or undergoing survival follow-up may be enrolled in an extension study or a non-interventional study.*

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 31 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Testing Atezolizumab in Combination with Carboplatin and Etoposide in Patients with ES-SCLC

Despite the initial response rates observed with first-line chemotherapy regimens, the prognosis for patients with ES-SCLC remains dismal, with a median OS of approximately 9–11 months. There is a significant need for new agents with novel

mechanisms of action and non-overlapping toxicity, which can be combined with established treatments.

Results from Study PCD4989g provide evidence of an acceptable safety profile and encouraging single-agent activity of atezolizumab in patients with SCLC. In addition, efficacy results from the POPLAR (GO28753) study demonstrate an OS benefit of single-agent atezolizumab compared with docetaxel in patients with advanced NSCLC. In the Phase Ib Study GP28328 evaluating atezolizumab in combination with carboplatin-based chemotherapy, ORRs ranging from 50%–75% were observed in patients with NSCLC at all levels of PD-L1 expression. No additive adverse effects were observed when atezolizumab was administered with chemotherapy.

On the basis of this, Study GO30081 will evaluate atezolizumab in combination with carboplatin and etoposide for patients with ES-SCLC. TC killing by cytotoxic chemotherapy may expose the immune system to high levels of tumor antigens, and invigorating tumor-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007), and this may reasonably occur in tumors regardless of PD-L1 expression.

3.3.2 Rationale for Control Arm

The current standard-of-care in the first-line treatment for ES-SCLC is platinum-based chemotherapy plus etoposide. In this study, patients in the control arm will receive four cycles of placebo + carboplatin + etoposide, followed by placebo until disease progression per RECIST v1.1. During the maintenance phase, prophylactic cranial irradiation is permitted as per local standard-of-care. This control arm treatment is recognized as a standard-of-care for the first-line treatment of ES-SCLC (see Section 1.1).

3.3.3 Rationale for Progression-Free Survival and Overall Survival as Co-Primary Endpoints

Investigator-assessed PFS and OS are the co-primary endpoints for this study.

PFS as an endpoint can reflect tumor growth and can be assessed before the determination of a survival benefit; additionally, its determination is not generally confounded by subsequent therapies. Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends upon the magnitude of the effect and the benefit-risk of the new treatment compared with available therapies (Guidance for Industry 2007; European Medicines Agency 2012). The PFS HR that will be targeted in the ITT population constitutes a clinically meaningful benefit in this patient population.

To ensure the validity of investigator-assessed PFS as the primary endpoint, a number of measures have been implemented: a substantial target magnitude of benefit and

study assessments that will allow a robust evaluation of benefit-risk (conventional RECIST v1.1 criteria to define radiographic disease progression with fixed assessment intervals that are identical in both treatment arms and a robust definition of PFS and prospectively-defined methods to assess, quantify, and analyze PFS, including sensitivity analyses).

OS is a co-primary endpoint in this study. Improvement in OS is generally accepted as the best measure of clinical benefit for patients with advanced/unresectable or metastatic lung cancer. In the randomized Phase II Study GO28753 (POPLAR) in patients with advanced NSCLC, an OS benefit in the atezolizumab arm was observed compared with the docetaxel arm (Fehrenbacher et al. 2016).

New treatment modalities, such as targeted therapies and immunotherapy, are emerging as highly effective regimens that are providing improvements in patient outcomes beyond what has been previously achieved (Ellis et al. 2014). In particular, immunotherapy has been correlated or associated with durable responses, prolongation of OS, and improvement of quality of life.

3.3.4 Rationale for Allowing Selected Patients to Continue Treatment beyond Radiographic Disease Progression per RECIST v1.1

Patients with ES-SCLC experience rapid tumor growth, fast clinical deterioration, and have an overall poor prognosis. First-line therapy with a platinum agent and etoposide has consistently demonstrated high response rates and significant clinical benefit. However, after disease progression, treatment options are limited and such options have shown limited efficacy and significant toxicity (see Section 1.1.1). Given that the highest opportunity to achieve a clinically significant benefit from therapy is in the front-line setting and given the poor efficacy and high toxicity profile of second-line therapies, patients may be considered for treatment beyond radiographic disease progression per RECIST v1.1 at the discretion of the investigator and after appropriate discussion with the patient and obtaining informed consent, only if they meet all of the criteria described in Section 3.1.

In addition, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Because of the potential for pseudoprogression/tumor-immune infiltration, this study will allow patients to remain on treatment after apparent radiographic disease progression per RECIST v1.1, provided all criteria in Section 3.1 are met. Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 should be closely monitored clinically and with a follow-up scan in 6 weeks, or sooner if symptomatic deterioration occurs. Treatment should be discontinued if clinical deterioration due to disease progression occurs at any time or if persistent disease growth is confirmed in a follow-up scan. In addition, patients should be discontinued for unacceptable toxicity or for any other signs or symptoms of

deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status (see Section 3.1).

3.3.5 Rationale for Patient-Reported Outcome Assessments

In the treatment of lung cancer, it is important to both increase survival and palliate symptoms because disease symptoms have negative impacts on health-related quality of life (HRQoL) (Hyde and Hyde 1974; Hopwood and Stephens 1995; Sarna et al. 2004). This is especially true for studies that have PFS as a primary endpoint, where it is important to better understand in what regard the delay in disease progression is meaningful to patients.

Chest pain, dyspnea, and cough have been regarded as the most frequent and clinically relevant disease-related symptoms experienced by patients with lung cancer. The BR.21 study (erlotinib vs. best supportive care in second- or third-line NSCLC) demonstrated that longer TTD in the pain, dyspnea, and cough scales of the EORTC QLQ-C30 and EORTC QLQ-LC13 was consistent with superior PFS, OS, and quality-of-life benefits in the erlotinib arm compared with the placebo arm (Aaronson et al. 1993; Bergman et al. 1994; Bezjak et al. 2006). Patients in the afatinib LUX-Lung first-line study also reported significant delay of TTD in lung cancer symptoms (chest pain, dyspnea, and cough) as measured by the EORTC QLQ-C30 and EORTC QLQ-LC13 (Yang et al. 2013).

In this study, the validated EORTC QLQ-C30 and EORTC QLQ-LC13 will be used to assess HRQoL, physical functioning, and symptom severity.

The EQ-5D-5L (see Appendix 8) is also included in this study to generate utility scores for use in economic models for reimbursement. Results from the EQ-5D-5L are not planned to be used for market authorization.

3.3.6 Rationale for Collection of Archival and/or Fresh Tumor Specimens

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PDL-1/anti–PD-1 therapy (Herbst et al. 2014; Topalian et al. 2012). This correlation was also observed with atezolizumab in Study PCD4989g and Study GO28753 (POPLAR) (Horn et al. 2015; Spira et al. 2015).

This study will allow for the evaluation of the efficacy of atezolizumab in the ITT population, as well as an exploratory analysis of the efficacy of atezolizumab in patients with PD-L1–expressing tumors (defined by expression of PD-L1 in TCs and/or tumor-infiltrating immune cells [ICs]). Therefore, in this study, pre-treatment archival and/or fresh tumor specimens must be submitted.

The assessment of other exploratory biomarkers as potential predictive and prognostic markers related to the clinical benefit and safety of atezolizumab, tumor immunobiology,

mechanisms of resistance, or tumor type, may also be analyzed. DNA, RNA, or other biological molecules may be extracted and analyzed to increase understanding of disease pathobiology.

3.3.7 Rationale for Blood Biomarker Assessments

An exploratory objective of this study is to evaluate blood-based biomarkers including plasma, serum, whole blood, and extracts thereof. Evaluation of blood biomarkers may provide evidence for biologic activity of atezolizumab in patients with SCLC and may allow for the development of blood-based biomarkers to help predict which patients may benefit from atezolizumab. These samples may also be used to evaluate the effects, if any, of chemotherapy on T cells, other immune cells, or related constituents of peripheral blood.

In addition, potential correlations of these biomarkers with the safety and activity of atezolizumab may be explored.

3.3.8 Rationale for the Collection of Tumor Specimens at Radiographic Progression

Anti-tumor immune responses, such as those associated with atezolizumab, may result in objective responses that are delayed and can be preceded by initial apparent radiographic progression. This initial apparent progression may occur as a result of either delayed anti-tumor activity and/or robust immune infiltration of the tumor with a concomitant increase in tumor size. In addition, lesions that would otherwise be undetectable with conventional imaging (i.e., micrometastatic disease) may increase in size as a result of these processes and be recorded as new lesions (Hales et al. 2010).

If clinically feasible, it is recommended that a tumor biopsy be performed at the time of radiographic progression in order to better understand the biological changes that drive the increase in size of the radiographically progressing lesion. In addition, mechanisms relating to progression, resistance, predictive, prognostic, and pharmacodynamic relationships in tumor biomarkers (including but not limited to PD-L1, CD8, mutation status, and others) and their efficacy will be evaluated. DNA and/or RNA extraction may be performed to enable NGS to identify somatic mutations that are associated with disease progression or acquired resistance to atezolizumab and to increase understanding of disease pathobiology.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

3.4.1.1 Primary Efficacy Outcome Measures

The primary efficacy outcome measures for this study are:

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first.

- OS, defined as the time from randomization to death from any cause.

3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are:

- Objective response, defined as PR or CR as determined by the investigator according to RECIST v1.1
- DOR, defined as the time interval from first occurrence of a documented objective response to the time of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever comes first
- PFS rates at 6 months and at 1 year
- OS rates at 1 and 2 years
- TTD in patient-reported lung cancer symptoms, defined as time from randomization to deterioration (10-point change) on each of the EORTC QLQ-C30 and EORTC QLQ-LC13 symptom subscales maintained for two assessments or one assessment followed by death from any cause within 3 weeks

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are:

- Incidence, nature, and severity of adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0
- Changes in vital signs, physical findings, and clinical laboratory results during and following study treatment administration
- Incidence of ATA response to atezolizumab and potential correlation with PK, pharmacodynamic, safety, and efficacy parameters

3.4.3 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are:

- Maximum observed serum atezolizumab concentration (C_{max}) after infusion
- Minimum observed serum atezolizumab concentration (C_{min}) prior to infusion at selected cycles, at treatment discontinuation, and at 120 days ($\pm$30 days) after the last dose of atezolizumab
- Plasma concentrations for carboplatin
- Plasma concentrations for etoposide

See Appendix 2 for specific sample collection times.

3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are:

- Objective response, PFS, and DOR as determined by the investigator according to modified RECIST

- Status of PD-L1-, immune-, and SCLC-related and other exploratory biomarkers in archival and/or freshly obtained tumor tissues, and blood (or blood derivatives) collected before, during, or after treatment with atezolizumab or at progression and association with disease status and/or response to atezolizumab
- Utility scores of the EQ-5D-5L
- Change from baseline in PROs of health-related quality of life, lung cancer–related symptoms, physical functioning, and health status as assessed by the EORTC QLQ-C30 and QLQ-LC13
- Changes in levels and type of peripheral and tumor-specific T-cell populations during and after induction therapy and its relationship to efficacy and safety outcomes

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients may be eligible if they are chemotherapy-naive and have ES-SCLC.

4.1.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry:

- Signed Informed Consent Form
- Male or female, 18 years of age or older
- ECOG performance status of 0 or 1 (see Appendix 9)
- Histologically or cytologically confirmed ES-SCLC (per the Veterans Administration Lung Study Group (VALG) staging system; (Micke et al. 2002; Appendix 3)
- No prior systemic treatment for ES-SCLC
- Patients who have received prior chemoradiotherapy for limited-stage SCLC must have been treated with curative intent and experienced a treatment-free interval of at least 6 months since last chemotherapy, radiotherapy, or chemoradiotherapy cycle from diagnosis of extensive-stage SCLC
- Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:

    Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)

    No ongoing requirement for corticosteroids as therapy for CNS disease

    No evidence of interim progression between the completion of CNS-directed therapy and randomization

    Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to randomization, if all other criteria are met.

- Measurable disease, as defined by RECIST v1.1

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

- Adequate hematologic and end organ function, defined by the following laboratory test results obtained within 14 days prior to randomization:

  ANC ≥ 1500 cells/μL without granulocyte colony-stimulating factor support

  Lymphocyte count $\geq 500/\mu L$

  Platelet count $\geq 100{,}000/\mu L$ without transfusion

  Hemoglobin ≥ 9.0 g/dL

  Patients may be transfused to meet this criterion.

  INR or aPTT $\leq 1.5 \times$ upper limit of normal (ULN)

  This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.

  AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ ULN, with the following exceptions:

  Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN

  Patients with documented liver or bone metastases: alkaline phosphatase $\leq 5 \times$ ULN.

  Serum bilirubin $\leq 1.25 \times$ ULN

  Patients with known Gilbert disease who have serum bilirubin level $\leq 3 \times$ ULN may be enrolled.

  Serum creatinine $\leq 1.5 \times$ ULN

- Patients must submit a pre-treatment tumor tissue sample. Any available tumor tissue sample can be submitted. The tissue sample should be submitted before or within 4 weeks after randomization; however, patients may be enrolled into the study before the pre-treatment tumor tissue sample is submitted.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 5 months after the last dose of study treatment.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of 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 study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during treatment with chemotherapy (i.e., carboplatin and etoposide) and for at least 6 months after the last dose of chemotherapy to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- [redacted]

4.1.2 Exclusion Criteria

Patients who meet any of the criteria below will be excluded from study entry:

- Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments
- 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 $\geq$1 week prior to randomization
- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed regardless of drainage frequency.

- Uncontrolled or symptomatic hypercalcemia

  Patients who are receiving denosumab prior to randomization must be willing and eligible to discontinue its use and replace it with a bisphosphonate while in the study.

- Malignancies other than SCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS $>$90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous-cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)

- Women who are pregnant, lactating, or intending to become pregnant during the study
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 11 for a more comprehensive list of autoimmune diseases)

    Patients with a history of autoimmune-related hypothyroidism on thyroid replacement hormone therapy are eligible.

    Patients with controlled Type I diabetes mellitus on an insulin regimen are eligible.

    Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are eligible for the study provided that they meet the following conditions:

        Rash must cover less than 10% of body surface area

        Disease is well controlled at baseline and only requires low potency topical steroids

        No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency, or oral steroids)
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

    History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive test result for HIV

    All patients must be tested for HIV; patients who test positive for HIV will be excluded.
- Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test result at screening) or hepatitis C virus (HCV)

    Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible. HBV DNA should be obtained in these patients prior to randomization.

    Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
- Active tuberculosis

- Severe infections at the time of randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to randomization, unstable arrhythmias, or unstable angina

  Patients 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.
- Major surgical procedure other than for diagnosis within 28 days prior to randomization or anticipation of need for a major surgical procedure during the course of the study
- Prior allogeneic bone marrow transplantation or solid organ transplant
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk for treatment complications
- Patients with illnesses or conditions that interfere with their capacity to understand, follow, and/or comply with study procedures
- Treatment with any other investigational agent with therapeutic intent within 28 days prior to randomization
- Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation that such a live attenuated vaccine will be required during the study

  Patients must not receive live, attenuated influenza vaccines (e.g., FluMist®) within 4 weeks prior to randomization, during treatment, and for 5 months following the last dose of atezolizumab/placebo.
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunosuppressive medications (including, but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [anti-TNF] agents) within 1 week prior to randomization

  Patients who have received acute systemic immunosuppressant medications (e.g., use of corticosteroids for nausea, vomiting, or management of or premedication for allergic reactions) may be enrolled in the study after discussion with and approval by the Medical Monitor. In those patients, the need and length of the washout period prior to randomization will also be established in conjunction with the Medical Monitor.

  The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of allergic reactions to carboplatin or etoposide

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a randomized, double-blind, placebo-controlled study.

After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established, the study site will obtain the patient's identification number and treatment assignment from the interactive voice or Web response system (IxRS) for eligible patients.

Randomization will occur in a 1:1 ratio using a permuted-block randomization method. Patients will be randomized to one of two treatment arms: A) atezolizumab + carboplatin + etoposide or B) placebo + carboplatin + etoposide. The randomization scheme is designed to ensure that an approximately equal number of patients will be enrolled in each treatment arm within the baseline characteristics of the following stratification factors:

- Sex (male vs. female)
- ECOG performance status (0 vs. 1)
- Presence of brain metastases (yes vs. no)

Patients should receive their first dose of study drug on the day of randomization if possible. If this is not possible, the first dose should occur within 5 days after randomization.

The Sponsor and its agents (with the exception of the IxRS service provider [the external independent statistical coordinating center responsible for verifying patient randomization and study treatment kit assignments], PK/pharmacodynamic laboratory personnel, and the iDMC members); the study site personnel, including the investigator; and the patient will be blinded to treatment assignment (see Sections 4.2.1 and 4.2.2).

While PK and ATA samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ATA assay results for atezolizumab in these patients are generally not needed for the safe conduct or proper interpretation of this study. Sponsor personnel responsible for performing PK and ATA assays will be unblinded to patients' treatment assignment to identify appropriate samples to be analyzed. Samples from patients assigned to the comparator arm will not be analyzed for atezolizumab concentration except by request (e.g., to evaluate a possible error in dosing). Atezolizumab ATA samples collected on Day 1 of Cycle 1 may

be analyzed for all patients, while subsequent samples from patients assigned to the comparator arm will not be analyzed for ATA unless requested.

[redacted]

4.2.1 Unblinding at the Patient Level

4.2.1.1 Emergency Unblinding

Study treatment assignment may be unblinded for serious, unexpected study drug–related toxicity (as part of the Investigational New Drug [IND] application safety reporting process).

If unblinding is necessary for patient management in the case of an adverse event for which patient management might be affected by knowledge of treatment assignment, the investigator will be able to break the treatment code via the IxRS. Emergency unblinding should be a last resort performed only in cases where knowledge of treatment assignment will affect ongoing treatment of the toxicity. Investigators are encouraged to consult with the Medical Monitor prior to performing emergency unblinding. The reason and date of unblinding should be documented in the electronic data capture (EDC) system.

4.2.2 Unblinding at the Study Level

For regulatory reporting purposes, if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected adverse reactions that are considered by the investigator or Sponsor to be related to study drug.

Treatment assignment will be unblinded to the Sponsor at the time of the primary analysis of PFS.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab and Placebo

For information on the formulation, packaging, and handling of atezolizumab and placebo, refer to the Atezolizumab Pharmacy Manual and Investigator's Brochure.

Atezolizumab and placebo will be supplied by the Sponsor.

4.3.1.2 Carboplatin and Etoposide

Carboplatin and etoposide are background treatment and are considered non-investigational medicinal products (NIMPs). Carboplatin and etoposide will be used in the commercially available formulation.

For information on the formulation, packaging, and handling of carboplatin and etoposide, refer to the prescribing information for each drug.

4.3.2 Dosage, Administration, and Compliance

The induction phase of the study will consist of four cycles of atezolizumab/placebo plus chemotherapy, with each cycle being 21 days in duration. On Day 1 of each cycle, all eligible patients will be administered study drug infusions in the following order:

Arm A: atezolizumab → carboplatin → etoposide

Arm B: placebo → carboplatin → etoposide

For Cycle 1, premedication administered for atezolizumab/placebo is not permitted. Patients should receive anti-emetics and IV hydration for carboplatin and etoposide according to the local standard-of-care and manufacturer's instruction. However, because of the immunomodulatory effects of steroids, premedication with steroids should be minimized to the extent that is clinically feasible (see Section 4.4.2). All medications must be recorded on the appropriate Concomitant Medications eCRF.

During the induction phase, study treatment should be administered in the following manner on Day 1:

1. Atezolizumab/placebo administered intravenously over 60 (±15) minutes (for the first infusion and shortening to 30 [±10] minutes for subsequent infusions) (see Table 6), followed by
2. Carboplatin administered intravenously over 30–60 minutes to achieve an initial target area under the concentration–time curve (AUC) of 5 mg/mL/min (Calvert formula dosing), followed by
3. Etoposide (100 mg/m^2) administered intravenously over 60 minutes

During the induction phase, etoposide (100 mg/m^2) will be administered intravenously over 60 minutes on Days 2 and 3.

Cycles in which no chemotherapy is given do not count toward the total number of induction chemotherapy cycles.

After the induction phase, patients will begin maintenance therapy with atezolizumab/placebo.

During treatment (induction or maintenance), upon radiographic disease progression per RECIST v1.1, patients may be considered for treatment beyond radiographic disease progression per RECIST v1.1, provided all criteria specified in Section 3.1 are met.

The suggested infusion times for carboplatin and etoposide may be adapted in accordance with local standard-of-care.

For patients undergoing additional PK assessments for carboplatin and etoposide, refer to Appendix 2 for the schedule of PK sampling.

Guidelines for dose modification and treatment interruption or discontinuation for carboplatin and etoposide are provided in Sections 5.1.5.1 and Section 5.1.7.

4.3.2.1 Atezolizumab/Placebo

Patients will receive atezolizumab/placebo 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered by IV infusion every 21 (±3) days in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions.

Atezolizumab/placebo infusions will be administered per the instructions outlined in Table 6.

Table 6 Administration of First and Subsequent Infusions of Atezolizumab/Placebo

First Infusion	Subsequent Infusions
• No premedication is allowed. • Record patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • Infuse atezolizumab/placebo (1200 mg in a 250 mL 0.9% NaCl intravenous infusion bag) over 60 (±15) minutes. • If clinically indicated, record patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) during the infusion at 15, 30, 45, and 60 minutes (±5-minute windows are allowed for all time points). • If clinically indicated, record patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) at 30 (± 10) minutes after the infusion. • Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction during any previous infusion, premedication with antihistamines may be administered for Cycles ≥2 at the discretion of the treating physician. • Record patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • If the patient tolerated the first infusion well, without infusion-associated adverse events, the second infusion may be administered over 30 (±10) minutes. • If no reaction occurs, subsequent infusions may be administered over 30 (± 10) minutes. Continue to record vital signs within 60 minutes before starting infusion. Record vital signs during and after the infusion if clinically indicated. • If the patient had an infusion-related reaction during the previous infusion, the subsequent infusion must be administered over 60 (±15) minutes. Record patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) during the infusion if clinically indicated or if patient experienced symptoms during the previous infusion. Record patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) 30 (± 10) minutes after the infusion if clinically indicated or if patient experienced symptoms during previous infusion.

NaCl = sodium chloride.

Dose modifications to atezolizumab/placebo are not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events are provided in Sections 5.1.5.2 and 5.1.6.

Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

4.3.2.2 Carboplatin + Etoposide

Carboplatin

Carboplatin will be administered after completion of atezolizumab/placebo by IV infusion over 30–60 minutes to achieve an initial target AUC of 5 mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines. Because the effects of corticosteroids on T-cell proliferation have the potential to attenuate atezolizumab-mediated anti-tumor immune activity, premedication with corticosteroids should be minimized to the extent that is clinically feasible (see Section 4.4.2). Carboplatin infusion times may be adapted in accordance with local standard-of-care.

The carboplatin dose of AUC 5 will be calculated using the Calvert formula (Calvert et al. 1989):

Calvert Formula

Total dose (mg) = (target AUC) × (glomerular filtration rate [GFR] + 25)

NOTE: The GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min.

For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance (CRCL). The CRCL is calculated by institutional guidelines or by the method of Cockcroft and Gault (1976) using the following formula:

$$\text{CRCL} = \frac{(140 - \text{age})\ (\text{wt})}{72 \times \text{Scr}}\ (\times 0.85 \text{ if female})$$

Where: CRCL = creatinine clearance in mL/min
age = patient's age in years
wt = patient's weight in kg
Scr = serum creatinine in mg/dL

NOTE: For patients with an abnormally low serum creatinine level, estimate the GFR through use of a minimum creatinine level of 0.8 mg/dL or cap the estimated GFR at 125 mL/min.

If a patient's GFR is estimated based on serum creatinine measurements by the isotope dilution mass spectroscopy method, the FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. On the basis of the Calvert formula described in the carboplatin label, the maximum doses can be calculated as follows:

Maximum carboplatin dose (mg) = target AUC (mg × min/mL) × (GFR + 25 mL/min)

The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC = 5, the maximum dose is $5 \times 150 = 750$ mg.
For a target AUC = 4, the maximum dose is $4 \times 150 = 600$ mg.

Refer to the FDA's communication regarding carboplatin dosing with use of the following Web site for more details:

http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm228974.htm

Etoposide

During the induction phase, on Day 1 of each cycle, etoposide (100 mg/m^2) will be administered by IV infusion over 60 minutes following carboplatin administration. On Days 2 and 3 of each cycle, etoposide (100 mg/m^2) will be administered by IV infusion over 60 minutes. Premedication should be administered according to local standard-of-care. Because the effects of corticosteroids on T-cell proliferation have the potential to attenuate atezolizumab-mediated anti-tumor immune activity, premedication with corticosteroids should be minimized to the extent that is clinically feasible (see Section 4.4.2). Etoposide infusion times may be adapted in accordance with local standard-of-care.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab/placebo) will be provided by the Sponsor where required by local health authorities. The study site will acknowledge receipt of the IMPs using IxRS to confirm shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any 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 Inventory Log.

4.3.4 Post-Study Access to Atezolizumab

The Sponsor will evaluate the appropriateness of continuing to provide atezolizumab to patients assigned to this treatment after evaluating the primary and secondary efficacy outcome measures and safety data gathered in the study and in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

These analyses may be conducted prior to completion of the study.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening until the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Premedication with antihistamines may be administered for any atezolizumab/placebo infusions after Cycle 1.

The following therapies should continue while patients are in the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin or warfarin at a stable dose level)
- Palliative radiotherapy (e.g., treatment of known bony metastases) provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion being irradiated is not the only site of disease, as that would render the patient not evaluable for response by tumor assessments according to RECIST v1.1)

  It is not a requirement to withhold atezolizumab/placebo during palliative radiotherapy
- Inactive influenza vaccinations
- Megestrol administered as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)
- Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency

In general, investigators should manage a patient's care with supportive therapies as clinically indicated per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist per standard practice (for sites outside the United States, equivalent medications may be substituted per local 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 10).

All concomitant medications must be recorded on the appropriate Concomitant Medications eCRF.

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations where systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered first by the treating physician. If the alternatives are not clinically appropriate, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the treating physician except in the case of patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance) (see also Section 4.4.3).

Systemic corticosteroids are recommended, with caution, at the discretion of the treating physician, for the treatment of specific adverse events when associated with atezolizumab therapy.

Refer to *Appendix 12* for additional information on the management of adverse events *associated with atezolizumab*.

4.4.3 Prohibited Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the anti-cancer agent (see Section 4.1.2), and during study treatment until disease progression is documented and the patient has discontinued study treatment. This includes, but is not limited to chemotherapy, hormonal therapy, immunotherapy, radiotherapy, non-approved experimental agents, or herbal therapy (unless otherwise noted).

The following medications are prohibited while in the study, unless otherwise noted:

- Denosumab; patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead
- Any live, attenuated vaccine (e.g., FluMist®) within 4 weeks prior to randomization, during treatment, and for 5 months following the last dose of atezolizumab/placebo
- Use of steroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance); in such patients, non-contrast CT scans of the chest and non-contrast CT scans or MRIs of the abdomen and pelvis should be performed

The concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, their use for patients in the study is allowed at the discretion of the

investigator, provided that there are no known interactions with any study treatment. As noted above, herbal therapies intended for the treatment of cancer are prohibited.

4.5 STUDY ASSESSMENTS

The schedules of study assessments are provided in Appendix 1 and Appendix 2.

Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Patients who show radiographic disease progression per RECIST v1.1 may be considered for treatment beyond radiographic disease progression, provided all criteria specified in Section 3.1 are met, and patients must sign consent at that time to acknowledge deferring other treatment options in favor of continuing study treatment.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit.

SCLC cancer history will include prior cancer therapies and procedures.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at

baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of pulse rate, respiratory rate, and systolic and diastolic blood pressures while the patient is in a seated position and temperature.

Vital signs will be measured and recorded at screening and as described in Table 7.

Table 7 Vital Sign Measurements at Cycle 1 and All Subsequent Cycles

Cycle 1	
Treatment Arm	Timepoints
Arms A and B	• Within 60 minutes prior to atezolizumab/placebo infusion • During the atezolizumab/placebo infusion (every 15 [±5] minutes) and within 30 (±10) minutes after atezolizumab/placebo infusion, if clinically indicated • During the carboplatin and etoposide infusions and within 30 (±10) minutes after etoposide infusion, if clinically indicated
Subsequent Cycles	
Treatment Arm	Timepoints
Arms A and B	• Within 60 minutes prior to atezolizumab/placebo infusion • During and within 30 (±10) minutes after atezolizumab/placebo infusion if clinically indicated or symptoms occurred during the prior infusion • During the carboplatin and etoposide infusions and within 30 (±10) minutes after etoposide infusion if clinically indicated or if symptoms occurred during the prior infusion

4.5.5 Tumor and Response Evaluations

Screening assessments must include CT scans (with oral/IV contrast unless contraindicated) or MRIs of the chest and abdomen. A CT or MRI scan of the pelvis is required at screening and as clinically indicated or as per local standard-of-care at subsequent response evaluations. A spiral CT scan of the chest may be obtained but is not a requirement.

A CT (with contrast if not contraindicated) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients. An MRI scan of the brain is

required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. Patients with active or untreated CNS metastases are not eligible for the study (see Section 4.1.2).

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.

Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

Tumor assessments performed as standard-of-care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Response will be assessed by the investigator using RECIST v1.1 (see Appendix 4) and modified RECIST criteria (see Appendix 5). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

Patients will undergo tumor assessments at baseline and every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1, regardless of treatment dose delays. After completion of the Week 48 tumor assessment, tumor assessments will be required every 9 weeks (±7 days) thereafter, regardless of treatment dose delays. Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first. Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will continue to undergo tumor assessments every 6 weeks (±7 days), or sooner if symptomatic deterioration occurs. For these patients, tumor assessments will continue every 6 weeks (±7 days) regardless of time in the study, until study treatment is discontinued.

Patients who discontinue treatment for reasons other than 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 patient had remained on study treatment (i.e., every 6 weeks [±7 days] for 48 weeks following Cycle 1, Day 1 and then every 9 weeks [±7 days] thereafter, regardless of treatment dose delays) until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.

4.5.6 Laboratory Assessments and Biomarker Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistries (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total CO_2 if considered standard of care in the region, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin)
- Coagulation (aPTT or INR)
- Serum pregnancy test for women of childbearing potential, including women who have had a tubal ligation; urine pregnancy tests will be performed at Day 1 of each cycle during treatment prior to administration of study treatment. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

  Childbearing potential is defined as not having undergone surgical sterilization, hysterectomy, and/or bilateral oophorectomy or not being postmenopausal ($\geq$12 months of amenorrhea).
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood); dipstick permitted
- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4)

  Total T3 will be tested only at sites where free T3 is not performed.
- HBV serology: HBsAg, antibodies against HBsAg, total HBcAb

  HBV DNA should be obtained prior to randomization if the patient has a negative serology for HbsAg and a positive serology for HBcAb
- HCV serology: HCV antibody (anti-HCV)

  HCV RNA must be obtained prior to randomization if patient tests positive for anti-HCV
- HIV testing

  All patients will be tested for HIV prior to inclusion into the study and HIV-positive patients will be excluded from the study

A central laboratory will coordinate the sample collection of tissue and blood samples for research-related testing at central laboratories or at the Sponsor. Instruction manuals and supply kits will be provided for all central laboratory assessments. Samples for the following laboratory tests will be sent to one or several central laboratories or to the Sponsor for analysis:

- ATA assays

Serum samples will be assayed for the presence of ATAs to atezolizumab with use of validated immunoassays. Accompanying PK samples will be collected at the same timepoints.

- PK assays

  Blood samples for PK assessments will be obtained according to the schedule in Appendix 2.

  Serum samples will be assayed for atezolizumab concentration with use of a validated immunoassay.

  At select sites, a subset of approximately 40 patients will undergo additional PK assessments for carboplatin and etoposide.

  Plasma carboplatin and etoposide concentrations will be assayed using validated methods.

- Biomarker assays in blood samples

  Blood samples will be obtained for biomarker evaluation (including, but not limited to biomarkers that are related to SCLC or tumor immune biology) from all eligible patients according to the schedule in Appendix 1 and Appendix 2. Samples will be processed to obtain plasma and serum for the determination of changes in blood-based biomarkers (e.g., circulating tumor DNA). Whole blood samples may be processed to obtain their derivatives (e.g., RNA, DNA, and other biological molecules) and evaluated for immune-related, tumor type–related, and other exploratory biomarkers (e.g., alterations in gene expression or single nucleotide polymorphisms).

- For patients who consent to the optional collection of samples for the Roche Clinical Repository (RCR), any leftover material from the above sample collection will be stored and used for exploratory analyses as indicated in Section 4.5.11.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed 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.

4.5.7 Tumor Tissue Samples

4.5.7.1 Archival and Freshly Collected Tumor Tissue Samples

Patients may enroll into the study before submitting a pre-treatment tumor tissue sample. A pre-treatment tumor tissue (archival or freshly obtained) sample should be submitted before or within 4 weeks after randomization.

This specimen must be accompanied by the associated pathology report. Although any available tumor tissue sample can be submitted, it is strongly encouraged that representative tumor specimens in paraffin blocks (preferred) or 10 (or more) serial, freshly cut, unstained slides be submitted for exploratory biomarker analysis (including, but not limited to PD-L1 status, markers related to immune- or SCLC-biology such as

T-cell markers or non-inherited biomarkers identified through NGS on extracted DNA, RNA, or other biological molecules).

Preferred sample types include:

- Formalin-fixed paraffin-embedded (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]) is acceptable.

Tumor tissue should be of good quality based on total and viable tumor content. Tumor tissue from bone metastases that is subject to decalcification is not advisable.

For archival samples, the remaining tumor tissue block for all patients enrolled will be returned to the site upon request or 18 months after final closure of the study database, whichever is sooner. Tissue samples from patients who are deemed ineligible to enroll into the study will be returned no later than 6 weeks after eligibility determination.

NGS may be performed by Foundation Medicine on evaluable pre-treatment tissue (e.g., with adequate tumor content) if requested by the investigator. If performed by Foundation Medicine, the investigator can obtain results from the pre-treatment samples in the form of an NGS report, which is available upon request directly from Foundation Medicine. The investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions.

4.5.7.2 Optional Tumor Samples after Completion of Induction Treatment

If clinically feasible, and if the patient signs the Optional Biopsy Consent, an optional tumor biopsy after the completion of induction treatment may be obtained. 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]) is acceptable.

The status of immune-related, tumor type–related, and other exploratory biomarkers (including, but not limited to T-cell markers and non-inherited biomarkers on fixed tissue identified through NGS on extracted DNA and/or RNA or identified through other methods on extracted DNA, RNA, or other biological molecules) in tumor tissue samples may be evaluated.

NGS may be performed by Foundation Medicine on evaluable tissue (e.g., with adequate tumor content) if requested by the investigator. If performed by Foundation Medicine, the investigator can obtain results from the post-induction treatment samples in the form of an NGS report, which is available upon request directly from Foundation

Medicine. The investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions.

4.5.7.3 Optional Tumor Samples at the Time of Radiographic Progression

If clinically feasible, and if the patient signs the Optional Biopsy Consent, it is recommended that a tumor biopsy be performed to obtain a tumor sample at the time of radiographic disease progression (preferably within 40 days of 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]) is acceptable.

The status of immune-related, tumor type–related and other exploratory biomarkers (including but not limited to T-cell markers and non-inherited biomarkers identified through NGS on extracted DNA and/or RNA) in tumor tissue samples may be evaluated.

NGS may be performed by Foundation Medicine on evaluable tissue (e.g., with adequate tumor content) if requested by the investigator. If performed by Foundation Medicine, the investigator can obtain results from the disease progression samples in the form of an NGS report, which is available upon request directly from Foundation Medicine. The investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions.

4.5.7.4 Tumor Samples at Other Timepoints

If a patient undergoes a medically indicated procedure (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) any time during the course of the study that has the likelihood of yielding tumor tissue, any remaining samples or a portion of the sample not necessary for medical diagnosis (leftover tumor tissue) may be obtained for exploratory analysis.

Patients with additional tissue samples from procedures performed at different times during the course of their study participation (during treatment and during survival follow-up) who have signed the RCR optional consent will be requested (but not required) to also submit these optional fresh tumor biopsy samples for central testing. Tumor tissue samples collected at the time of clinical events (e.g., clinical response, etc.) are preferred. Tissue samples obtained at multiple times for individual patients will greatly contribute to an improved understanding of the dynamics of PD-L1 expression and relationship with intervening anti-cancer therapy.

4.5.7.5 Use and Storage of Remaining Samples from Study-Related Procedures

The remainder of samples obtained for study-related procedures will be destroyed no later than 5 years after the end of the study or earlier depending on local regulations. If the patient provides optional consent for storing samples in the RCR for future research (see Section 4.5.11), the samples will be destroyed no later than 15 years after the date of final closure of the clinical database.

Serum samples collected for PK and immunogenicity analysis that may be used for additional method development, assay validation, and characterization will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

4.5.8 Anti-Therapeutic Antibody Testing

Treatment with atezolizumab may elicit an immune response. Patients with signs of any potential immune response to atezolizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect ATAs at multiple timepoints before, during, and after treatment with atezolizumab (see Appendix 1 and Appendix 2 for the schedule). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Rosenberg and Worobec 2004; Koren et al. 2008) to characterize ATA responses to atezolizumab in support of the clinical development program. This tiered strategy will include an assessment of whether ATA responses correlate with relevant clinical endpoints. Implementation of ATA characterization assays will depend on the safety profile and clinical immunogenicity data.

4.5.9 Electrocardiograms

Twelve-lead ECG is required at screening and as clinically indicated. ECGs should be obtained on the same machine whenever possible. Lead placement should be as consistent as possible. ECG recordings should be performed after the patient 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 tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.10 Patient-Reported Outcomes

PRO data will be collected via the EORTC QLQ-C30, the EORTC QLQ-LC13, and the EQ-5D-5L to more fully characterize the clinical profile of atezolizumab.

The questionnaires will be translated into the local language as required. To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety by the patient prior to the performance of non-PRO assessments and the administration of study treatment.

Patients will use an electronic PRO (ePRO) device to capture PRO data. The ePRO device and/or instructions for completing the PRO questionnaires electronically will be provided by the investigator staff. The data will be transmitted via a prespecified transmission method (e.g., Web or wireless) automatically after entry to a centralized database at the ePRO vendor. The data can be accessed by appropriate study personnel securely via the internet.

The EORTC QLQ-C30 (see Appendix 6) is a validated and reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) that consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scale scores can be obtained for the multi-item scales.
The EORTC QLQ-C30 module takes approximately 15 minutes to complete. This questionnaire will be completed on the ePRO tablet at each scheduled study visit during study treatment and during survival follow-up at 3 months (±30 days) and 6 months (±30 days) following radiographic disease progression per RECIST v1.1 (or at 3 months [±30 days] and 6 months [±30 days] after treatment is discontinued for patients who continue treatment after disease progression per RECIST v1.1).

The EORTC QLQ-LC13 (see Appendix 7) module incorporates one multiple-item scale to assess dyspnea and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. The EORTC QLQ-LC13 module takes approximately 15 minutes to complete. This questionnaire will be completed on the ePRO tablet at each scheduled study visit during study treatment and during survival follow-up at 3 months (±30 days) and 6 months (±30 days) following radiographic disease progression per RECIST v1.1 (or at 3 months (±30 days) and 6 months (±30 days) after treatment is discontinued for patients who continue treatment after disease progression per RECIST v1.1).

The EQ-5D-5L is a generic, preference-based health utility measure with questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that is used to build a composite of the patient's health status (see Appendix 8). The EQ-5D-5L takes approximately 2 minutes to complete. The EQ-5D-5L will be utilized in this study for economic modeling. This questionnaire will be completed on the ePRO tablet at each scheduled study visit during study treatment and during survival follow-up at 3 months (±30 days) and 6 months (±30 days) following radiographic disease progression per RECIST v1.1 (or at 3 months (±30 days) and 6 months (±30 days) after treatment is discontinued for patients who continue treatment after disease progression per RECIST v1.1).

Patients who discontinue study treatment for any reason other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will complete EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L at each tumor assessment visit

until radiographic disease progression per RECIST v1.1, unless the patient withdraws consent or the Sponsor terminates the study, whichever occurs first.

The Sponsor will not derive adverse events reports from PRO data (see Section 5.3.5.13).

Patients whose native language is not available on the ePRO device or who are deemed by the investigator incapable of inputting their ePRO assessment after undergoing appropriate training are exempted from completing all ePRO assessments.

4.5.11 Samples for Roche Clinical Repository

4.5.11.1 Overview of the Roche Clinical Repository

The RCR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR 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 RCR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples may be collected for patients who have signed the RCR optional consent:

- Optional fresh biopsy samples
- Leftover tumor tissue samples

- Remaining fluids (serum, plasma, blood cell derivatives) after study-related tests have been performed
- Remaining FFPE tissue (with the exception of archival FFPE blocks, which will be returned to sites) after study-related tests have been performed

The following sample will be used for identification of genetic (inherited) biomarkers:

- Whole blood sample for DNA extraction (6 mL) (see Appendix 1 and Appendix 2)

For all samples, dates of consent should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens collected for the RCR will undergo additional processes to ensure confidentiality as described below.

4.5.11.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

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

Patient medical information associated with RCR specimens 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 patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

4.5.11.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. *After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient.* A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

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

4.5.11.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the study is closed. A patient's withdrawal from Study GO30081 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study GO30081. *If a patient wishes to withdraw consent to the testing of his or her RCR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:*

[redacted]

4.5.11.7 Monitoring and Oversight

RCR specimens 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 specimens as specified in this protocol and in the Informed Consent Form. Monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. 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 RCR samples.

4.5.12 Timing of Assessments

4.5.12.1 Screening and Baseline Assessments

Screening tests and evaluations will be performed within 28 days prior to Cycle 1, Day 1. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1, Day 1 may be used; such tests do not need to be repeated for screening.

See Appendix 1 for the schedule of screening assessments and Appendix 2 for the schedule of PK, pharmacodynamic, ATA, and biomarker sampling.

4.5.12.2 Assessments during Treatment

All treatment visits must occur ±3 days from the scheduled date unless otherwise noted (see Appendix 1). All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion unless otherwise noted.

If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule. If treatment was postponed for fewer than 3 days, the patient can resume the original schedule.

After completion of the induction phase, one of three cycles may be delayed by 1 week (28 days instead of 21 days for one cycle) to allow for vacations/holidays. Following the delay, the next cycle must be administered 21 days from the previous dose administration; two consecutive 28 cycles are not permitted. If a dose modification is required due to toxicity, refer to Section 5.1.

Tumor assessments will occur every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1 and every 9 weeks (±7 days) thereafter after the completion of the Week 48 tumor assessment, regardless of treatment dose delays, until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Patients who continue treatment beyond radiographic disease

progression per RECIST v1.1 will continue to undergo tumor assessments every 6 weeks (±7 days), or sooner if symptomatic deterioration occurs. For these patients, tumor assessments will continue every 6 weeks (±7 days) regardless of time on study, until study treatment is discontinued.

Patients who discontinue treatment for reasons other than 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 patient had remained on study treatment (i.e., every 6 weeks [±7 days] for the 48 weeks following Cycle 1, Day 1 and then every 9 weeks [±7 days]) thereafter, regardless of treatment dose delays) until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.

The following assessments may be performed ≤96 hours before Day 1 of each cycle:

- ECOG performance status
- Limited physical examination
- Local laboratory tests

Screening assessments performed ≤96 hours before Cycle 1, Day 1 are not required to be repeated for Cycle 1, Day 1.

See Appendix 1 for the schedule of assessments performed during the treatment period and Appendix 2 for the schedule of PK, pharmacodynamic, ATA, and biomarker sampling.

4.5.12.3 Assessments at Study Drug Discontinuation Visit

When a patient discontinues all study treatment, regardless of the reason for discontinuation, the patient will be asked to return to the clinic within 30 days after the last treatment for a study drug discontinuation visit. The visit at which the decision is made to discontinue treatment (e.g., disease progression occurs) may be used as the study-drug discontinuation visit.

See Appendix 1 and Appendix 2 for the schedule of follow-up assessments.

4.5.12.4 Follow-Up Assessments

After the study drug discontinuation visit, adverse events should be followed as outlined in Section 5.3.1.

For patients who discontinue study treatment for any reason other than radiographic progressive disease per RECIST v1.1, tumor assessments will continue at the same frequency as would have been followed if the patient 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.

Patients who start a new anti-cancer therapy in the absence of radiographic disease progression per RECIST v1.1 will continue tumor assessments according to the protocol schedule of response assessments until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Follow-up data collection will also include PROs. EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L will be completed at the site on the ePRO tablet at 3 months (±30 days) and 6 months (±30 days) after disease progression per RECIST v1.1 (or at 3 months (±30 days) and 6 months (±30 days) after treatment is discontinued for patients who continue treatment after disease progression per RECIST v1.1). Patients who discontinue study treatment for any reason other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will complete the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L at each tumor assessment visit until radiographic disease progression per RECIST v1.1, unless the patient withdraws consent or the Sponsor terminates the study, whichever occurs first.

Adverse events will be followed as described in Section 5.5.

Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits every 3 months or more frequently until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from the study (this request must be documented in the source documents and signed by the investigator). If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) when permissible, to obtain information about survival status only.

See Appendix 1 and Appendix 2 for the schedule of follow-up assessments.

4.5.12.5 Assessments at Unplanned Visits

Assessments for unscheduled visits related to a patient's underlying SCLC, study drug, or adverse event should be performed as clinically indicated and entered into Unscheduled Visit eCRFs.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study

- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results if available, and the patient's clinical status
- Intolerable toxicity related to atezolizumab, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Intolerable toxicity related to other components of study treatment
- If one component of study treatment is discontinued permanently because of tolerability concerns, the patient may continue with other components of study treatment until disease progression if agreed upon by the investigator and patient
- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment
- Use of another non–protocol-specified anti-cancer therapy (see Section 4.4.3)
- Pregnancy
- Radiographic disease progression per RECIST v1.1

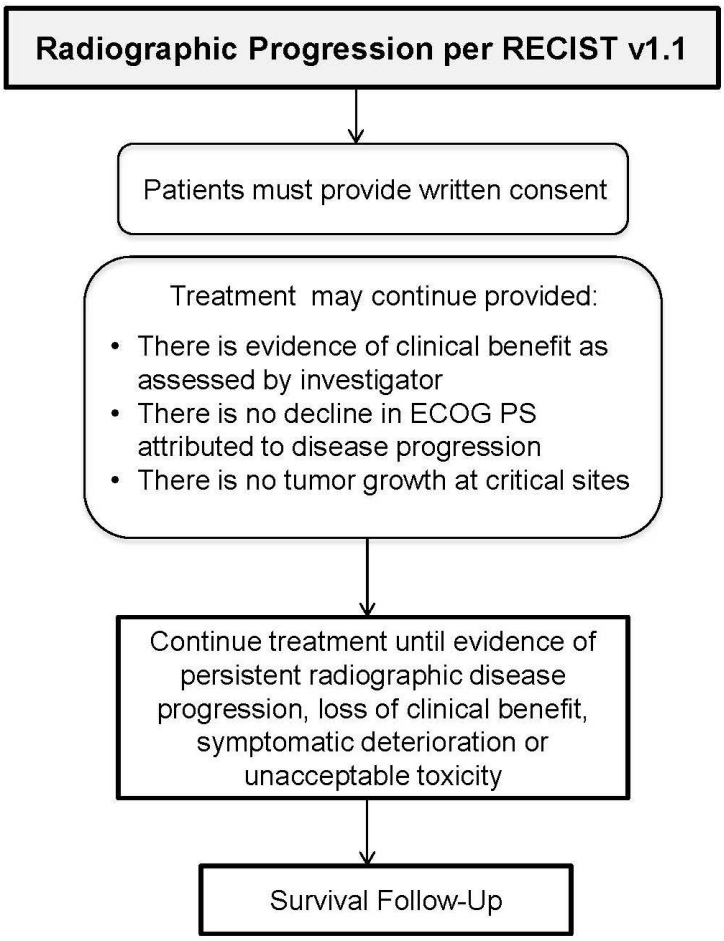
However, to better accommodate standard clinical practice which is guided by the fact that patients with ES-SCLC whose disease progresses after first-line treatment have limited treatment options and such options also have limited efficacy and significant toxicity, patients may be considered for treatment beyond radiographic progression per RECIST v1.1 at the discretion of the investigator and after appropriate discussion with the patient and obtaining informed consent, only if all of the following criteria are met:

- Evidence of clinical benefit as assessed by the investigator
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial progression.

Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 should be closely monitored clinically and a follow-up scan should be

performed in 6 weeks, or sooner if symptomatic deterioration occurs. Treatment should be discontinued if clinical deterioration due to disease progression occurs at any time or if persistent disease growth is confirmed in a follow-up scan. In addition, patients should be discontinued for unacceptable toxicity or for any other signs or symptoms of deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status.

Figure 2 Criteria for Continuing Treatment in the Presence of Increased Radiographic Tumor Size



ECOG PS = Eastern Cooperative Oncology Group performance status; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include but are not limited to the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.

- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

The important safety risks for atezolizumab are provided below. Refer to the Atezolizumab Investigator's Brochure for a complete summary of safety information.

5.1 SAFETY PLAN

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2) and close monitoring (as indicated below and in Section 4.5). See Section 5.3 (Methods and Timing for Capturing and Assessing Safety Parameters) for complete details regarding safety reporting for this study. An iDMC has also been incorporated into the study design to periodically review safety data (see the iDMC Charter for a detailed monitoring plan).

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. All serious adverse events and adverse events of special interest will be recorded during the study and for up to 90 days after the last dose of study treatment or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. All other adverse events will be recorded during the study and for up to 30 days after the last dose of study treatment or until the initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first.

After the adverse event reporting period, all deaths should continue to be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment (see Section 5.6). These events 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 Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or e-mail address provided to investigators.

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-related hypothyroidism, hyperthyroidism, adrenal insufficiency, Type 1 diabetes mellitus, pancreatitis, hepatitis, pneumonitis, colitis, meningoencephalitis, myasthenia gravis or myasthenic syndrome, Guillain-Barré syndrome, *hypophysitis, myocarditis, and nephritis. In addition, systemic immune activation is considered a potential risk for atezolizumab. Refer to Appendix 12 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.*

5.1.2 Risks Associated with Etoposide

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. Patients will be monitored for etoposide-related adverse events.

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

5.1.3 Risks Associated with Carboplatin

Carboplatin is known to cause bone marrow suppression including myelosuppression, anemia, and thrombocytopenia. Carboplatin-based chemotherapy is considered to be moderately emetogenic. Patients will be monitored for carboplatin-related adverse events.

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

5.1.4 Management of Patients Who Experience Specific Adverse Events

5.1.4.1 Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events defined and graded according to NCI CTCAE v4.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Laboratory values must be reviewed prior to each infusion.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Appendix 1 for the list and timing of study assessments).

During the study, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

All serious adverse events and protocol-defined events of special interest (see Sections 5.2.2 and 5.2.3) will be reported in an expedited fashion (see Section 5.4.2). In addition, the iDMC and Medical Monitor will review and evaluate observed adverse events on a regular basis.

Patients will be followed for adverse events (including deaths, serious adverse events, and adverse events of special interest during and after the adverse event reporting period as described in Sections 5.3.1, 5.3.5.8, 5.5, and 5.6.

5.1.5 Dose Modification

5.1.5.1 General Notes Regarding Dose Modification

Reasons for dose modifications including dose delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF. The severity of adverse events will be graded according to the NCI CTCAE v4.0 grading system.

- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment and the dose or administration of that component is delayed or modified, the dose or administration of the other study treatment components do not require modification and may be administered if there is no contraindication.
- When treatment is temporarily interrupted because of toxicity caused by atezolizumab/placebo, carboplatin, or etoposide, the treatment cycles should be restarted such that the atezolizumab/placebo infusions remain synchronized and aligned with the chemotherapy schedule.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one chemotherapy drug, the dose of the other chemotherapy drug does not require modification.

The investigator may use discretion in modifying or accelerating the dose modification guidelines described below depending on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing patient compliance and access to supportive care.

5.1.5.2 Atezolizumab Dose Modification, Treatment Delays, or Treatment Discontinuation and Management of Specific Adverse Events

There will be no dose reduction for atezolizumab/placebo in this study. Patients may temporarily suspend study treatment with atezolizumab/placebo for up to 105 days beyond the last dose if they experience an adverse event that requires a dose to be withheld. If atezolizumab/placebo is withheld because of adverse events for more than 105 days beyond the last dose, then the patient will be discontinued from atezolizumab/placebo treatment. Exceptions require Medical Monitor approval.

If a patient must be tapered off steroids used to treat adverse events, atezolizumab may be withheld for additional time beyond 105 days from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤10 mg/day. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Dose interruptions for reason(s) other than adverse events, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

5.1.6 Management of Atezolizumab-Specific Adverse Events

Refer to *Appendix 12* for details on the management of atezolizumab-specific adverse events*, including systemic immune activation*. See Appendix 10 for precautions for anaphylaxis.

5.1.7 Chemotherapy Dose Modifications, Treatment Delays, or Treatment Discontinuation and Management of Specific Adverse Events

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

Dose modification guidelines are provided below. Once reduced, the dose cannot be increased back to 100%.

Treatment with carboplatin or etoposide should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or Grade 4 toxicity after two dose reductions or treatment is delayed for more than 63 days due to toxicities.

Hematologic Toxicity

At the start of each cycle, the ANC should be ≥1500/μL and the platelet count should be ≥100,000/μL. Treatment should be delayed for up to 63 days to allow sufficient time for recovery. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO) and NCCN guidelines (Smith et al. 2006; NCCN 2015). Upon

recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest platelet and neutrophil values from the previous cycle (see Table 8).

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Table 8 Chemotherapy Dose Modification for Hematologic Toxicities

Toxicity [a]	Dose
ANC $<$ 500/μL and platelets $\geq$ 50,000/μL	75% of previous dose
Platelets $<$ 25,000/μL, regardless of ANC	75% of previous dose
Platelets $<$ 50,000/μL with Grade $\geq$ 2 bleeding, regardless of ANC	50% of previous dose
ANC $<$ 1000/μL plus fever of $\geq$ 38.5°C	75% of previous dose

[a] Nadir of prior cycle.

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, or febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

If chemotherapy is withheld because of hematologic toxicity, full blood counts (including differential WBC) should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment can then be resumed.

No dose reductions are recommended for anemia. Patients should be supported per the investigator's institution's guidelines.

Non-Hematologic Toxicity

For a non-hematologic toxicity (see Table 9), treatment should be delayed for up to 63 days until resolution to less than or equal to the patient's baseline value (or Grade $\leq$ 1 if the patient did not have that toxicity at baseline). Dose reductions at the start of the subsequent cycle should be made on the basis of non-hematologic toxicities from the dose administered in the preceding cycle. Table 9 provides recommended dose modifications for non-hematologic toxicities.

Table 9 Dose Modifications or Treatment Discontinuation for Non-Hematologic Toxicities

Toxicity		Adjusted Dose as % of Previous Dose [a]
Diarrhea	Grade 3 or 4 [b]	75%
Nausea/vomiting	Grade 3 or 4 [c]	75%
Neurotoxicity	Grade 2	75%
	Grade 3 or 4	50% or permanent discontinuation
Transaminase elevation	Grade 3	75%
	Grade 4	Discontinue
Other	Grade 3 or 4	75%

AUC = area under the concentration–time curve.

[a] If deemed appropriate by the investigator, adjust carboplatin dose to the specified percentage of the previous AUC.

[b] Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication or any grade of diarrhea requiring hospitalization.

[c] Despite the use of anti-emetics.

Diarrhea should be controlled with adequate anti-diarrhea medication. Nausea and/or vomiting may be controlled with adequate anti-emetics. For Grade 3 or 4 neurotoxicity chemotherapy should be resumed at 50% of the previous dose upon improvement or discontinued immediately (based on investigator's clinical judgment).

Suggested recommendations for dose modification of etoposide for renal impairment are provided in Table 10.

Table 10 Etoposide Dose Modification for Renal Impairment

Creatinine clearance (mL/min)	Etoposide Dose
> 50	100%
15–50	75% of dose

5.1.8 Potential Overlapping Toxicities

The risk of overlapping toxicities between atezolizumab, carboplatin, and etoposide is thought to be minimal. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hepatotoxicity, skin and gastrointestinal toxicity) may be ambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with carboplatin and etoposide (e.g., dermatitis, infusion-associated symptoms) could be exacerbated by the immunostimulatory activity of atezolizumab.

Toxicities should initially be managed according to the recommendations in Sections 5.1.6 and 5.1.7 and *Appendix 12,* with dose holds and modifications (if applicable) applied to the component of the study drug judged to be the primary cause. For severe (Grade 3) or persistent Grade 1–2 diarrhea, an endoscopic evaluation should be considered. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology for adverse events listed above. If, in the opinion of the investigator, atezolizumab is a potential inciting factor, the dose of atezolizumab may be held for a maximum of 105 days beyond the last *infusion* (see Section 5.1.5.2). Exceptions require Medical Monitor approval. Prompt symptomatic management is appropriate for mild immune-mediated adverse events. In severe cases, immune-mediated toxicities may be acutely managed with systemic corticosteroids or TNF-α inhibitors. These cases should be discussed with the Medical Monitor.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug

- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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 NCI CTCAE criteria; see Section 5.3.3); 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 learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

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 learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- The following confirmed treatment-emergent autoimmune conditions:

  Pneumonitis

Colitis

Endocrinopathies: diabetes mellitus, pancreatitis, or adrenal insufficiency or hyperthyroidism

Hepatitis

Transaminitis: Grade ≥ 2 (AST or ALT $> 3 \times$ ULN and bilirubin $> 2 \times$ ULN) OR AST/ALT $> 10 \times$ ULN

Systemic lupus erythematosus

Neurologic: Guillain-Barré syndrome, myasthenia gravis, meningoencephalitis

Nephritis

- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome (SIRS), systemic immune activation, or infusion-reaction syndromes
- 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 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, 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 patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained, **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 11 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 11 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
5	Death related to adverse event

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

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

[a] Instrumental activities of daily living refers to 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 patients 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 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after the end of study drug infusion and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related 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 eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events, 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 one 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.

5.3.5.3 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 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 three 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.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity) 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 intensity 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 learning that the event became serious; see Section 5.4.2 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 patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage 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., alkaline phosphatase and bilirubin 5 × 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 if 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage 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 (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) 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 $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value 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 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of SCLC should be recorded only on the Death Attributed to Progressive Disease eCRF. All other deaths occurring during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). The iDMC 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 one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"Death due to Unknown Cause"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), the event 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 that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 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" or “worsened headache”).

5.3.5.10 Lack of Efficacy or Worsening of SCLC

Events that are clearly consistent with the expected pattern of progression of SCLC should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST criteria. In rare cases, the determination of clinical progression will be based

on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient 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 5.2.2), 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 drug administration or to perform an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient 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 patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical study. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming 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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted], M.D.
Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

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. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to Roche 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 with use of the fax number or e-mail address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study treatment or initiation of new systemic anti-cancer therapy after the last dose of study drug, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study treatment or initiation of new systemic anti-cancer therapy after the last dose of study drug, whichever occurs first.

Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the 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 Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to Roche 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 with use of 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 adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of study treatment. A 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 learning of the pregnancy), either by faxing or by scanning and e-mailing the form with use of 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 patient, discussing the risks of the

pregnancy and the possible effects on the fetus. Monitoring of the patient 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/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.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their female partner becomes pregnant during chemotherapy study treatment (i.e., carboplatin and etoposide) or within 6 months after the last dose of chemotherapy study treatment. A 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 learning of the pregnancy), either by faxing or by scanning and e-mailing the form with use of 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 patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient 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.

5.4.3.3 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 learning of the event; see Section 5.4.2).

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 learning of the event; see Section 5.4.2). 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.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug 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 learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow the reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic 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.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (as defined in Section 5.3.1), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-up eCRF.

In addition, if the investigator becomes aware of a serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment, the event 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 Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or e-mail address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the Atezolizumab Investigator's Brochure for atezolizumab.

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 iDMC will monitor safety data during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a randomized, Phase I/III, global, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin + etoposide compared with treatment with placebo and carboplatin + etoposide in patients who have ES-SCLC and are chemotherapy-naive for their extensive-stage disease.

All analyses discussed in this section will be restricted to the patients enrolled in the global enrollment phase only [redacted] unless otherwise noted. The analysis populations used in this section, such as the ITT (i.e., all randomized patients) and the PD-L1–selected populations will not [redacted] unless otherwise noted.

The analyses of PFS and OS will be performed on all randomized patients (ITT), with patients grouped according to the treatment assigned at randomization, regardless of whether they receive any assigned study drug. ORR will be analyzed using all randomized patients who have measurable disease at baseline. DOR will be assessed in patients who have an objective response. TTD analyses will be conducted on all patients with a non-missing baseline PRO assessment. Change from baseline analysis on PROs will be performed using patients who have both a non-missing baseline

assessment and at least one post-baseline assessment with patients grouped according to the treatment assigned at randomization.

Safety analyses will be performed on all randomized patients who received any amount of study drug, with patients grouped according to whether any full or partial dose of atezolizumab was received.

6.1 DETERMINATION OF SAMPLE SIZE

Approximately 400 patients will be randomized into the global enrollment phase of this study to the atezolizumab + carboplatin + etoposide arm and the placebo + carboplatin + etoposide arm in a 1:1 ratio.

There are two co-primary efficacy endpoints: PFS and OS. To control the overall two-sided Type I error rate at 0.05, the two-sided significance levels of 0.005 and 0.045 are allocated to the primary comparisons for PFS and OS, respectively.

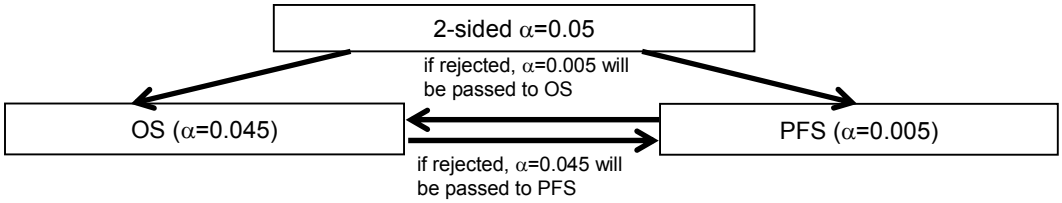
The following sample size calculation applies to the global enrollment phase, [redacted] unless otherwise noted.

The sample size of the study is determined by the analysis of OS. To detect an improvement of HR = 0.68 in OS using a log-rank test, approximately 306 deaths in the ITT population will be required to achieve 91% power at a two-sided significance level of 0.045. One OS interim analysis will be performed when approximately 240 OS events in the ITT population are observed, which by estimation will occur at approximately 25 months after the first patient is randomized.

The primary analysis of PFS is planned to be conducted at the time of the OS interim analysis, and is estimated to be when approximately 295 PFS events in the ITT population have occurred, which is expected at approximately 25 months after the first patient is randomized. This provides 99% power to detect an improvement of HR = 0.55 in PFS at a two-sided significance level of 0.005. There will be no interim analysis for PFS.

By a group sequential Holm procedure (Ye et al., 2011), if the primary analysis of PFS is significant, then the two-sided 0.005 alpha will be recycled to OS; the detailed testing boundary is provided in Section 6.8.1. Otherwise, if the OS analysis at either interim or final is significant, the allocated test mass of two-sided 0.045 alpha can be returned to PFS so PFS primary analysis can be tested at a two-sided 0.05 level (see Figure 3). Additional details will be provided in the Statistical Analysis Plan.

Figure 3 Group Sequential Holm Procedure



The final analysis of OS will be performed when approximately 306 OS events in the ITT population have been observed, which is expected at approximately 36 months after the first patient is randomized.

The calculation of sample size and estimates of the analysis timelines are based on the following assumptions:

- PFS and OS are exponentially distributed.
- The median duration of PFS in the control arm is 6 months.
- The median duration of OS in the control arm is 10 months.
- The interim and final analyses of OS use the Lan-DeMets alpha spending function to approximate the O'Brien-Fleming boundary.
- The dropout rate is 5% over 12 months for PFS and OS.

6.1.1 [redacted]

[redacted]

[redacted]

6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment, study drug administration, reasons for discontinuation from the study drug, and reasons for study termination will be summarized by treatment arm for the ITT population. Major protocol deviations, including major deviations of inclusion/exclusion criteria, will be reported and summarized by treatment arm for the ITT population.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic characteristics, such as age, sex, race/ethnicity, and baseline disease characteristics (e.g., ECOG performance status) will be summarized by treatment arm for the ITT population. Descriptive statistics (mean, median, SD, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

Baseline measurements are the last available data obtained prior to the patient receiving the first dose of any component of protocol treatment.

6.4 EFFICACY ANALYSES

The stratification factors will be those used for randomization from the IxRS (i.e., sex, ECOG performance status, and brain metastases). Due to the potential risk of over-stratification (Akazawa et al. 1997), if at least one stratum (i.e., a combination of stratification factor levels across sex [male vs female], ECOG performance status [0 vs 1], and brain metastasis [Yes vs No] per IxRS) has less than 10 events (PFS or OS events), the stratification factor (one of 3 stratification factors: sex, ECOG performance status, and brain metastasis per IxRS) which contains the level with the smallest number of patients will be removed from the stratified analyses. The removal of the stratification factor will continue until there is no stratum with less than 10 events (PFS or OS events). The final set of stratification factors used in stratified analyses will be applied to all endpoints where stratified analyses are planned. Analyses based on stratification factors recorded on the electronic Case Report Form (eCRF) will also be provided if considerable discrepancy is observed between IxRS and eCRF records.

6.4.1 Primary Efficacy Endpoints

To adjust for multiplicity due to having two co-primary endpoints, a group sequential Holm's procedure will be implemented: initially the hypothesis test for PFS will be conducted at a two-sided alpha of 0.005 and OS will be tested at a two-sided alpha of 0.045. Once a null hypothesis is rejected, the test mass predefined for that endpoint becomes available and can be recycled to the other unrejected test.

The null and alternative hypotheses regarding PFS or OS in the ITT population can be phrased in terms of the PFS or OS survival functions $S_A(t)$ and $S_B(t)$ for Arm A (atezolizumab + carboplatin + etoposide) and Arm B (placebo + carboplatin + etoposide), respectively:

$$H0: S_A(t) = S_B(t) \text{ versus } H1: S_A(t) \neq S_B(t)$$

One of the co-primary efficacy endpoints is PFS as assessed by the investigator using RECIST v1.1. PFS is defined as the time between the date of randomization and the date of first documented disease progression or death, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

The *stratified* log-rank test, will be used as the primary analysis to compare PFS between the two treatment arms. The results from the unstratified log-rank will also be provided.

The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. The Brookmeyer-Crowley methodology (Brookmeyer and Crowley 1982) will be used to construct the 95% CI for the median PFS for each treatment arm. Cox proportional-hazards models will be used to estimate the *stratified* HR and its 95% CI. The unstratified HR will also be presented.

OS, the other co-primary efficacy endpoint, is defined as the time from the date of randomization to the date of death from any cause. Patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Patients with no post-baseline information will be censored at the date of randomization plus 1 day. Methods for OS analyses are similar to those described for the PFS endpoint.

The final analysis of OS will occur after approximately *306* OS events in the ITT population have occurred. One interim analysis of OS will be conducted at the time that approximately *240* OS events or approximately *295* PFS events have occurred in the ITT population, whichever occurs later. It is projected that approximately 220 OS events in the ITT population will be observed at *25* months after the first patient is randomized. To control the two-sided significance level at 0.045 for the OS interim and final analyses, the Lan-DeMets alpha spending function will be used to approximate the O'Brien-Fleming boundary (DeMets and Lan 1994). See Section 6.8.1 (Planned Interim Analysis) for additional information.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Objective Response Rate

An objective response is defined as either an unconfirmed CR or a PR, as determined by the investigator using RECIST v1.1. Patients not meeting these criteria, including patients without any post-baseline tumor assessment, will be considered non-responders.

ORR is defined as the proportion of patients who had an objective response. The analysis population for ORR will be all randomized patients with measurable disease at baseline. An estimate of ORR and its 95% CI will be calculated using the Clopper Pearson method for each treatment arm. CIs for the difference in ORRs between the two treatment arms will be determined using the normal approximation to the binomial distribution.

6.4.2.2 Duration of Response

DOR will be assessed in patients who had an objective response as determined by the investigator using RECIST v1.1. DOR is defined as the time interval from the date of the first occurrence of a CR or PR (whichever status is recorded first) until the first date that progressive disease or death is documented, whichever occurs first. Patients 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. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR plus 1 day. DOR is based on a non-randomized subset of patients (specifically, patients who achieved an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes. The methodologies detailed for the PFS analysis will be used for the DOR analysis.

6.4.2.3 Landmark Analysis on Progression-Free Survival and Overall Survival

The PFS rates at 6 months and at 1 year after randomization will be estimated using Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated using 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 using the normal approximation method.

Similar analyses will be performed for the OS rates at 1 and 2 years after randomization.

6.4.2.4 Patient-Reported Outcomes

TTD using EORTC is defined as the time from baseline to the first time the patient's score shows a $\geq$10-point increase above baseline in any of the following EORTC-transformed symptom subscale scores (whichever occurs first): cough, dyspnea (single item), dyspnea (multi-item subscale), chest pain, or arm/shoulder pain, whichever occurs first. The linear transformation gives each individual symptom

subscale a possible score of 0−100. In order for the symptom to be considered "deteriorated," a score increase of ≥10 points above baseline must be held for at least two consecutive assessments or an initial score increase of ≥10 points is followed by death within 3 weeks from the last assessment. A ≥10-point change in the symptoms subscale score is perceived by patients as clinically significant (Osoba et al. 1998). Patients will be censored at the last time when they completed an assessment if they have not deteriorated. If no post-baseline assessment is performed, patients will be censored at the randomization date plus 1 day. TTD using the EORTC scale will be analyzed using the same methods as for PFS. The analysis populations for TTD will be all randomized patients with a non-missing baseline PRO assessment.

PROs of HRQoL, lung cancer–related symptoms, and health status will be measured using EORTC QLQ-C30 and EORTC QLQ-LC13. Summary statistics (mean, SD, 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 subscales of the EORTC QLQ-C30 questionnaire and the QLQ-LC13 according to the EORTC scoring manual guidelines. Completion and compliance rates will be summarized at each timepoint by treatment arm. The analysis populations for PRO changes will be all randomized patients with a non-missing baseline assessment and at least one non-missing post-baseline assessment.

6.4.3 Handling of Missing Data

For PFS, patients without a date of disease progression will be analyzed as censored observations on the date of the last tumor assessment. If no post-baseline tumor assessment is available, PFS will be censored at the date of randomization plus 1 day.

For objective response, patients without any post-baseline assessment will be considered non-responders.

For OS, patients who are not reported as having died will be analyzed as censored observations on the date they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization plus 1 day.

For DOR, patients who have not progressed and who have not died at the time of analysis will be censored at the time of the last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR plus 1 day.

For TTD with use of the EORTC, patients who have not deteriorated at the time of analysis will be censored at the last time they completed an assessment. If no post-baseline assessment is performed, patients will be censored at the randomization date plus 1 day.

6.5 SAFETY ANALYSES

Safety analyses will be performed on the safety-evaluable population, which is defined as all randomized patients who receive any amount of any component of protocol treatment. Patients will be allocated according to whether any full or partial dose of atezolizumab was received.

Drug exposure will be summarized to include treatment duration, number of doses, and dose intensity.

Verbatim description of adverse events will be mapped to thesaurus terms and graded according to NCI CTCAE v4.0. All adverse events occurring during or after the first study drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grade ≥ 3), adverse events of special interest, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity.

Laboratory data with values outside the normal ranges will be identified. In addition, selected laboratory data will be summarized by treatment arm and grade.

Changes in vital signs will be summarized by treatment arm.

Deaths reported during the study will be summarized by treatment arm.

6.6 PHARMACOKINETIC ANALYSES

PK samples will be collected in this study as outlined in Appendix 2. Atezolizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, and SDs, as appropriate.

Plasma concentrations of carboplatin and etoposide will be collected in this study as outlined in Appendix 2. The concentrations of carboplatin and etoposide will be summarized using descriptive statistics as described above.

Additional PK analyses will be conducted, as appropriate, based on the availability of data.

6.7 EXPLORATORY ANALYSES

6.7.1 Objective Response Rate, Duration of Response, and Progression-Free Survival per Modified RECIST

Analyses using modified RECIST criteria (see Appendix 5) for ORR, DOR, and PFS, as determined by the investigator will also be conducted (for atezolizumab-treated patients only). Comparisons between the treatment arms will not be made. The methods outlined for the primary and secondary efficacy endpoint analyses to estimate the median PFS or ORR for each treatment arm will be used for these analyses.

6.7.2 Exploratory Analyses of Progression-Free Survival

6.7.2.1 Non–Protocol-Specified Anti-Cancer Therapy

The impact of non–protocol-specified anti-cancer therapy on PFS will be assessed depending on the number of patients who receive non–protocol-specified anti-cancer therapy before a PFS event. If >5% of patients received non–protocol-specified anti-cancer therapy before a PFS event in any treatment arm, a sensitivity analysis will be performed for the comparisons between treatment arms in which patients who receive non–protocol-specified anti-cancer therapy before a PFS event will be censored at the last tumor assessment date before receipt of non–protocol-specified anti-cancer therapy.

6.7.2.2 Subgroup Analysis

To assess the consistency of the study results in subgroups defined by demographics (e.g., age, sex, and race/ethnicity), baseline prognostic characteristics (e.g., ECOG performance status, smoking status, presence of brain metastases), and PD-L1 tumor expression status, the duration of PFS in these subgroups will be examined. Summaries of PFS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median PFS, will be produced separately for each level of the categorical variables for the comparisons between treatment arms.

6.7.2.3 Sensitivity Analyses

One sensitivity analysis will be performed to evaluate the potential impact of missing scheduled tumor assessments on the primary analysis of PFS, as determined by the investigator using a PFS event imputation rule.

If a patient misses two or more assessments scheduled immediately prior to the date of the PFS event, the patient will be counted as having progressed on the date of the first of these missing assessments.

Another sensitivity analysis is that data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits.

The imputation rule will be applied to patients in both treatment arms. Statistical methodologies that are analogous to those used in the primary analysis of PFS as specified in Section 6.4.1 will be used for this sensitivity analysis.

The impact of non-protocol-specified anti-cancer therapy on OS will be assessed, in which data from patients who receive non-protocol-specified anti-cancer therapy before a PFS event will be censored at the date before receipt of non-protocol-specified anti-cancer therapy.

6.7.3 Exploratory Analyses of Overall Survival

6.7.3.1 Subgroup Analysis

To assess the consistency of the study results in subgroups defined by demographics (e.g., age, sex, and race/ethnicity), baseline prognostic characteristics (e.g., ECOG performance status, smoking status, presence of brain metastases at baseline), and PD-L1 tumor expression status, the duration of OS in these subgroups will be examined. Summaries of survival, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median survival time, will be produced separately for each level of the categorical variables for the comparisons between treatment arms.

6.7.4 Exploratory Biomarker Analysis

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with study drug response, including efficacy and/or adverse events. The tumor biomarkers include but are not limited to PD-L1 and CD8, as defined by IHC, qRT-PCR, or other methods. Additional pharmacodynamic analyses will be conducted as appropriate.

6.8 INTERIM ANALYSES

6.8.1 Planned Interim Analyses

There will be no interim analyses planned for PFS in this study. An external iDMC will be set up to evaluate safety data on an ongoing basis. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an iDCC. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRBs/ECs. A detailed plan will be included in the iDMC Charter.

One interim efficacy analysis of OS is planned when approximately *240* OS events have been observed. The primary analysis of PFS will be conducted at the same time of the interim OS analysis *and is estimated to occur when approximately 295 PFS events in the ITT population have occurred, which is expected at approximately 25 months after the first patient is randomized*.

The final OS analysis will be conducted when approximately *306* OS events in the ITT population have been observed. This is expected to occur approximately *36* months after the first patient is randomized, but the exact timing of this analysis will depend on the actual number of OS events.

To control the type I error for OS, the stopping boundaries for OS interim and final analyses are to be computed with use of the Lan-DeMets approximation to the O'Brien-Fleming boundary (DeMets and Lan 1994) as shown in Table 12.

Table 12 Analysis Timing and Stopping Boundary of Overall Survival

Analysis Timing	Information Fraction (Number of Events)	Estimated Time from First Patient In (months)	Stopping Boundary in HR (p-value)	
			PFS is Statistically Significant	PFS is Not Statistically Significant
OS interim analysis	78.4%(240)	25	HR ≤ 0.7453 (p ≤ 0.0228)	HR ≤ 0.7405 (p ≤ 0.02)
OS final analysis	100% (306)	36	HR ≤ 0.7937 (p ≤ 0.0433)	HR ≤ 0.7899 (p ≤ 0.039)

HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

6.8.2 Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim efficacy analysis for the co-primary endpoints of PFS and OS beyond what is specified in Section 6.8.1. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

If an interim analysis is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC Charter will document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC Charter will also be made available to relevant health authorities.

6.9 [redacted]

[redacted]

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patient-reported data will be collected electronically through use of electronic devices provided by an ePRO vendor. The electronic device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with the FDA regulations for electronic records (21 Code of Federal Regulations, Part 11). The data will be transmitted to a centralized database at the ePRO vendor. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. Regular data transfers will occur from the centralized database at the vendor to the database at the Sponsor.

Once the study is complete, the data, audit trail, and study and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept

with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for study-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, the name of the person making the change, and the date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the *applicable* laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. IND application will comply with the FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) *and applicable local, regional, and national laws*.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Form or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Informed Consent Form will contain a separate section that addresses the use of remaining samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature

will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not provide a separate signature.

The Informed Consent Form will also contain the following additional signature pages:

- A signature page for patients who meet all of the criteria specified in Section 3.1 and continue treatment beyond radiographic disease progression per RECIST v1.1. This separate consent is to be signed after initial radiographic disease progression has occurred and patients have discussed other available treatment options and the potential risks of continuing treatment.
- A signature page for patients to sign to consent to undergoing optional tumor biopsies during the study (after induction completion of induction treatment or after radiographic disease progression per RECIST v1.1).

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for 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. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study 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 patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 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 course of the study and for 1 year after completion of the study.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient 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.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann-La Roche Ltd. Approximately 150 sites globally will participate in the study and approximately 400 patients will be randomized during the initial global enrollment phase of the study. [redacted]

Randomization will occur through use of an IxRS. Central facilities will be used for study assessments throughout the study (e.g., specified laboratory tests and PK analyses). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific

congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical study results within 6 months after the availability of the respective clinical study report. In addition, for all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

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 multicenter studies only in their entirety and not as individual center 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 formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

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.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

Procedure	Screening	All Treatment Cycles [a]		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1–4)	Maintenance Phase		
	Days −28 to −1	Every 21 Days (±3 Days) [b]	Every 21 Days (±3 Days)	≤30 Days after Last Dose of Study Treatment	Every 3 Months after Disease Progression
Informed consent	x				
Pre-treatment tumor tissue specimen for biomarker testing	x [c]	x [c]	x [c]		
Demographic data	x				
Medical history and baseline conditions	x				
SCLC cancer history	x				
Vital signs [d]	x	x	x	x	
Weight	x	x	x	x	
Height	x				
Complete physical examination	x				
Limited physical examination [e]		x	x	x	
ECOG performance status	x	x	x	x	
12-lead ECG	x	x [f]	x [f]	x [f]	
Hematology [g]	x [h]	x	x	x	
Serum chemistry [i]	x [h]	x	x	x	
Coagulation test (aPTT or INR)	x [h]			x	

Appendix 1
Schedule of Assessments (cont.)

Procedure	Screening	All Treatment Cycles [a]		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1–4)	Maintenance Phase		
	Days −28 to −1	Every 21 Days (±3 Days) [b]	Every 21 Days (±3 Days)	≤30 Days after Last Dose of Study Treatment	Every 3 Months after Disease Progression
Pregnancy test (women of childbearing-potential only)	x [j]	x [k]	x [k]	x [k]	
TSH, free T3, free T4 [l]	x	x [m]	x [m]	x	
HIV, HBV, HCV serology [n]	x				
Urinalysis [o]	x [o]	x [o]	x [o]	x [o]	
Induction treatment administration Arm A: atezolizumab + etoposide + carboplatin Arm B: placebo + etoposide + carboplatin		x [p]			
Maintenance treatment administration Arm A: atezolizumab Arm B: placebo			x [p]		
Prophylactic cranial irradiation			x [q]		
Tumor response assessment	x [r]	x [s]	x [s]		x [t]
Serum sample for atezolizumab ATA assessment [u]		x	x	x	120 (±30) days after last dose of atezolizumab
Serum sample for atezolizumab PK sampling [u]		x	x	x	120 (±30) days after last dose of atezolizumab
Carboplatin and etoposide PK sampling [u]		x			

Appendix 1
Schedule of Assessments (cont.)

Procedure	Screening	All Treatment Cycles [a]		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1–4)	Maintenance Phase		
	Days −28 to −1	Every 21 Days (±3 Days) [b]	Every 21 Days (±3 Days)	≤30 Days after Last Dose of Study Treatment	Every 3 Months after Disease Progression
Blood samples for PD biomarkers [u]		x	x	x	120 (±30) days after last dose of atezolizumab
Optional tumor biopsy after induction treatment (if patient signs consent)		After induction treatment			
Optional tumor biopsy at time of radiographic progression (if patient signs consent) [v]		At time of initial radiographic progression			
Optional tumor biopsy at other time points (RCR only)		Any time during study treatment or during survival follow-up			
Optional blood for DNA extraction (RCR only) [u, w]		x			
Adverse events	x	x	x	x [x]	x [x]
Concomitant medications	x [y]	x [y]	x [y]	x [y]	
Patient-reported outcomes (EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L) [z]		x [z]	x [z]		x [z]
Survival and anti-cancer therapy follow-up					x [aa]

Appendix 1
Schedule of Assessments (cont.)

ATA = anti-therapeutic antibody; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC = European Organization for Research and Treatment of Cancer; ePRO = electronic Patient-Reported Outcome; EQ-5D-5L = EuroQoL 5 Dimensions 5-Level Version; FFPE = formalin-fixed paraffin-embedded; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; NSCLC = non–small cell lung cancer; PCI = prophylactic cranial irradiation; PCR = polymerase chain reaction; PD = pharmacodynamic; PD-L1 = programmed death–ligand 1; PK = pharmacokinetic; PRO = Patient-Reported Outcome; QLQ-C30 = Quality-of-Life Questionnaire Core 30; QLQ-LC13 = Quality-of-Life Questionnaire Lung Cancer module; RCR = Roche Clinical Repository; RECIST = Response Evaluation Criteria in Solid Tumors; SCLC = small cell lung cancer; TSH = thyroid-stimulating hormone.

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

[b] Cycle 1 must be performed within 5 days after the patient is randomized. Screening assessments performed ≤ 96 hours before Cycle 1, Day 1 are not required to be repeated for Cycle 1, Day 1. In addition, ECOG performance status, limited physical examination, and local laboratory tests may be performed ≤ 96 hours before Day 1 of each cycle as specified in Section 4.5.12.2.

[c] A pre-treatment tumor tissue (archival or freshly obtained) sample should be submitted before or within 4 weeks after randomization. This specimen must be accompanied by the associated pathology report. Although any available tumor tissue sample can be submitted, it is strongly encouraged that representative tumor specimens in paraffin blocks (preferred) or 10 (or more) serial, freshly cut, unstained slides be submitted. See Section 4.5.7.1 for details.

[d] Vital signs include pulse rate, respiratory rate, blood pressures, and temperature. Vital signs should be recorded as described in Section 4.5.4.

[e] Symptom-directed physical examinations; see Section 4.5.3 for details.

[f] ECG recordings will be obtained when clinically indicated.

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

[h] At screening, the patient must have adequate hematologic and end-organ function defined by laboratory test results obtained within 14 days prior to randomization. See Section 4.1.1 for details.

[i] Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total CO_2 if considered standard of care in the region, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.

[j] Serum pregnancy test within 14 days before Cycle 1, Day 1.

[k] Urine pregnancy tests; if a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

[l] Total T3 will be tested only at sites where free T3 is not performed.

[m] Thyroid function testing (TSH, free T3, free T4) collected on Day 1 of Cycles 1, 4, 8, and 12, and every fourth cycle thereafter.

Appendix 1
Schedule of Assessments (cont.)

[n] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the study. Patients with active hepatitis B (chronic or acute; defined as having a positive HBsAg test result at screening) will be excluded from the study. Patients 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 patients prior to randomization. Patients with HCV will be excluded from the study; patients who test positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

[o] Urinalysis by dipstick (specific gravity, pH, glucose, protein, ketones, and blood). Urinalysis is required at screening and will be obtained when clinically indicated.

[p] For atezolizumab/placebo, 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. For carboplatin and etoposide, study drug will be administered as described in Section 4.3.2.

[q] During the maintenance phase, PCI is permitted as per local standard-of-care and will be reported on the Prophylactic Cranial Irradiation eCRF.

[r] CT scans (with oral/IV contrast unless contraindicated) or MRI scans of the chest and abdomen. A CT or MRI scan of the pelvis is required at screening and as clinically indicated or as per local standard-of-care at subsequent response evaluations. A CT (with contrast) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients. See Section 4.5.5 for details.

[s] Perform every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1 and then every 9 weeks (±7 days) thereafter, after completion of the Week 48 tumor assessment, 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. Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will continue to undergo tumor assessments every 6 weeks (±7 days) or sooner if symptomatic deterioration occurs. For these patients, tumor assessments will continue every 6 weeks (±7 days), regardless of time on study, until study treatment is discontinued. See Section 4.5.5 for details.

[t] If the patient discontinued study treatment for any reason other than 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 patient had remained on study treatment (i.e., every 6 weeks [± 7 days] for 48 weeks following Cycle 1, Day 1 and then every 9 weeks [± 7 days] thereafter) until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first, even if the patient starts another anti-cancer therapy after study treatment discontinuation, unless consent is withdrawn. See Section 4.5.5 for details.

[u] See Appendix 2 for detailed schedule.

[v] Optional tumor biopsy at radiographic disease progression, if clinically feasible, preferably within 40 days of radiographic progression or prior to start of the next anti-cancer therapy, whichever occurs is sooner.

[w] The optional RCR whole blood sample requires an additional informed consent and the sample can be collected at any time during the course of the study.

[x] All serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study drug, whichever occurs first. All other adverse events,

regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study drug, whichever occurs first. After this period, all deaths should continue to be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment (see Section 5.6). These events should be reported through use of the Adverse Event eCRF.

[y] From 7 days before screening until the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

[z] EORTC QLQ-C30, EORTC QLQ-LC13, and the EQ-5D-5L questionnaires will be completed by the patients on the ePRO tablet at each scheduled study visit prior to administration of study drug and prior to any other study assessment(s). During survival follow-up, the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L questionnaires will be completed at 3 months (±30 days) and 6 months (±30 days) following radiographic disease progression per RECIST v1.1 (or at 3 months [±30 days] and 6 months [±30 days] after treatment is discontinued for patients who continue treatment after disease progression per RECIST v1.1). Patients who discontinue study treatment for any reason other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will complete EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L at each tumor assessment visit until radiographic disease progression per RECIST v1.1, unless the patient withdraws consent or the Sponsor terminates the study, whichever occurs first. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. Patients whose native language is not available in the ePRO device or who are deemed by the investigator incapable of inputting their ePRO assessment after undergoing appropriate training are exempt from all ePRO assessments.

[aa] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits every 3 months or more frequently until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up (this request must be documented in the source documents and signed by the investigator). If the patient 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.

Appendix 2
Schedule of Pharmacokinetic, Pharmacodynamic, Biomarker, and Anti-Therapeutic Antibody Assessments

Study Visit	Time	Atezolizumab/Placebo + Carboplatin + Etoposide
Cycle 1, Day 1 [a]	Predose (same day as treatment administration) (for biomarker sampling, prior to first dose of steroids)	• Atezolizumab ATA • Atezolizumab PK • Carboplatin PK [b] • Etoposide PK [b] • Biomarkers [c]
	30 (± 10) minutes after end of atezolizumab infusion	Atezolizumab PK
	5–10 minutes before the end of carboplatin infusion [b]	Carboplatin PK [b]
	1 hour (± 15 minutes) after end of carboplatin infusion [b]	Carboplatin PK [b]
	5–10 minutes before the end of etoposide infusion [b]	Etoposide PK [b]
	1 hour (± 15 minutes) after end of etoposide infusion [b]	Etoposide PK [b]
	4 hours (± 30 minutes) after end of etoposide infusion [b]	Etoposide PK [b]
Cycle 2, Day 1	Predose (same day as treatment administration)	• Atezolizumab ATA • Atezolizumab PK • Biomarkers [d]
Cycle 3, Day 1	Predose (same day as treatment administration)	• Atezolizumab ATA • Atezolizumab PK • Carboplatin PK [b] • Etoposide PK [b] • Biomarkers [c]

Appendix 2
Schedule of Pharmacokinetic, Pharmacodynamic, Biomarker, and Anti-Therapeutic Antibody Assessments (cont.)

Study Visit	Time	Atezolizumab/Placebo + Carboplatin + Etoposide
Cycle 3, Day 1	5–10 minutes before the end of carboplatin infusion [b]	Carboplatin PK [b]
	1 hour (± 15 minutes) after end of carboplatin infusion [b]	Carboplatin PK [b]
	5–10 minutes before the end of etoposide infusion [b]	Etoposide PK [b]
	1 hour (± 15 minutes) after end of etoposide infusion [b]	Etoposide PK [b]
	4 hours (± 30 minutes) after end of etoposide infusion [b]	Etoposide PK [b]
Cycles 4, 8, and 16, Day 1	Predose (same day as treatment administration)	• Atezolizumab ATA • Atezolizumab PK • Biomarkers [d]
After Cycle 16, every 8th cycle, Day 1	Predose (same day as treatment administration)	• Atezolizumab ATA • Atezolizumab PK • Biomarkers [d]
At time of fresh biopsy (on-treatment including during follow-up)	At visit	• Biomarkers [d]
Treatment discontinuation visit	At visit	• Atezolizumab ATA • Atezolizumab PK • Biomarkers [d]
120 (± 30 days) after last dose of atezolizumab/placebo	At visit	• Atezolizumab ATA • Atezolizumab PK • Biomarkers [d]
Any time point during the study (RCR consent required)		Optional RCR blood (DNA extraction) [e]

ATA = anti-therapeutic antibody; PK = pharmacokinetic; RCR = Roche Clinical Repository.

Note: Serum PK samples for atezolizumab; plasma PK samples for carboplatin and etoposide.

[a] Biomarker sampling before Cycle 1, Day 1 should be performed before patients are treated with first dose of steroids.

[b] At select sites, a subset of approximately 40 patients will undergo the additional PK assessments for carboplatin and etoposide. The additional PK assessments should be taken only if the patient is receiving both carboplatin and etoposide at the cycle.

[c] Plasma, serum, whole blood for biomarkers.

[d] Plasma and serum for biomarkers.

[e] The optional RCR blood sample (for DNA extraction) requires an additional informed consent and can be collected at any time during the course of the study.

Appendix 3
Veterans Administration Lung Study Group (VALG) Staging System for SCLC

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.
Source: Micke et al. 2002.

Appendix 4
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows.

a. Measurable Tumor 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 of:

- 10 mm by computed tomography (CT) or magnetic resolution imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 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 no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with $\geq$ 10 to $<$ 15 mm short axis), 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 masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

Appendix 4
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

c. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure 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 patient, 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. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

a. Measurement of Lesions

All measurements should be recorded in metric notation, using 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.

b. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging-based evaluation should always be the preferred option.

Appendix 4
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Clinical Lesions. Clinical lesions will be considered measurable only when they are superficial and ≥ 10 mm in diameter as assessed using 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 scan 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, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan on the basis of the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT scan or MRI scan (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after a baseline contrast CT scan is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) scan 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 patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

Appendix 4
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION 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 in instances where patients 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 recorded as non-target lesions (even if the size is > 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs but, additionally, 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. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI scan 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 < 10 mm are considered non-pathological and should not be recorded or followed.

Appendix 4
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Lesions irradiated within 3 weeks prior to Cycle 1 Day 1 may not be counted as target lesions.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, 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").

RESPONSE CRITERIA

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

b. Special Notes on the Assessment of Target Lesions

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 nodes regress to < 10 mm on study. This means that

when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis $<$10 mm.

Target Lesions That Become Too Small to Measure. While on study, all lesions (nodal and non-nodal) 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 measure 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 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 BML (below measurable limit) 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 BML should also be ticked.)

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. 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 maximal longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. Although 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 protocol.

- 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).

Appendix 4
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

- Non-CR/Non-PD: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, 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 disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease; that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. Although it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. 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 patient'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, then progression should be declared using the date of the initial scan.

EVALUATION OF RESPONSE

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Appendix 4
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Table 1 Timepoint Response: Patients 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 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.

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, 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 lesion(s) would not change the assigned timepoint response. This would be most likely to happen

in the case of PD. For example, if a patient 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 patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be “unable to assess” except where there is clear progression. Overall response would be “unable to assess” if either the target response or the non-target response is “unable to assess,” except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Appendix 4
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

c. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of 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 document objective

progression 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 patients is to be determined by evaluation of target and non-target disease as shown in Table 1–Table 3.

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.

If a patient undergoes an excisional biopsy or other appropriate approach (e.g., multiple passes with large core needle) of a new lesion or an existing solitary progressive lesion that following serial sectioning and pathological examination reveals no evidence of malignancy (e.g., inflammatory cells, fibrosis, etc.), then the new lesion or solitary progressive lesion will not constitute disease progression.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 5
Modified Response Evaluation Criteria in Solid Tumors

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions. Therefore, modified response criteria have been developed that account for the possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment.

Modified Response Evaluation Criteria in Solid Tumors (RECIST) is derived from RECIST, Version 1.1 (v1.1) conventions[3, 4, 5] and immune-related response criteria[5, 6, 7] (irRC). When not otherwise specified, RECIST v1.1 conventions will apply.

Modified RECIST and RECIST v1.1: Summary of Changes

	RECIST v1.1	Modified RECIST
New lesions after baseline	Define progression	New measurable lesions are added into the total tumor burden and followed.
Non-target lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of ≥20% increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease

RECIST = Response Evaluation Criteria in Solid Tumors.

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3 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1) Eur J Cancer 2009;45:228–47.

4 Topalian et al. Safety activity, and immune correlates of anti–PD-L1 antibody in cancer. N Engl J Med 2012;366:2443–54.

5 Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immunetherapy activity in solid tumors: immune-related response criteria Clin Can Res 2009;15:7412–20.

6 Nishino M, Gargano M, Suda M, et al. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab. J Immunother Can 2014;2:17.

7 Nishino M, Giobbie-Hurder A, Gargano M et al. Developing a common language for tumor response to immuno therapy: immune-reated response criteria using unidimensional measurements. Clin Can Res 2013;19:3936–43.

Appendix 5
Modified Response Evaluation Criteria in Solid Tumors (cont.)

A. DEFINITIONS OF MEASURABLE/NON-MEASURABLE LESIONS

All measurable and non-measurable lesions should be assessed at Screening and at the protocol-specified tumor assessment timepoints. Additional assessments may be performed, as clinically indicated for suspicion of progression.

A.1 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 no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

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 no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

A.2 NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter $<$10 mm or pathological lymph nodes with short axis $\geq$10 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.

A.3 SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions

Bone scan, positron emission tomography (PET) scan, or 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 as 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 as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, 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. Study protocols should detail the conditions under which such lesions would be considered measurable.

B. TUMOR RESPONSE EVALUATION

B.1 DEFINITIONS OF TARGET/NON-TARGET LESIONS

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 patients 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 recorded as non-measurable lesions (even if the size is $>$10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and 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.

Appendix 5
Modified Response Evaluation Criteria in Solid Tumors (cont.)

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. Nodal 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.

Lesions irradiated within 3 weeks prior to Cycle 1 Day 1 may not be counted as target lesions.

Non-Target Lesions

All other lesions (or sites of disease), 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”).

After baseline, changes in non-target lesions will contribute only in the assessment of CR (i.e., a CR is attained only with the complete disappearance of all tumor lesions, including non-target lesions) and will not be used to assess progressive disease.

New Lesions

During the study, all new lesions identified and recorded after baseline must be assessed at all tumor assessment timepoints. New lesions will also be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST, (e.g., non–lymph node lesions must be ≥ 10mm; see note for new lymph node lesions below). Up to a maximum of five new lesions total (and a maximum of two lesions per organ), all with measurements at all timepoints, can be included in the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the tumor response evaluation.

New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint will be measured from that point on and contribute to the sum of longest diameters (SLD), if the maximum number of 5 measurable new lesions being followed has not been reached.

B.2 CALCULATION OF SUM OF THE DIAMETERS

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as a measure of tumor burden.

The sum of the diameters is calculated at baseline and at each tumor assessment for the purpose of classification of tumor responses.

Sum of the Diameters at Baseline: The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

Sum of the Diameters at Tumor Assessment: For every on-study tumor assessment collected per protocol or as clinically indicated the sum of the diameters at tumor assessment will be calculated using tumor imaging scans. All target lesions selected at baseline and up to five new measurable lesions (with a maximum of two new lesions per organ) that have emerged after baseline will contribute to the sum of the diameters at tumor assessment. Hence, each net percentage change in tumor burden per assessment with use of modified RECIST accounts for the size and growth kinetics of both old and new lesions as they appear.

Note: In the case of new lymph nodes, RECIST v1.1 criteria for measurability (equivalent to baseline target lesion selection) will be followed. That is, if at first appearance the short axis of a new lymph node lesion ≥ 15 mm, it will be considered a measureable new lesion and will be tracked and included in the SLD. Thereafter, the lymph node lesion will be measured at subsequent timepoints and measurements will be included in the SLD, even if the short axis diameter decreases to < 15 mm (or even < 10 mm). However, if it subsequently decreases to < 10 mm, and all other lesions are no longer detectable (or have also decreased to a short axis diameter of < 10 mm if lymph nodes), then a response assessment of CR may be assigned.

If at first appearance the short axis of a new lymph node is ≥ 10 mm and < 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion. It will not be included in the SLD unless it subsequently becomes measurable (short axis diameter ≥ 15 mm).

The appearance of new lymph nodes with diameter < 10 mm should not be considered pathological and not considered a new lesion.

Appendix 5
Modified Response Evaluation Criteria in Solid Tumors (cont.)

B.3 RESPONSE CRITERIA

Timepoint Response

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

Complete Response (CR): Disappearance of all target and non-target lesions. Lymph nodes that shrink to <10 mm short axis are considered normal.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.

Note: the appearance of new measurable lesions is factored into the overall tumor burden, but *does not automatically qualify as progressive disease* until the sum of the diameters increases by $\geq 20\%$ when compared with the sum of the diameters at nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the diameters while on study.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and selected new measurable lesions, taking as reference the smallest sum on study (nadir SLD; this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Impact of New Lesions on Modified RECIST

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall modified RECIST tumor response.

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is considered not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would only happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed but

those gave a sum of 80 mm, the patient will be assigned PD status, regardless of the contribution of the missing lesion.

Table 1 Modified RECIST Timepoint Response Definitions

% Change in Sum of the Diameters [a]	Non-Target Lesion Response Assessment	Overall Modified RECIST Timepoint Response
−100% from baseline [b]	CR	CR
−100% from baseline [b]	Non-CR or not all evaluated	PR
≤ −30% from baseline	Any	PR
> −30% to < +20%	Any	SD
Not all evaluated	Any	NE
≥ +20%from nadir SLD	Any	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; SLD = sum of the longest diameter.

[a] Percent change in sum of the diameters (including measurable new lesions when present).

[b] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm in order to meet the definition of CR.

Appendix 6
EORTC QLQ-C30

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):

		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

Appendix 6
EORTC QLQ-C30 (cont.)

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 7
EORTC QLQ-LC13

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 8
EQ-5D-5L

Health Questionnaire

English version for the USA

Appendix 8
EQ-5D-5L (cont.)

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 ❑

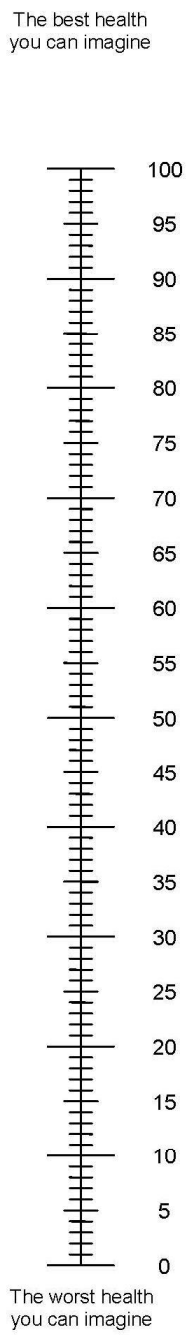
ANXIETY / DEPRESSION

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 ❑

Appendix 8
EQ-5D-5L (cont.)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> 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 9
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all predisease 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
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study drug infusion, the following procedures should be performed:

1. Stop the study drug infusion.
2. Maintain an adequate airway.
3. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
4. Continue to observe the patient and document observations.

Appendix 11
Preexisting Autoimmune Diseases

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects 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 subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on thyroid replacement hormone therapy are 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). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

Acute disseminated encephalomyelitis	Epidermolysis bullosa acquista	Ord's thyroiditis
Addison's disease	Gestational pemphigoid	Pemphigus
Ankylosing spondylitis	Giant cell arteritis	Pernicious anemia
Antiphospholipid antibody syndrome	Goodpasture's syndrome	Polyarteritis nodusa
Aplastic anemia	Graves' disease	Polyarthritis
Autoimmune hemolytic anemia	Guillain-Barré syndrome	Polyglandular autoimmune syndrome
Autoimmune hepatitis	Hashimoto's disease	Primary biliary cirrhosis
Autoimmune hypoparathyroidism	IgA nephropathy	Psoriasis
Autoimmune hypophysitis	Inflammatory bowel disease	Reiter's syndrome
Autoimmune myocarditis	Interstitial cystitis	Rheumatoid arthritis
Autoimmune oophoritis	Kawasaki's disease	Sarcoidosis
Autoimmune orchitis	Lambert-Eaton myasthenia syndrome	Scleroderma
Autoimmune thrombocytopenic purpura	Lupus erythematosus	Sjögren's syndrome
Behcet's disease	Lyme disease - chronic	Stiff-Person syndrome
Bullous pemphigold	Meniere's syndrome	Takayasu's arteritis
Chronic fatigue syndrome	Mooren's ulcer	Ulcerative colitis
Chronic inflammatory demyelinating polyneuropathy	Morphea	Vitiligo
	Multiple sclerosis	Vogt-Kovanagi-Harada disease
Chung-Strauss syndrome	Myasthenia gravis	Wegener's granulomatosis
Crohn's disease	Neuromyotonia	
Dermatomyositis	Opsoclonus myoclonus syndrome	
Diabetes mellitus type 1	Optic neuritis	
Dysautonomia		

Appendix 12
Risks Associated with Atezolizumab and 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.

Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events 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-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients 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, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 1.

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	*Management*
Pulmonary event, Grade 1	• *Continue atezolizumab and monitor closely.* • *Re-evaluate on serial imaging.* • *Consider patient referral to pulmonary specialist.*
Pulmonary event, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *For recurrent events, treat as a Grade 3 or 4 event.*
Pulmonary event, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Bronchoscopy or BAL is recommended.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

BAL = bronchoscopic alveolar lavage.

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

HEPATIC EVENTS

Immune-related hepatitis has been associated with the administration of atezolizumab. Eligible patients 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 2.

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

Table 2 Management Guidelines for Hepatic Events

Event	*Management*
Hepatic event, Grade 1	• *Continue atezolizumab.* • *Monitor LFTs until values resolve to within normal limits or to baseline values.*
Hepatic event, Grade 2	***All events:*** • *Monitor LFTs more frequently until return to baseline values.* ***Events of > 5 days' duration:*** • *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]

LFT = liver function tests.

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	*Management*
Hepatic event, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

LFT =liver function tests.

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

GASTROINTESTINAL EVENTS

Immune-related colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 3.

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 three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	*Management*
Diarrhea or colitis, Grade 1	• *Continue atezolizumab.* • *Initiate symptomatic treatment.* • *Endoscopy is recommended if symptoms persist for >7 days.* • *Monitor closely.*
Diarrhea or colitis, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Initiate symptomatic treatment.* • *Patient referral to GI specialist is recommended.* • *For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Diarrhea or colitis, Grade 3	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to GI specialist for evaluation and confirmatory biopsy.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]

GI =gastrointestinal.

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	*Management*
Diarrhea or colitis, Grade 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Refer patient to GI specialist for evaluation and confirmation biopsy.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

GI =gastrointestinal.

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 4.

Patients 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 patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine 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.

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events

Event	*Management*
Asymptomatic hypothyroidism	• *Continue atezolizumab.* • *Initiate treatment with thyroid replacement hormone.* • *Monitor TSH weekly.*
Symptomatic hypothyroidism	• *Withhold atezolizumab.* • *Initiate treatment with thyroid replacement hormone.* • *Monitor TSH weekly.* • *Consider patient referral to endocrinologist.* • *Resume atezolizumab when symptoms are controlled and thyroid function is improving.*
Asymptomatic hyperthyroidism	***TSH ≥0.1 mU/L and <0.5 mU/L:*** • *Continue atezolizumab.* • *Monitor TSH every 4 weeks.* ***TSH <0.1 mU/L:*** • *Follow guidelines for symptomatic hyperthyroidism.*
Symptomatic hyperthyroidism	• *Withhold atezolizumab.* • *Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.* • *Consider patient referral to endocrinologist.* • *Resume atezolizumab when symptoms are controlled and thyroid function is improving.* • *Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-related hyperthyroidism.* [c]

MRI =magnetic resonance imaging; TSH =thyroid-stimulating hormone.

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	*Management*
Symptomatic adrenal insufficiency, Grade 2–4	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to endocrinologist.* • *Perform appropriate imaging.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Hyperglycemia, Grade 1 or 2	• *Continue atezolizumab.* • *Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines.* • *Monitor for glucose control.*
Hyperglycemia, Grade 3 or 4	• *Withhold atezolizumab.* • *Initiate treatment with insulin.* • *Monitor for glucose control.* • *Resume atezolizumab when symptoms resolve and glucose levels are stable.*

MRI =magnetic resonance imaging; TSH =thyroid-stimulating hormone.

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	*Management*
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to endocrinologist.* • *Perform brain MRI (pituitary protocol).* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *Initiate hormone replacement if clinically indicated.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *For recurrent hypophysitis, treat as a Grade 4 event.*
Hypophysitis (pan-hypopituitarism), Grade 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Refer patient to endocrinologist.* • *Perform brain MRI (pituitary protocol).* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *Initiate hormone replacement if clinically indicated.*

MRI =magnetic resonance imaging; TSH =thyroid-stimulating hormone.

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

Event	*Management*
Ocular event, Grade 1	• *Continue atezolizumab.* • *Patient referral to ophthalmologist is strongly recommended.* • *Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.* • *If symptoms persist, treat as a Grade 2 event.*
Ocular event, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Patient referral to ophthalmologist is strongly recommended.* • *Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Ocular event, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Refer patient to ophthalmologist.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-RELATED MYOCARDITIS

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients 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.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 6 Management Guidelines for Immune-Related Myocarditis

Event	*Management*
Immune-related myocarditis, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset* [a] *and contact Medical Monitor.* • *Refer patient to cardiologist.* • *Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate.* • *Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Immune-related myocarditis, Grade 3-4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Refer patient to cardiologist.* • *Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

ECMO =extracorporeal membrane oxygenation; VAD =ventricular assist device.

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

INFUSION-RELATED REACTIONS

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) with Cycle 1 of atezolizumab

may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

Guidelines for medical management of IRRs during Cycle 1 are provided in Table 7. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table 7 Management Guidelines for Infusion-Related Reactions

Event	*Management*
IRR, Grade 1	• *Reduce infusion rate to half the rate being given at the time of event onset.* • *After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate.* • *If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.*
IRR, Grade 2	• *Interrupt atezolizumab infusion.* • *Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids).* • *After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset.* • *For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs.*
IRR, Grade 3 or 4	• *Stop infusion.* • *Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids).* • *Permanently discontinue atezolizumab and contact Medical Monitor.* [a]

IRR = infusion-related reaction.

[a] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. 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 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	*Management*
Amylase and/or lipase elevation, Grade 2	***Amylase and/or lipase >1.5–2.0 ×ULN:*** • *Continue atezolizumab.* • *Monitor amylase and lipase weekly.* • *For prolonged elevation (e.g., >3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone.* ***Asymptomatic with amylase and/or lipase >2.0–5.0 ×ULN:*** • *Treat as a Grade 3 event.*
Amylase and/or lipase elevation, Grade 3 or 4	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to GI specialist.* • *Monitor amylase and lipase every other day.* • *If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.* [c]

GI =gastrointestinal.

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	*Management*
Immune-related pancreatitis, Grade 2 or 3	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to GI specialist.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Immune-related pancreatitis, Grade 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Refer patient to GI specialist.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

GI =gastrointestinal.

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self limited, with or without pruritus. 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 9.

Table 9 Management Guidelines for Dermatologic Events

Event	*Management*
Dermatologic event, Grade 1	• *Continue atezolizumab.* • *Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).*
Dermatologic event, Grade 2	• *Continue atezolizumab.* • *Consider patient referral to dermatologist.* • *Initiate treatment with topical corticosteroids.* • *Consider treatment with higher-potency topical corticosteroids if event does not improve.*
Dermatologic event, Grade 3	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to dermatologist.* • *Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Dermatologic event, Grade 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c]

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients 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 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	*Management*
Immune-related neuropathy, Grade 1	• *Continue atezolizumab.* • *Investigate etiology.*
Immune-related neuropathy, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Investigate etiology.* • *Initiate treatment as per institutional guidelines.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Immune-related neuropathy, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Initiate treatment as per institutional guidelines.*
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Refer patient to neurologist.* • *Initiate treatment as per institutional guidelines.* • *Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.*

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

IMMUNE-RELATED MENINGOENCEPHALITIS

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any patient 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 patients 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.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for Immune-Related Meningoencephalitis

Event	*Management*
Immune-related meningoencephalitis, all grades	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [a] • *Refer patient to neurologist.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

[a] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

RENAL EVENTS

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients 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 patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Renal Events

Event	*Management*
Renal event, Grade 1	• *Continue atezolizumab.* • *Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.*
Renal event, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to renal specialist.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Renal event, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* • *Refer patient to renal specialist and consider renal biopsy.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

IMMUNE-RELATED MYOSITIS

Immune-related myositis has been associated with the administration of atezolizumab. 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 signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13 Management Guidelines for Immune-Related Myositis

Event	*Management*
Immune-related myositis, Grade 1	• *Continue atezolizumab.* • *Refer patient to rheumatologist or neurologist.* • *Initiate treatment as per institutional guidelines.*
Immune-related myositis, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset* [a] *and contact Medical Monitor.* • *Refer patient to rheumatologist or neurologist.* • *Initiate treatment as per institutional guidelines.* • *Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

Table 13 Management Guidelines for Immune-Related Myositis (cont.)

Immune-related myositis, Grade 3	• *Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor.* • *Refer patient to rheumatologist or neurologist.* • *Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases.* • *Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, resume atezolizumab. [b]* • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]* • *For recurrent events, treat as a Grade 4 event.*
Immune-related myositis, Grade 4	• *Permanently discontinue atezolizumab and contact Medical Monitor. [c]* • *Refer patient to rheumatologist or neurologist.* • *Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases.* • *Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.*

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

SYSTEMIC IMMUNE ACTIVATION

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk for atezolizumab.

Recommendations regarding early identification and management of systemic immune activation are provided below. In the event of suspected systemic immune activation, atezolizumab should be withheld and clinical specialists (e.g., rheumatology, clinical immunology, or solid organ or hematopoietic stem cell transplant specialists) and the Medical Monitor should be consulted for additional guidance.

Early disease recognition is critical, and systemic immune activation should be suspected if, in the absence of an alternative etiology, the patient meets two or more of the following criteria:

- *Hypotension that is refractory to aggressive IV fluid challenge*

  Vasopressor support may be required.
- *Respiratory distress that requires aggressive supportive care*

  Supplemental oxygen and intubation may be required.
- *Fever >38.5 ℃*
- *Acute renal or hepatic failure*
- *Bleeding from coagulopathy*
- *Any of the following unexplained laboratory abnormalities (change from baseline): cytopenias (in two or more lineages), significant transaminitis, or coagulopathy*

For patients with suspected systemic immune activation, an initial evaluation should include the following:

- *CBC with peripheral smear*
- *PT, PTT, fibrinogen, and D-dimer*
- *Ferritin*
- *Soluble interleukin 2 (IL-2) receptor (soluble CD25)*
- *Triglycerides*
- *AST, ALT, and direct bilirubin*
- *LDH*
- *Complete neurologic and abdominal examination (assess for hepatosplenomegaly)*

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Laboratory tests with normal results should be repeated frequently in patients for whom a high clinical suspicion of systemic immune activation exists.

If neurologic abnormalities are present, consider cerebrospinal fluid analysis and/or an MRI of the brain.

If cytopenias are present (Grade ≥2 in two or more lineages) or ferritin is ≥3000 ng/mL, the following evaluations should also be performed:

- *Bone marrow biopsy and aspirate (assess for evidence of hemophagocytosis)*
- *Adenovirus, cytomegalovirus, Epstein-Barr virus, herpes-simplex virus, and human herpesvirus 6, 7, and 8 evaluation (for reactivated or active disease)*

Diagnostic criteria and recommended management for systemic immune activation are provided in Table 14. The diagnostic criteria apply only when alternative etiologies have been excluded.

An adverse event of systemic immune activation should be reported on the Adverse Event eCRF if it meets the criteria for "consistent with systemic immune activation" or "probable systemic immune activation" as outlined in Table 14.

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 14 Diagnostic Criteria and Recommended Management for Systemic Immune Activation

<table>
<tr><td colspan="3">Systemic Immune Activation Diagnostic Criteria
(applicable only when alternative etiologies have been excluded)</td></tr>
<tr><td colspan="2">Major Criteria</td><td>Minor Criteria</td></tr>
<tr><td colspan="2">• Fever ≥38.5 ℃ on more than one occasion
• Ferritin ≥3000 ng/mL
• Cytopenias (Grade ≥2 in two or more lineages)
• Age-adjusted soluble interleukin-2 receptor elevated by ≥2 standard deviations
• Severe (Grade ≥3) or progressive dysfunction in two or more organs
• Decreased fibrinogen</td><td>• Splenomegaly
• Hemophagocytosis in bone marrow, spleen, or lymph nodes
• Elevated γ-glutamyl transpeptidase (GGT) or liver function tests (AST, ALT, or direct bilirubin)
• Elevated triglycerides
• Elevated LDH
• Decreased natural killer cell activity</td></tr>
<tr><td colspan="3">Diagnosis and Management of Systemic Immune Activation</td></tr>
<tr><td>Number of Criteria</td><td>Diagnosis</td><td>Action to Be Taken</td></tr>
<tr><td>≥4 major criteria</td><td>Consistent with systemic immune activation</td><td>• Permanently discontinue atezolizumab.
• Consider treatment with an immunosuppressive agent (i.e., cytokine inhibitors) and IV corticosteroids (i.e., methylprednisolone 1 g once daily or equivalent, or dexamethasone ≥10 mg/m² once daily if neurologic abnormalities are present).
• Contact the Medical Monitor for additional recommendations.
• Consider HLH-2004 protocol (Henter et al. 2007) if there is no clinical improvement.</td></tr>
<tr><td>3 major criteria
<u>OR</u>
2 major plus ≥3 minor criteria</td><td>Probable systemic immune activation</td><td>• Depending on clinical severity, follow guidelines for "Consistent with systemic immune activation" or "Possible systemic immune activation" diagnosis.
• Clinical specialists and the Medical Monitor may be contacted for recommendations.</td></tr>
<tr><td>2 major plus ≤2 minor criteria
<u>OR</u>
1 major plus ≥4 minor criteria</td><td>Possible systemic immune activation</td><td>• Withhold atezolizumab.
• Consider treatment with IV corticosteroids.
• Clinical specialists and the Medical Monitor may be contacted for additional recommendations.
• Follow guidelines for "Consistent with systemic immune activation" diagnosis if there is no clinical improvement or if clinical worsening occurs.
• If clinical improvement occurs, atezolizumab may be resumed following a benefit-risk assessment by the Medical Monitor.</td></tr>
</table>

Notes: Criteria are adapted from a Delphi Survey of 26 experts who provided helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients (Hejblum et al. 2014).
Grades are based on National Cancer Institute Common Terminology Criteria for Adverse Events.
These recommendations do not replace clinical judgment and are intended as suggested guidance.

REFERENCES

Hejblum G, Lambotte O, Galicier L, et al. A web-based Delphi study for eliciting helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients. PLoS ONE 2014;9(4):e94024. doi: 10.1371/journal.pone.0094024.

Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–31.

STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE I/III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF CARBOPLATIN PLUS ETOPOSIDE WITH OR WITHOUT ATEZOLIZUMAB (MPDL3280A, ANTI–PD-L1 ANTIBODY) IN PATIENTS WITH UNTREATED EXTENSIVE-STAGE SMALL CELL LUNG CANCER**

PROTOCOL NUMBER: GO30081

STUDY DRUG: Atezolizumab

VERSION NUMBER: 3

IND NUMBER: 117296

EUDRACT NUMBER: 2015-004861-97

SPONSOR: F. Hoffmann-La Roche Ltd.

PLAN PREPARED BY: [redacted], Ph.D.

DATE FINAL: 1 December 2017

DATE AMENDED: See electronic date stamp below

Name	Reason for Signing	Date and Time (UTC)
[redacted]	Company Signatory	14-May-2018 19:00:15

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. BACKGROUND

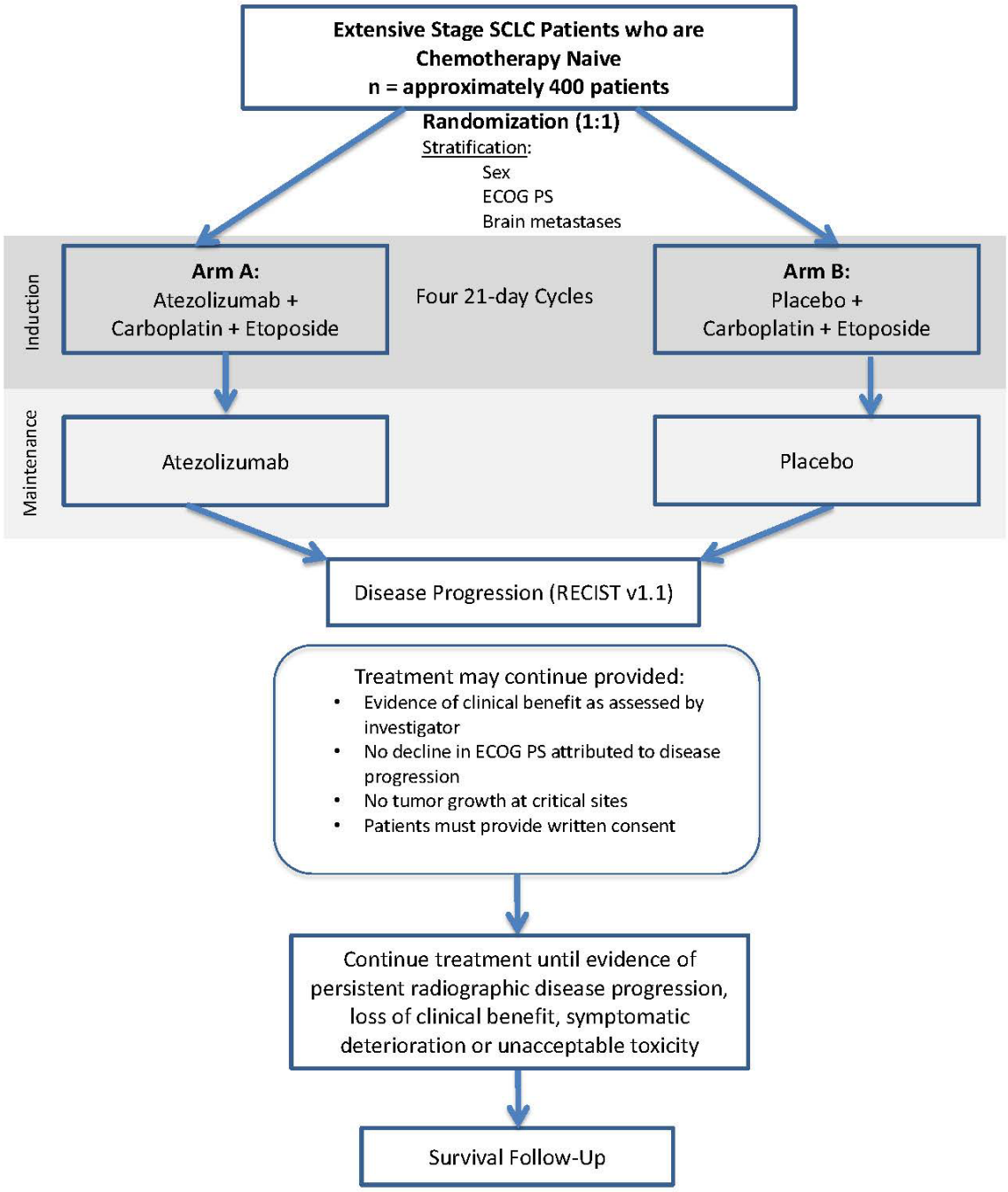
This Statistical Analysis Plan (SAP) is based on Protocol GO30081 (IMpower133), "A Phase I/III, Randomized, Double-Blind, Placebo-Controlled Study of Carboplatin plus Etoposide with or without Atezolizumab (Anti–PD-L1 Antibody) in Patients with Untreated Extensive-Stage Small Cell Lung Cancer". This SAP provides details of the planned analyses and statistical methods for Study GO30081 to support potential registration for carboplatin plus etoposide with atezolizumab as first-line treatment for patients with extensive-stage small cell lung cancer (ES-SCLC). The background for the study can be found in the study protocol. Any analyses that are beyond those outlined in the protocol are delineated in this document.

In this study, the global population will include all patients enrolled during the global enrollment phase [redacted]

2. STUDY DESIGN

This is a randomized, Phase I/III, multicenter, double-blinded, placebo-controlled study designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin + etoposide compared with placebo + carboplatin + etoposide in patients who have ES-SCLC and who are chemotherapy-naive for their extensive-stage disease. Figure 1 illustrates the study design.

Figure 1 Study Schema



ECOG PS = Eastern Cooperative Oncology Group performance status; SCLC = small cell lung cancer; RECIST = Response Evaluation Criteria in Solid Tumors.

Eligible patients are stratified by sex (male vs. female), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1), and presence of brain metastases

(yes vs. no) and randomized 1:1 to receive one of the following treatment regimens as shown in Table 1.

Table 1 Study GO30081 Treatment Arms

Treatment Arm	Induction (Four 21-Day Cycles)	Maintenance (21-Day Cycles)
A	atezolizumab + carboplatin + etoposide	atezolizumab
B	placebo + carboplatin + etoposide	placebo

Induction treatment was administered on a 21-day cycle for four cycles.

Following the induction phase, patients continued on maintenance therapy with either atezolizumab or placebo.

Patients undergo tumor assessments at baseline and every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1, regardless of treatment dose delays. After completion of the Week 48 tumor assessment, tumor assessments are required every 9 weeks (±7 days) thereafter, regardless of treatment dose delays. Patients will undergo tumor assessments until radiographic disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first.

Treatment is discontinued in all patients (in both treatment arms) who exhibit evidence of disease progression per RECIST v1.1. However, patients may be considered for treatment beyond radiographic disease progression per RECIST v1.1, at the discretion of the investigator and after appropriate discussion with the patient and obtaining informed consent, only if all of the following criteria are met:

- Evidence of clinical benefit as assessed by the investigator
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial progression

Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 should be closely monitored clinically and with a follow-up scan in 6 weeks or sooner if symptomatic deterioration occurs. Treatment should be discontinued if clinical deterioration due to disease progression occurs at any time, or if persistent disease growth is confirmed in a follow-up scan. In addition, patients should be discontinued for unacceptable toxicity or for any other signs or symptoms of deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status.

Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will continue to undergo tumor assessments every 6 weeks (±7 days), regardless of time in the study, or sooner if symptomatic deterioration occurs, until study treatment is discontinued.

Patients who discontinue treatment for reasons other than 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 patient had remained on study treatment (i.e., every 6 weeks [±7 days] for 48 weeks following Cycle 1, Day 1 and then every 9 weeks [±7 days] thereafter, regardless of treatment dose delays) until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.

The co-primary efficacy endpoints are progression-free survival (PFS) as assessed by the investigator according to RECIST v1.1 and overall survival (OS). See Section 2.2 for further details on the co-primary efficacy endpoints, as well as secondary and other safety, pharmacokinetic (PK), and exploratory endpoints.

There are no interim analyses planned for PFS and one interim analysis planned for OS in this study. See Section 2.4 for detailed analysis timing.

An external independent Data Monitoring Committee (iDMC) was set up to evaluate safety data on an ongoing basis.

[redacted] See Section 5 for more details.

2.1 PROTOCOL SYNOPSIS

The protocol synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 OUTCOME MEASURES

2.2.1 Primary Efficacy Outcome Measures

The co-primary efficacy outcome measures for this study are:

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first
- OS, defined as the time from randomization to death from any cause

2.2.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are:

- Objective response (OR), defined as complete response (CR) or partial response (PR) as determined by the investigator according to RECIST v1.1
- Duration of response (DOR), defined as the time interval from first occurrence of a documented objective response to the time of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever comes first
- PFS rates at 6 months and at 1 year, defined as the proportion of patients who are alive without disease progression 6 months and 1 year after randomization, respectively
- OS rates at 1 and 2 years, defined as the proportion of patients who are alive 1 year and 2 years after randomization, respectively
- Time to deterioration (TTD) in patient-reported lung cancer symptoms, defined as time from randomization to deterioration (10-point change) on each of the European Organization for the Research and Treatment of Cancer (EORTC QLQ-C30) and supplemental lung cancer module (QLQ-LC13) symptom subscales maintained for two assessments or one assessment followed by death from any cause within 3 weeks

2.2.3 Exploratory Efficacy Outcome Measures

The exploratory efficacy outcome measures for this study are:

- OR, PFS, and DOR as determined by the investigator according to immune-modified RECIST
- Status of blood-based tumor mutational burden (bTMB), immune-, and SCLC-related and other exploratory biomarkers in archival and/or freshly obtained tumor tissues, and blood (or blood derivatives) collected before, during, or after treatment with atezolizumab or at progression and association with disease status and/or response to atezolizumab
- Change from baseline in patient-reported outcome (PROs) of health-related quality of life, lung cancer–related symptoms, physical functioning, and health status as assessed by the EORTC QLQ-C30 and QLQ-LC13

- Changes in levels and type of peripheral and tumor-specific T-cell populations during and after induction therapy and its relationship to efficacy and safety outcomes

2.2.4 Pharmacokinetic Efficacy Outcome Measures

The PK outcome measures for this study are:

- Maximum observed serum atezolizumab concentration (C_{max}) after infusion
- Minimum observed serum atezolizumab concentration (C_{min}) prior to infusion at selected cycles, at treatment discontinuation, and at 120 days (±30 days) after the last dose of atezolizumab
- Plasma concentrations for carboplatin
- Plasma concentrations for etoposide

2.2.5 Safety Outcome Measures

The safety outcome measures for this study are:

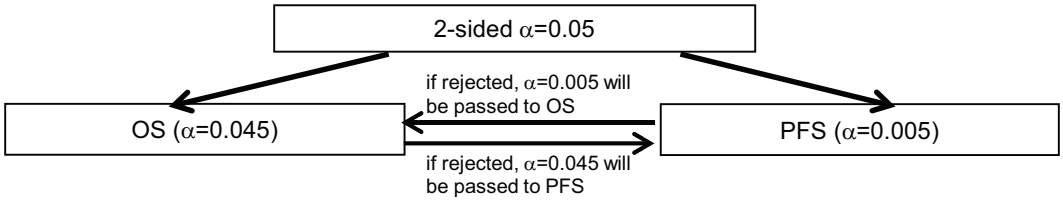
- Incidence, nature, and severity of adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4 (NCI CTCAE v4.0)
- Changes in vital signs, physical findings, and clinical laboratory results during and following study treatment administration
- Incidence of anti-drug antibody (ADA) response to atezolizumab and potential correlation with PK, safety, and efficacy

2.3 DETERMINATION OF SAMPLE SIZE

Determination of sample size is based on patients enrolled during the global enrollment phase of this study to the atezolizumab + carboplatin + etoposide arm and the placebo + carboplatin + etoposide arm in a 1:1 ratio. This study plans to randomize 400 patients during the global enrollment phase. [redacted]

To control the overall two-sided type I error rate at 0.05 in the analyses of patients enrolled during the global enrollment phase, a group sequential weighted Holm procedure (Ye et al. 2011) will be used wherein the two-sided significance levels of 0.005 and 0.045 are allocated to the primary comparisons for PFS and OS, respectively. If PFS in the intent-to-treat (ITT) population is statistically significant at the two-sided α level of 0.005, OS in the ITT population will be tested at a two-sided α level of 0.05. Additionally, if OS in the ITT population is statistically significant at the two-sided α level of 0.045, PFS in the ITT population will be tested at a two-sided α level of 0.05. The overview of the type I error rate control strategy is shown in Figure 2.

Figure 2 Group Sequential Weighted Holm Procedure



The sample size of the study is determined by the analysis of OS. To detect an improvement of hazard ratio (HR)=0.68 in OS using a log-rank test, approximately 306 deaths in the ITT population will be required to achieve an 91% power at a two-sided significance level of 0.045. One OS interim analysis will be performed when approximately 240 OS events in the ITT population are observed, which by estimation will occur at approximately 25 months after the first patient is randomized.

The primary analysis of PFS is planned to be conducted at the time of the OS interim analysis and is estimated to occur when approximately 295 PFS events in the ITT population have occurred, which is expected at approximately 25 months after the first patient is randomized. This provides a 99% power to detect an improvement of HR=0.55 in PFS at a two-sided significance level of 0.005. There will be no interim analyses for PFS.

The calculation of sample size and estimates of the analysis timelines are based on the following assumptions:

- PFS and OS follow one piece exponentially distributions respectively.
- The median duration of PFS in the control arm is 6 months.
- The median duration of OS in the control arm is 10 months.
- The interim and final analyses of OS use the Lan-DeMets alpha spending function to approximate the O'Brien-Fleming boundary.
- The dropout rate is 5% over 12 months for PFS and OS.

With these assumptions, the expected number of events and the minimum detectable difference of HRs in each co-primary endpoint are presented in Table 2.

Table 2 Power and Minimum Detectable Difference for the Proposed Design of Each Primary Endpoint

Primary Endpoint	Expected No. of Events	Target HR	Two-Sided Type I Error	Power	MDD HR
PFS	295	0.55	0.005	99%	0.721
PFS	295	0.55	0.05	99.9%	0.796
OS	306	0.68	0.045	91%	0.790 [a]
OS	306	0.68	0.05	92%	0.794 [a]

HR = hazard ratio; MDD = minimum detectable difference; PFS = progression-free survival; OS = overall survival.

[a] At final analysis conditional on interim analysis with 78% information fraction.

Sample Size [redacted]

After approximately 400 patients had been randomized into the study, the global enrollment will be closed. [redacted]

[redacted]

[redacted]

2.4 INTERIM AND FINAL ANALYSES TIMING

There will be no interim analyses planned for PFS in this study.

One interim efficacy analysis of OS is planned for when approximately 240 OS events have been observed. The primary analysis of PFS will be conducted at the same time as the interim OS analysis, and the exact timing of the analysis depends on when 240 OS events in the ITT population have occurred.

The final OS analysis will be conducted when approximately 306 OS events in the ITT population have been observed. This is expected to occur approximately 36 months after the first patient is randomized, but the exact timing of this analysis will depend on the actual number of OS events.

To control the type I error for OS, the stopping boundaries for the OS interim and final analyses are to be computed with use of the LanDeMets approximation to the O'Brien-Fleming boundary (DeMets and Lan 1994) as shown in Table 3.

Table 3 Analysis Timing and Stopping Boundary of Overall Survival

Analysis Timing	Information Fraction (Number of Events)	Estimated Time from First Patient In (months)	Stopping Boundary in HR (two-sided p-value)	
			PFS is Statistically Significant	PFS is Not Statistically Significant
OS interim analysis	78.4% (240)	25	HR≤0.7453 (p≤0.0228)	HR≤0.7405 (p≤0.02)
OS final analysis	100% (306)	36	HR≤0.7937 (p≤0.0433)	HR≤0.7899 (p≤0.039)

HR=hazard ratio; OS=overall survival; PFS=progression-free survival.

[redacted]

3. STUDY CONDUCT

3.1 RANDOMIZATION

Eligible patients will be randomized in a 1:1 ratio to receive either atezolizumab+carboplatin+etoposide or placebo+carboplatin+etoposide with the use of a stratified permuted-block randomization. The randomization will be stratified for the following factors:

- Sex (male vs. female)

- ECOG performance status (0 vs. 1)
- Presence of brain metastases (yes vs. no)

The same randomization method is implemented for the [redacted]

3.2 DATA MONITORING

An iDMC has been used to evaluate safety during the study on a regular basis. All summaries and analyses by treatment arm for the iDMC review are prepared by an external independent Data Coordinating Center. Members of the iDMC are external to the Sponsor and follow a separate iDMC Charter that outlines their roles and responsibilities, as well as a detailed monitoring plan. Refer to the iDMC Charter for further details.

4. STATISTICAL METHODS

The analyses described in this SAP will override those specified in Protocol GO30081.

[redacted]

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

The ITT population is defined as all randomized patients, regardless of whether the patient has received the assigned treatment. ITT patients will be analyzed according to the treatment assigned at randomization by the interactive voice/Web response system (IxRS).

4.1.2 Pharmacokinetic-Evaluable Population

PK analyses will be based on PK observations from all patients who have received atezolizumab, carboplatin, or etoposide treatment and who have provided at least one evaluable PK sample.

4.1.3 Safety Population

The safety population is defined as patients who received any amount of study treatment. Patients who received any amount of atezolizumab will be analyzed as part of Arm A even if atezolizumab was given in error. Patients who were randomized to the study but did not receive any study drug will not be included in the safety population.

4.2 ANALYSIS OF STUDY CONDUCT

Enrollment, major protocol deviations (including major deviations of inclusion and/or exclusion criteria), and reasons for discontinuation from the study will be summarized by treatment arm for the ITT population. Study treatment administration and reasons

for discontinuation from study treatment will be summarized by treatment arm for the safety population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic characteristics, such as age and race/ethnicity, and baseline disease characteristics, current disease status, and stratification factors (i.e., sex, ECOG performance status, and brain metastases), will be summarized by treatment arm for the ITT population.

Baseline values are the last available data obtained prior to a patient receiving the first dose of any study treatment on Cycle 1, Day 1 visits unless otherwise noted. Descriptive statistics (mean, median, SD, range) will be presented for continuous variables, and frequencies and percentages will be presented for categorical variables.

4.4 EFFICACY ANALYSIS

The primary PFS and OS analyses will be conducted on the ITT population. [redacted]
Patients will be grouped according to the treatment assigned at randomization by IxRS. Analysis populations for other efficacy endpoints will be described in later sections.

The stratification factors will be those used for randomization from the IxRS (i.e., sex, ECOG performance status, and brain metastases). [redacted] if at least one stratum (i.e., a combination of stratification factor levels across sex [male vs female], ECOG performance status [0 vs 1], and brain metastasis [Yes vs No] per IxRS) has less than 10 events (PFS or OS events), the stratification factor (one of 3 stratification factors: sex, ECOG performance status, and brain metastasis per IxRS) which contains the level with the smallest number of patients will be removed from the stratified analyses. The removal of the stratification factor will continue until there is no stratum with less than 10 events (PFS or OS events). The final set of stratification factors used in stratified analyses will be applied to all endpoints where stratified analyses are planned. Analyses based on stratification factors recorded on the electronic Case Report Form (eCRF) will also be provided if considerable discrepancy is observed between IxRS and eCRF records.

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Progression-Free Survival

One of the co-primary endpoints for this study is PFS. PFS is defined as the time from randomization to the first occurrence of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

Treatment comparisons will be based on the stratified log-rank test. If the null hypothesis of the OS testing is rejected at a two-sided significance level of 0.045, PFS will be tested at the two-sided significance level of 0.05. Otherwise, PFS will be tested at the two-sided significance level of 0.005.

The null and alternative hypotheses can be phrased in terms of the survival functions $S_{PFS\_A}(t)$ and $S_{PFS\_B}(t)$ in Arm A and Arm B, respectively:

$$H_0: S_{PFS\_A}(t) = S_{PFS\_B}(t) \text{ versus } H_1: S_{PFS\_A}(t) \neq S_{PFS\_B}(t)$$

Kaplan-Meier methodology will be used to estimate median PFS for each treatment arm and to construct survival curves for each treatment arm. The Brookmeyer-Crowley methodology and log-log transformation for normal approximation will be used to construct the 95% CI for the median PFS for each treatment arm (Brookmeyer and Crowley 1982).

The HR, $\lambda_{PFS\_A}/\lambda_{PFS\_B}$, where λ_{PFS_A} and λ_{PFS_B} represent the hazard of the PFS event in Arm A and Arm B, respectively, will be estimated with a stratified Cox regression model and the same stratification variables used for the stratified log-rank test and the 95% CI will be estimated by normal approximation.

Results from an unstratified analysis will also be provided.

4.4.1.2 Overall Survival

The other co-primary endpoint for this study is OS, which is defined as the time from randomization to death from any cause. Patients who are not reported as having died will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.

OS will be analyzed with the same methodologies as PFS. Treatment comparisons will be based on the stratified log-rank test, and as described in Section 2.3, if the null hypothesis of the PFS testing is rejected at a two-sided significance level of 0.005, OS will be tested at the two-sided significance level of 0.05. Otherwise, OS will be tested at the two-sided significance level of 0.045. As described in Section 2.4, two analyses for OS are planned, including one interim analysis. If the two-sided p-value corresponding to the stratified log-rank test is less than or equal to the two-sided level of significance at the corresponding analysis, the null hypothesis will be rejected. The null and alternative hypotheses can be phrased in terms of the survival functions $S_{OS\_A}(t)$ and $S_{OS\_B}(t)$ in Arm A and Arm B, respectively:

$$H_0: S_{OS\_A}(t) = S_{OS\_B}(t) \text{ versus } H_1: S_{OS\_A}(t) \neq S_{OS\_B}(t)$$

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 Objective Response Rate

Objective response rate (ORR) is defined as the proportion of patients who had an objective response by the investigator using RECIST v1.1. The analysis population for ORR will be all randomized patients with measurable disease at baseline. An estimate

of ORR and its 95% CI will be calculated with the Clopper Pearson method (Clopper and Pearson 1934) for each treatment arm. CIs for the difference in ORRs between the two treatment arms will be determined with use of the normal approximation to the binomial distribution.

Confirmation of response according to RECIST v1.1 will not be required, but for the exploratory purposes, ORR with confirmation will be reported as needed.

4.4.2.2 Duration of Response

DOR will be assessed for patients who had an objective response as determined by the investigator using RECIST v1.1. Patients whose disease has not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR plus 1 day. DOR is based on a non-randomized subset of patients (specifically, patients who achieved an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes. The methodologies detailed for the PFS analysis will be used for the DOR analysis.

4.4.2.3 Overall Survival Rate at 1 year and 2 years, and Progression-Free Survival Rate at 6 months and 1 year

The OS rates at 1 and 2 years will be estimated with the use of Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated with the standard error derived from Greenwood's formula. The 95% CI for the difference in OS rates between the two treatment arms will be estimated with the normal approximation method.

Similar analyses will be performed for the PFS rates at 6 months and 1 year after randomization.

4.4.2.4 Patient-Reported Outcomes of Lung-Disease Related Symptoms

PROs of HRQoL, lung cancer–related symptoms will be measured using EORTC QLQ-C30 and EORTC QLQ-LC13.

The ITT population will be used for TTD analyses and to document completion rates. Missing PRO scores will not be imputed. Patients whose symptoms have not deteriorated before the last PRO assessment is completed will be censored at the date of the last PRO assessment. Patients with no baseline assessment or post-baseline assessments will be censored at the date of randomization plus 1 day.

TTD according to the EORTC QLQ-C30 and EORTC QLQ-LC13 measures will be evaluated in each of the following linearly transformed symptom scores: cough, dyspnea (single item), dyspnea (multi-item subscale), chest pain, or arm/shoulder pain. The linear transformation gives each individual symptom subscale a possible score of 0 to 100. For the symptom to be considered "deteriorated," a score increase of ≥ 10 points above baseline must be held for at least two consecutive assessments or an initial score increase of ≥ 10 points is followed by death within 3 weeks from the last assessment. A ≥ 10-point change in the symptoms subscale score is perceived by patients as clinically significant (Osoba et al. 1998). The methodologies outlined for the analysis of PFS will be used for the analyses of TTD of the pre-specified symptoms of the EORTC QLQ-C30 and EORTC QLQ-LC13 measures. The estimated Kaplan-Meier plots will be provided for each symptom separately.

In the ITT population, completion rates will be summarized by number and proportion of patients among those expected to complete the QLQ-C30 at each time point. If collected, reasons for non-completion will be summarized at each time point by treatment arm.

In addition, to interpret lung-disease related symptoms evolution over time and further support the clinical findings regarding delay in symptom deterioration, the following may be documented in population with all randomized patients with a non-missing baseline assessment and at least one non-missing post-baseline assessment until treatment discontinuation:

- The mean change in symptom scores from baseline at each timepoint including end of treatment, and disease progression. Repeated measures mixed-effect model will be used for comparing the aforementioned symptoms scale scores between treatment arms. The model will include a term for intercept, a term for linear time trend, a term for treatment group, and a term of treatment-by-time interaction. Repeated measured over time will be accounted for by unstructured covariance structure.
- The number and proportion of patients with a clinically meaningful change will be summarized by treatment arm for each of the symptom scores aforementioned, The 95% CI around the proportion will be calculated using the Clopper-Pearson method

for each treatment arm. The difference in proportions between the two treatment arms will be presented with a two-sided 95% CI based on a normal approximation to the binomial distribution.

- Cumulative distribution function (CDF) curves by treatment arm may be generated and used to evaluate absolute change in scores from baseline to RECIST-defined disease progression.

4.4.3 Exploratory Efficacy Endpoints

4.4.3.1 Objective Response Rate, Duration of Response, and Progression-Free Survival per Immune-Modified RECIST

Analyses using immune-modified RECIST criteria (see Appendix 4 of the Protocol GO30081 for further details) for ORR, DOR, and PFS, as determined by the investigator, will also be conducted (for atezolizumab-treated patients only). Comparisons between the treatment arms will not be made.

PFS by immune-modified RECIST is defined as the time from randomization to disease progression as determined by the investigator per immune-modified RECIST or death from any cause, whichever occurs first. A patient is considered to have disease progression by immune-modified RECIST if either of the following conditions were met:

a) Immune-modified RECIST for progression was met at a tumor assessment and no subsequent tumor assessment was performed.

b) Immune-modified RECIST for progression was met at a tumor assessment, and at the subsequent tumor assessment, the criteria for progression by immune-modified RECIST were also met, i.e., confirmed.

For patients who meet criterion a), the date of progression is the date of the tumor assessment that meets the criteria by immune-modified RECIST. For patients who meet criterion b), the date of progression is the date of the tumor assessment at which the immune-modified RECIST for progression was first met. Patients who did not meet either of these criteria are not considered to have had disease progression by immune-modified RECIST.

The investigator-assessed ORR is defined as the proportion of patients whose best overall response is either a PR or CR per immune-modified RECIST.

For patients who experienced objective response (CR or PR per immune-modified RECIST) as assessed by the investigator, DOR is defined as the time from the first tumor assessment that supports the patient's objective response (CR or PR, whichever is recorded first) to disease progression per immune-modified RECIST or death from any cause, whichever occurs first. Data for patients who are alive and who have not experienced disease progression at the time of analysis will be censored at the last tumor assessment date.

The methods outlined for the primary and secondary efficacy endpoint analyses to estimate the median PFS or ORR for each treatment arm will be used for these analyses.

4.4.3.2 Biomarker Analysis

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with study drug response, including efficacy and/or adverse events. The tumor biomarkers include but are not limited to bTMB using the cut-offs of ≥10 and ≥16 separately (given data availability), and CD8, as defined by immunohistochemistry (IHC), quantitative reverse transcriptase–polymerase chain reaction (qRT–PCR), or other methods. Additional pharmacodynamic analyses of predictive, prognostic, and exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status, mechanisms of resistance, and/or response to study treatment will be conducted as appropriate. These exploratory analyses may be provided in a separate report.

4.4.3.3 Patient-Reported Outcomes of Health-Related Quality of Life

Additional PROs of health-related quality of life (Global Health Status score), function (Physical function and Role function), and symptoms (i.e., Fatigue, Haemoptysis, Sore mouth, Peripheral neuropathy, Pain in chest, Pain in arm or shoulder and Pain in other parts), assessed according to the EORTC QLQ-C30 and EORTC QLQ-LC13 will be scored according to the EORTC scoring manual guidelines.

Summary statistics (mean, SD, median, 25th and 75th percentiles, and range) and the mean change from baseline of linear-transformed scores will be reported for the aforementioned scales and scales detailed in Section 4.4.2.4).

Similar longitudinal analyses (change from baseline and number and proportion of patients with a clinically meaningful change as described in Section 4.4.2.4) will be performed on patients with a non-missing baseline assessment and at least one non-missing post-baseline assessment will be included in the analyses. Missing PRO scores will not be imputed.

4.4.4 Sensitivity Analyses

Impact of Missing Scheduled Tumor Assessments on Primary PFS

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

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

- Patients who missed two or more consecutive assessments scheduled immediately prior to the date of disease progression per RECIST v1.1 or death will be counted as having progressed on the date of the first of these missing assessments.

The imputation rule will be applied to patients in both treatment arms.

Impact of Non–Protocol-Specified Anti-Cancer Therapy

The impact of non–protocol-specified anti-cancer therapy on PFS determined by the investigator may be assessed depending on the number of patients who receive non–protocol-specified anti-cancer therapy before a PFS event. If >5% of patients received non–protocol-specified anti-cancer therapy before a PFS event in any treatment arm, patients who received non–protocol-specified anti-cancer therapy before a PFS event will be censored at the last tumor assessment date before they received non–protocol-specified anti-cancer therapy in PFS analyses that may be performed for the comparisons between treatment arms.

The impact of subsequent NPT on OS may be assessed depending on the number of patients who received NPT. If > 10% of patients received an NPT in the control arm, the following analysis may be performed to compare treatment arms.

The discount method uses a “discounted” survival time after switching for patients who switch treatments based on a user-specified assumption for the effect on OS. OS will be discounted in accordance with a range of possible effects on OS of the subsequent NPT after treatment switching occurred (e.g., 10%, 20%, 30%). After adjustments are made for the effect of subsequent non–protocol-specified immunotherapy or anti-cancer therapy on OS, the methods outlined for the primary efficacy endpoint analyses will be used for these analyses.

Delayed Clinical Effect

If a delayed separation of the PFS and/or OS Kaplan-Meier curves is observed at the beginning of the curves and the delay is ≥3 months, the following analyses may be conducted to assess a potential delayed clinical effect for the treatment group. The delayed clinical effect sensitivity analyses may not be included in the CSR.

Milestone Analysis

To assess the potential effect delayed clinical effects, a milestone analysis may be conducted (Chen 2015). The milestone time points will be chosen such that the patients included in the analysis will achieve a certain patient-event ratio.

The milestone analysis will be conducted only when the milestone duration has elapsed from the time the last patient entered the study, using the same methods as those specified for the primary analysis.

Restricted Mean Survival Time

The restricted mean survival time (RMST) may be computed using the area under the curve from baseline to several timepoints. RMST will be computed for each treatment arm and the difference with its 95% CI will be displayed.

Weighted Log-Rank Analysis

Where the delayed clinical effect is $>10\%$ of the median time of the control group, an analysis may be performed using the weighted log-rank test based on the Rho-Gamma weight function family (Fleming and Harrington 1991) or piece-wise linear weight functions (Lin and Leon 2017) that weight more heavily on late events to account for the delayed clinical effect (Fine 2007). In addition, hazard ratio estimates based on the corresponding Cox model (Lin and Leon 2017) using the piece-wise linear weight functions may also be provided to enhance clinical interpretation of the treatment effect that varies over time.

Lost to Follow-Up

The impact of loss to follow-up on OS will be assessed depending on the number of patients who are lost to follow-up. If $>5\%$ of patients are lost to follow-up for OS in either treatment arm, a sensitivity analysis will be performed for the comparisons between two treatment arms in which patients who are lost to follow-up will be considered as having died at the last date they were known to be alive.

4.4.5 Subgroup Analyses

To assess the consistency of the study PFS and OS results, results in subgroups will be examined. The following subgroups will be considered:

- Demographics (e.g., age, sex, and race/ethnicity etc)
- Baseline prognostic characteristics (e.g., sex, ECOG performance status, smoking status, presence of brain metastases etc)

Summaries of PFS and OS, including unstratified HRs estimated from Cox proportional hazards models, will be displayed in a forest plot (Lewis and Clarke 2001).
Kaplan-Meier estimates of median PFS and OS will be produced separately for each level of the categorical variables for the comparisons between treatment arms.

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

PK analyses will be performed for the pharmacokinetic-evaluable population.

PK samples will be collected in this study as outlined in Appendix 3. Atezolizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, and SDs, as appropriate.

Plasma concentrations of carboplatin and etoposide will be collected in this study as outlined in Appendix 3. The concentrations of carboplatin and etoposide will be summarized using descriptive statistics as described above.

Additional PK analyses will be conducted as appropriate, on the basis of the availability of data. These additional PK analyses may not be included in the CSR.

4.6 SAFETY ANALYSES

Unless specified otherwise, safety analyses described in this section will be conducted for the safety population, with patients grouped according to whether they received any atezolizumab treatment (i.e., patients who received any dose of atezolizumab will be included in the atezolizumab arm for the safety analyses).

4.6.1 Exposure of Study Medication

Study drug exposure statuses, which include treatment duration, number of cycles, and dose intensity, will be summarized for each treatment arm with descriptive statistics.

4.6.2 Adverse Events

Verbatim description of adverse events will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded by the investigator according to NCI CTCAE v4.0. Treatment-emergent adverse events will be summarized by mapped term, appropriate thesaurus level, NCI CTCAE grade, and treatment arm. In addition, serious adverse events, severe adverse events (Grade ≥ 3), adverse events of special interest, immune-related adverse events, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum grade.

For reporting purposes, “treatment emergent” is defined as adverse events occurring on or after the first dose of study drug is administered until the clinical cutoff date.

All safety analyses of adverse events will also include all adverse events with onset on or after the first study drug treatment until the clinical cutoff date.

Deaths reported during the study treatment period and the follow-up period after treatment completion and/or discontinuation will be summarized by treatment arm.

4.6.3 Laboratory Data

Laboratory data will be summarized by treatment arm. Values outside the normal ranges will be summarized by treatment arm. In addition, selected laboratory data will be summarized by treatment arm and NCI CTCAE grade according to NCI CTCAE grade v4.0.

4.6.4 Vital Signs

Changes in selected vital signs will be summarized by treatment arm and by change over time, which includes change from baseline. Baseline is defined as the measurement obtained on Cycle 1, Day 1 before the first dose of study drug is administered.

4.6.5 Anti-Drug Antibody

Incidence of ADA against atezolizumab will be summarized. The analyses of pharmacokinetics, key efficacy, and safety by ADA status will be conducted to explore the potential impact of immunogenicity.

4.7 MISSING DATA

See Section 4.4.3.3 and Section 4.6 for methods for handling missing data for the primary and secondary endpoints.

4.8 INTERIM ANALYSES

Please refer to Section 2.4 for details of planned interim analysis.

4.8.1 Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim efficacy analysis for the co-primary endpoints of PFS and OS beyond what is specified in Section 2.4. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be amended in this SAP, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

5. [redacted]

[redacted]

[redacted]

[redacted]

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Appendix 1
Protocol Synopsis

TITLE:	**A PHASE I/III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF CARBOPLATIN PLUS ETOPOSIDE WITH OR WITHOUT ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) IN PATIENTS WITH UNTREATED EXTENSIVE-STAGE SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO30081
VERSION NUMBER:	4
EUDRACT NUMBER:	2015-004861-97
IND NUMBER:	117296
TEST PRODUCT:	Atezolizumab (MPDL3280A, RO5541267)
PHASE:	I/III
INDICATION:	Small cell lung cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

The following objective statements apply to the global enrollment phase [redacted]

Efficacy Objectives

Primary Efficacy Objectives

The co-primary objectives of this study are the following:

- To evaluate the efficacy of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the intent-to-treat (ITT) population as measured by investigator-assessed progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)
- To evaluate the efficacy of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the ITT population as measured by overall survival (OS)

Secondary Efficacy Objectives

The secondary efficacy objectives for this study are:

- To evaluate the efficacy of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the ITT population as measured by investigator-assessed objective response rate (ORR) according to RECIST v1.1
- To evaluate the efficacy of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the ITT population as measured by investigator-assessed duration of response (DOR) according to RECIST v1.1
- To evaluate the PFS rate at 6 months and at 1 year in each treatment arm for the ITT population
- To evaluate the OS rate at 1 and 2 years in each treatment arm for the ITT population

- To determine the impact of atezolizumab as measured by time to deterioration (TTD) in patient-reported lung cancer symptoms of cough, dyspnea (single item and multi-item subscales), chest pain, arm/shoulder pain, or fatigue using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13) in patients treated with atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the ITT population

Safety Objectives

The safety objectives for this study are:

- To evaluate the safety and tolerability of atezolizumab in combination with carboplatin + etoposide compared with carboplatin + etoposide
- To evaluate the incidence and titers of anti-drug antibodies (ADAs; equivalent to ATA) against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the pharmacokinetics of atezolizumab, carboplatin, and etoposide in chemotherapy-naive patients with extensive-stage small cell lung cancer (ES-SCLC).

Exploratory Objectives

The exploratory objectives for this study are:

- To evaluate investigator-assessed PFS, ORR, DCR, DOR, TIR, and TTR according to modified RECIST for the atezolizumab-containing treatment arm in the ITT population
- To evaluate the relationship between tumor biomarkers (including but not limited to PD-L1, programmed death-1 (PD-1), somatic mutations, and others), as defined by immunohistochemistry (IHC) or quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR), next generation sequencing (NGS), and/or other methods and measures of efficacy
- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue, blood, plasma and serum and their association with disease status, mechanisms of resistance, and/or response to study treatment
- To evaluate and compare patient's health status as assessed by the EuroQoL 5 Dimensions 5-Level (EQ-5D-5L) questionnaire to generate utility scores for use in economic models for reimbursement
- To determine the impact of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide as measured by change from baseline in patient-reported outcomes (PRO) of health-related quality of life, lung cancer–related symptoms, physical functioning, and health status as assessed by the EORTC QLQ-C30 and LC13
- To evaluate the impact of chemotherapy (both carboplatin and etoposide) on peripheral and tumor-specific T-cell populations during and after induction therapy and its relationship to efficacy and safety outcomes

Study Design

Description of Study

This is a randomized, Phase I/III, multicenter, double-blinded, placebo-controlled study designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin + etoposide compared with treatment with placebo + carboplatin + etoposide in patients who have ES-SCLC and are chemotherapy-naive for their extensive-stage disease.

Eligible patients will be stratified by sex (male vs. female), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1), and presence of brain metastases (yes vs. no) and randomized 1:1 to receive one of the following treatment regimens: A) atezolizumab + carboplatin ± etoposide or B) placebo + carboplatin + etoposide.

Induction treatment will be administered on a 21-day cycle for four cycles.

Following the induction phase, patients will continue maintenance therapy with either atezolizumab or placebo. During the maintenance phase, prophylactic cranial irradiation is permitted as per local standard-of-care and *will* be reported on the Prophylactic Cranial Irradiation electronic Case Report Form (eCRF). Thoracic radiation with curative intent or the intent to eliminate residual disease is not permitted. Palliative thoracic radiation is allowed.

Treatment should be discontinued in all patients (in both treatment arms) who exhibit evidence of disease progression per RECIST v1.1. However, to better accommodate standard clinical practice which is guided by the fact that patients with ES-SCLC whose disease progresses after first-line treatment have limited treatment options and such options have limited efficacy and significant toxicity, patients may be considered for treatment beyond radiographic disease progression per RECIST v1.1, at the discretion of the investigator and after appropriate discussion with the patient and obtaining informed consent, only if all of the following criteria are met:

- Evidence of clinical benefit as assessed by the investigator
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial progression

Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 should be closely monitored clinically and with a follow-up scan in 6 weeks or sooner if symptomatic deterioration occurs. Treatment should be discontinued if clinical deterioration due to disease progression occurs at any time, or if persistent disease growth is confirmed in a follow-up scan. In addition, patients should be discontinued for unacceptable toxicity or for any other signs or symptoms of deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status.

If clinically feasible, it is recommended that the patient undergo a tumor biopsy sample collection at the time of radiographic disease progression. These data will be used to explore whether radiographic findings are consistent with the presence of a tumor. Additionally, these data will be analyzed to evaluate the association between changes in tumor tissue and clinical outcome and to further understand the potential mechanisms of progression and resistance to atezolizumab as compared with such mechanisms after treatment with chemotherapy alone. This exploratory biomarker evaluation will not be used for any treatment-related decisions.

Patients will undergo tumor assessments at baseline and every 6 weeks (± 7 days) for 48 weeks following Cycle 1, Day 1, regardless of treatment dose delays. After completion of the Week 48 tumor assessment, tumor assessments will be required every 9 weeks (± 7 days) thereafter, regardless of treatment dose delays. Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first.

Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will continue to undergo tumor assessments every 6 weeks (±7 days), or sooner if symptomatic deterioration occurs. For these patients, tumor assessments *will* continue every 6 weeks (±7 days), regardless of time in the study, until study treatment is discontinued.

Patients who discontinue treatment for reasons other than 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 patient had remained on study treatment (i.e., every 6 weeks [±7 days] for 48 weeks following Cycle 1, Day 1 and then every 9 weeks [±7 days] thereafter, regardless of treatment dose delays) until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.

In case of an early termination of the study, patients who are deriving clinical benefit from treatment with atezolizumab will be permitted to continue treatment with atezolizumab at the discretion of the investigator.

Note: After approximately 400 patients have been randomized into the study, [redacted]

Number of Patients

Approximately 400 patients will be randomized into the global enrollment phase of this study. [redacted]

Target Population

Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry:

- Signed Informed Consent Form
- Male or female, 18 years of age or older
- ECOG performance status of 0 or 1
- Histologically or cytologically confirmed ES-SCLC (per the Veterans Administration Lung Study Group (VALG) staging system
- No prior systemic treatment for ES-SCLC
- Patients who have received prior chemoradiotherapy for limited-stage SCLC must have been treated with curative intent and experienced a treatment-free interval of at least 6 months since last chemotherapy, radiotherapy, or chemoradiotherapy cycle from diagnosis of extensive-stage SCLC
- Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:

    Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)

    No ongoing requirement for corticosteroids as therapy for CNS disease

    No evidence of interim progression between the completion of CNS-directed therapy and randomization

    Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to randomization, if all other criteria are met.
- Measurable disease, as defined by RECIST v1.1

    Previously irradiated lesions can only be considered as measurable disease if disease progression has been unequivocally documented at that site since radiation and the previously irradiated lesion is not the only site of disease.
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to randomization:

    ANC $\geq$ 1500 cells/μL without granulocyte colony-stimulating factor support

    Lymphocyte count $\geq$ 500/μL

    Platelet count $\geq$ 100,000/μL without transfusion

    Hemoglobin $\geq$ 9.0 g/dL

        Patients may be transfused to meet this criterion.

    INR or aPTT $\leq$ 1.5 $\times$ upper limit of normal (ULN)

This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.

AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ ULN, with the following exceptions:

Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN

Patients with documented liver or bone metastases: alkaline phosphatase $\leq 5 \times$ ULN.

Serum bilirubin $\leq 1.25 \times$ ULN

Patients with known Gilbert disease who have serum bilirubin level $\leq 3 \times$ ULN may be enrolled.

Serum creatinine $\leq 1.5 \times$ ULN

- Patients must submit a pre-treatment tumor tissue sample. Any available tumor tissue sample can be submitted. The tissue sample should be submitted before or within 4 weeks after randomization; however, patients may be enrolled into the study before the pre-treatment tumor tissue sample is submitted.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 5 months after the last dose of study treatment.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of 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 patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during treatment with chemotherapy (i.e., carboplatin and etoposide) and for at least 6 months after the last dose of chemotherapy to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- *For patients enrolled in the extended China enrollment phase: current resident of mainland China, Hong Kong, or Taiwan and of Chinese ancestry*

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments
- 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 randomization
- Leptomeningeal disease

- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed regardless of drainage frequency.
- Uncontrolled or symptomatic hypercalcemia

  Patients who are receiving denosumab prior to randomization must be willing and eligible to discontinue its use and replace it with a bisphosphonate while in the study.
- Malignancies other than SCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS $>$ 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous-cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
- Women who are pregnant, lactating, or intending to become pregnant during the study
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

  Patients with a history of autoimmune-related hypothyroidism on thyroid replacement hormone therapy are eligible.

  Patients with controlled Type I diabetes mellitus on an insulin regimen are eligible.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are eligible for the study provided that they meet the following conditions:

  Rash must cover less than 10% of body surface area

  Disease is well controlled at baseline and only requires low potency topical steroids

  No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency, or oral steroids)
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive test result for HIV

  All patients must be tested for HIV; patients who test positive for HIV will be excluded.
- Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test result at screening) or hepatitis C virus (HCV)

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible. HBV DNA should be obtained in these patients prior to randomization.

  Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
- Active tuberculosis
- Severe infections at the time of randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to randomization, unstable arrhythmias, or unstable angina

  Patients 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.

- Major surgical procedure other than for diagnosis within 28 days prior to randomization or anticipation of need for a major surgical procedure during the course of the study
- Prior allogeneic bone marrow transplantation or solid organ transplant
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk for treatment complications
- Patients with illnesses or conditions that interfere with their capacity to understand, follow, and/or comply with study procedures
- Treatment with any other investigational agent with therapeutic intent within 28 days prior to randomization
- Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation that such a live attenuated vaccine will be required during the study

  Patients must not receive live, attenuated influenza vaccines (e.g., FluMist®) within 4 weeks prior to randomization, during treatment, and for 5 months following the last dose of atezolizumab/placebo.
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunosuppressive medications (including, but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 1 week prior to randomization

  Patients who have received acute systemic immunosuppressant medications (e.g., use of corticosteroids for nausea, vomiting, or management of or premedication for allergic reactions) may be enrolled in the study after discussion with and approval by the Medical Monitor. In those patients, the need and length of the washout period prior to randomization will also be established in conjunction with the Medical Monitor.

  The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of allergic reactions to carboplatin or etoposide

End of Study

The end of study is *will occur when all of the following criteria have been met:*

- *The last patient last visit (LPLV) has occurred (i.e., last patient in the global* [redacted]
- Approximately 2*80* deaths have been observed among the randomized patients in the global enrollment phase.
- [redacted] *(see Section 6.1.1).*

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

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3*1* months.

Outcome Measures

Efficacy Outcome Measures

Primary Efficacy Outcome Measures

The primary efficacy outcome measures for this study are:

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first.
- OS, defined as the time from randomization to death from any cause.

Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are:

- Objective response, defined as PR or CR as determined by the investigator according to RECIST v1.1
- DOR, defined as the time interval from first occurrence of a documented objective response to the time of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever comes first
- PFS rates at 6 months and at 1 year
- OS rates at 1 and 2 years
- TTD in patient-reported lung cancer symptoms, defined as time from randomization to deterioration (10-point change) on each of the EORTC QLQ-C30 and EORTC QLQ-LC13 symptom subscales maintained for two assessments or one assessment followed by death from any cause within 3 weeks

Safety Outcome Measures

The safety outcome measures for this study are:

- Incidence, nature, and severity of adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0
- Changes in vital signs, physical findings, and clinical laboratory results during and following study treatment administration
- Incidence of ATA response to atezolizumab and potential correlation with PK, pharmacodynamic, safety, and efficacy parameters

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are:

- Maximum observed serum atezolizumab concentration (C_{max}) after infusion
- Minimum observed serum atezolizumab concentration (C_{min}) prior to infusion at selected cycles, at treatment discontinuation, and at 120 days ($\pm$30 days) after the last dose of atezolizumab
- Plasma concentrations for carboplatin
- Plasma concentrations for etoposide

Exploratory Outcome Measures

The exploratory outcome measures for this study are:

- Objective response, PFS *and* DOR as determined by the investigator according to modified RECIST
- Status of PD-L1–, immune-, and SCLC-related and other exploratory biomarkers in archival and/or freshly obtained tumor tissues, and blood (or blood derivatives) collected before, during, or after treatment with atezolizumab or at progression and association with disease status and/or response to atezolizumab
- Utility scores of the EQ-5D-5L

- Change from baseline in PROs of health-related quality of life, lung cancer–related symptoms, physical functioning, and health status as assessed by the EORTC QLQ-C30 and QLQ-LC13
- Changes in levels and type of peripheral and tumor-specific T-cell populations during and after induction therapy and its relationship to efficacy and safety outcomes

Investigational Medicinal Products

The induction phase of the study will consist of four cycles of atezolizumab/placebo plus chemotherapy, with each cycle being 21 days in duration. On Day 1 of each cycle, all eligible patients will receive drug infusions in the following order:

Arm A: atezolizumab → carboplatin → etoposide

Arm B: placebo → carboplatin → etoposide

On Days 2 and 3, patients will receive etoposide alone.

After the induction phase, patients will begin maintenance therapy with atezolizumab/placebo every 3 weeks.

Test Product (Investigational Drug)

The test products in this study are atezolizumab and atezolizumab placebo. Patients will receive atezolizumab/placebo 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered by IV infusion every 21 [±2] days in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. For information on the formulation, packaging, and handling of atezolizumab and atezolizumab placebo refer to the atezolizumab Pharmacy Manual and Investigator's Brochure. Atezolizumab and atezolizumab placebo will be supplied by the Sponsor.

Non-Investigational Medicinal Products

Carboplatin and etoposide are background treatment and are considered non-investigational medicinal products (NIMPs). For information on the formulation, packaging, and handling of carboplatin and etoposide see the prescribing information for each drug.

Carboplatin should be administered after completion of atezolizumab/placebo by IV infusion over 30–60 minutes to achieve an initial target area under the concentration-time curve (AUC) of 5 mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines.

During the induction phase (Cycles 1–4), on Day 1 of each cycle, etoposide (100 mg/m^2) should be administered intravenously over 60 minutes following carboplatin administration. On Days 2 and 3 of each cycle, etoposide (100 mg/m^2) should be administered intravenously over 60 minutes. Premedication should be administered according to local standard-of-care.

Because the effects of corticosteroids on T-cell proliferation have the potential to attenuate atezolizumab-mediated anti-tumor immune activity, premedication with corticosteroids should be minimized to the extent that is clinically feasible.

Statistical Methods

All analyses will be restricted to the patients enrolled in the global enrollment phase only (i.e., [redacted] unless otherwise noted. The analysis populations used in this section, such as the ITT (i.e., all randomized patients) and the PD-L1–selected populations will not [redacted], unless otherwise noted.

The analyses of PFS and OS will be performed on all randomized patients (ITT), with patients grouped according to the treatment assigned at randomization, regardless of whether they receive any assigned study drug. ORR will be analyzed using all randomized patients who have measurable disease at baseline. DOR will be assessed in patients who have an objective response. TTD analyses will be conducted on all patients with a non-missing baseline PRO assessment. Change from baseline analysis on PROs will be performed using patients who have both a non-missing baseline assessment and at least one post-baseline assessment with patients grouped according to the treatment assigned at randomization.

Primary Analysis

To adjust for multiplicity due to having two co-primary endpoints, *a group sequential Holm's procedure* will be implemented: *initially* the hypothesis test for PFS will be conducted at a two-sided alpha of 0.005 and OS will be tested at a two-sided alpha of 0.045. *Once a null hypothesis is rejected, the test mass predefined for that endpoint becomes available and can be recycled to the other unrejected test.*

The null and alternative hypotheses regarding PFS or OS in the ITT population can be phrased in terms of the PFS or OS survival functions $S_A(t)$ and $S_B(t)$ for Arm A (atezolizumab + carboplatin + etoposide) and Arm B (placebo + carboplatin + etoposide), respectively:

$$H0: S_A(t) = S_B(t) \text{ versus } H1: S_A(t) \neq S_B(t)$$

One of the co-primary efficacy endpoints is PFS as assessed by the investigator using RECIST v1.1. PFS is defined as the time between the date of randomization and the date of first documented disease progression or death, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

The two-sided log-rank test, stratified by sex (male vs. female), ECOG performance status (0 vs. 1), and presence of brain metastases (yes vs. no), as recorded in the interactive voice/Web response system (IxRS), will be used as the primary analysis to compare PFS between the two treatment arms. The results from the unstratified log-rank test will also be provided.

The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm. Cox proportional hazards models, stratified by sex (male vs. female), ECOG performance status (0 vs. 1), and presence of brain metastases (yes vs. no) will be used to estimate the hazard ratio (HR) and its 95% CI. The unstratified HR will also be presented.

OS, the other co-primary efficacy endpoint, is defined as the time from the date of randomization to the date of death from any cause. Patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Patients with no post-baseline information will be censored at the date of randomization plus 1 day. Methods for OS analyses are similar to those described for the PFS endpoint.

Determination of Sample Size

Approximately 400 patients will be randomized into the global enrollment phase of this study to the atezolizumab + carboplatin + etoposide arm and the placebo + carboplatin + etoposide arm in a 1:1 ratio.

There are two co-primary efficacy endpoints: PFS and OS. To control the overall two-sided Type I error rate at 0.05, the two-sided significance levels of 0.005 and 0.045 are allocated to the primary comparisons for PFS and OS, respectively.

The following sample size calculation applies to the global enrollment phase, [redacted], unless otherwise noted.

The sample size of the study is determined by the analysis of OS. To detect an improvement of HR = 0.68 in OS using a log-rank test, approximately 2*80* deaths in the ITT population will be required to achieve *88*% power at a two-sided significance level of 0.045. *One OS interim analysis will be performed when approximately 220 OS events in the ITT population are observed, which by estimation will occur at approximately 23 months after the first patient is randomized.*

The primary analysis of PFS *is planned to be conducted at the time of the OS interim analysis, and is estimated to be* when approximately 2*75* PFS events in the ITT population have occurred, which is expected at approximately 2*3* months after the first patient is randomized. This provides 9*8*% power to detect an improvement of HR = 0.55 in PFS at a two-sided significance level of 0.005. *There will be no interim analysis for PFS.*

By a group sequential Holm procedure, if the primary analysis of PFS is significant, then the two-sided 0.005 alpha will be recycled to OS. Otherwise, iIf the OS analysis at either interim or final is significant, the allocated test mass of two-sided 0.045 alpha can be returned to PFS so PFS primary analysis can be tested at a two-sided 0.05 level. Additional details will be provided in the SAP.

The final analysis of OS will be performed when approximately 2*80* OS events in the ITT population have been observed, which is expected at approximately 3*1* months after the first patient is randomized.

The calculation of sample size and estimates of the analysis timelines are based on the following assumptions:

- PFS and OS are exponentially distributed.
- The median duration of PFS in the control arm is 6 months.
- The median duration of OS in the control arm is 10 months.
- The two interim and final analyses of OS use the Lan-DeMets alpha spending function to approximate the O'Brien-Fleming boundary.
- The dropout rate is 5% over 12 months for PFS and OS.

The sample size of the [redacted]

Interim Analyses

There will be no interim analyses planned for PFS in this study. An external independent Data Monitoring Committee (iDMC) will be set up to evaluate safety data on an ongoing basis. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an independent Data Coordinating Center. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the institutional review boards/ethics committees. A detailed plan will be included in the iDMC Charter.

One interim efficacy analysis of OS is planned when approximately 220 OS events have been observed. The primary analysis of PFS will be conducted at the same time of the interim OS analysis, and the exact timing of the analysis depends on when approximiately 275 PFS events or approximately 220 OS events have occurred, whichever occurs later.

The final OS analysis will be conducted when approximately 2*80* OS events in the ITT population have been observed. This is expected to occur approximately 3*1* months after the first patient is randomized, but the exact timing of this analysis will depend on the actual number of OS events.

To control the type I error for OS, the stopping boundaries for OS interim and final analyses are to be computed with use of the Lan-DeMets approximation to the O'Brien-Fleming boundary.

Appendix 2
Schedule of Assessments

Procedure	Screening	All Treatment Cycles [a]		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1–4)	Maintenance Phase		
	Days −28 to −1	Every 21 Days (±3 Days) [b]	Every 21 Days (±3 Days)	≤30 Days after Last Dose of Study Treatment	Every 3 Months after Disease Progression
Informed consent	x				
Pre-treatment tumor tissue specimen for biomarker testing	x [c]	x [c]	x [c]		
Demographic data	x				
Medical history and baseline conditions	x				
SCLC cancer history	x				
Vital signs [d]	x	x	x	x	
Weight	x	x	x	x	
Height	x				
Complete physical examination	x				
Limited physical examination [e]		x	x	x	
ECOG performance status	x	x	x	x	
12-lead ECG	x	x [f]	x [f]	x [f]	
Hematology [g]	x [h]	x	x	x	
Serum chemistry [i]	x [h]	x	x	x	

Appendix 2
Schedule of Assessments (cont.)

Procedure	Screening Days −28 to −1	All Treatment Cycles [a] Induction Phase (Cycles 1–4) Every 21 Days (±3 Days) [b]	All Treatment Cycles [a] Maintenance Phase Every 21 Days (±3 Days) [b]	Treatment Discontinuation Visit ≤30 Days after Last Dose of Study Treatment	Survival Follow-Up Every 3 Months after Disease Progression
Coagulation test (aPTT or INR)	x [h]			x	
Pregnancy test (women of childbearing-potential only)	x [j]	x [k]	x [k]	x [k]	
TSH, free T3, free T4 [l]	x	x [m]	x [m]	x	
HIV, HBV, HCV serology [n]	x				
Urinalysis [o]	x [o]	x [o]	x [o]	x [o]	
Induction treatment administration Arm A: atezolizumab + etoposide + carboplatin Arm B: placebo + etoposide + carboplatin		x [p]			
Maintenance treatment administration Arm A: atezolizumab Arm B: placebo			x [p]		
Prophylactic cranial irradiation			x [q]		
Tumor response assessment	x [r]	x [s]	x [s]		x [t]
Serum sample for atezolizumab ADA assessment [u]		x	x	x	120 (±30) days after last dose of atezolizumab
Serum sample for atezolizumab PK sampling [u]		x	x	x	120 (±30) days after last dose of atezolizumab

Appendix 2
Schedule of Assessments (cont.)

Procedure	Screening Days −28 to −1	All Treatment Cycles [a] Induction Phase (Cycles 1–4) Every 21 Days (±3 Days) [b]	All Treatment Cycles [a] Maintenance Phase Every 21 Days (±3 Days) [b]	Treatment Discontinuation Visit ≤30 Days after Last Dose of Study Treatment	Survival Follow-Up Every 3 Months after Disease Progression
Carboplatin and etoposide PK sampling [u]		x			
Blood samples for PD biomarkers [u]		x	x	x	120 (±30) days after last dose of atezolizumab
Optional tumor biopsy after induction treatment (if patient signs consent)		After induction treatment			
Optional tumor biopsy at time of radiographic progression (if patient signs consent) [v]		At time of initial radiographic progression			
Optional tumor biopsy at other time points (RCR only)		Any time during study treatment or during survival follow-up			
Optional blood for DNA extraction (RCR only) [u, w]		x			
Adverse events	x	x	x	x [x]	x [x]
Concomitant medications	x [y]	x [y]	x [y]	x [y]	
Patient-reported outcomes (EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L) [z]		x [z]	x [z]		x [z]

Appendix 2
Schedule of Assessments (cont.)

Procedure	Screening Days −28 to −1	All Treatment Cycles [a] Induction Phase (Cycles 1–4) Every 21 Days (±3 Days) [b]	All Treatment Cycles [a] Maintenance Phase Every 21 Days (±3 Days) [b]	Treatment Discontinuation Visit ≤30 Days after Last Dose of Study Treatment	Survival Follow-Up Every 3 Months after Disease Progression
Survival and anti-cancer therapy follow-up					x [aa]

ADA=anti-drug antibody; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; *eCRF=electronic case report form;* EORTC=European Organization for Research and Treatment of Cancer; ePRO=electronic Patient-Reported Outcome; EQ-5D-5L=EuroQoL 5 Dimensions 5-Level Version; FFPE=formalin-fixed paraffin-embedded; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; MRI=magnetic resonance imaging; NSCLC=non–small cell lung cancer; PCI=prophylactic cranial irradiation; *PCR=polymerase chain reaction;* PD=pharmacodynamic; PD-L1=programmed death–ligand 1; PK=pharmacokinetic; PRO=Patient-Reported Outcome; QLQ-C30=Quality-of-Life Questionnaire Core 30; QLQ-LC13=Quality-of-Life Questionnaire Lung Cancer module; RCR=Roche Clinical Repository; RECIST=Response Evaluation Criteria in Solid Tumors; SCLC=small cell lung cancer; TSH=thyroid-stimulating hormone.

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

[b] Cycle 1 must be performed within 5 days after the patient is randomized. Screening assessments performed ≤96 hours before Cycle 1, Day 1 are not required to be repeated for Cycle 1, Day 1. In addition, ECOG performance status, limited physical examination, and local laboratory tests may be performed ≤96 hours before Day 1 of each cycle as specified in Section 4.5.12.2.

[c] A pre-treatment tumor tissue (archival or freshly obtained) sample should be submitted before or within 4 weeks after randomization. This specimen must be accompanied by the associated pathology report. Although any available tumor tissue sample can be submitted, it is strongly encouraged that representative tumor specimens in paraffin blocks (preferred) or 10 (or more) serial, freshly cut, unstained slides be submitted. See Section 4.5.7.1 for details.

[d] Vital signs include *pulse* rate, respiratory rate, blood pressures, and temperature. Vital signs should be recorded as described in Section 4.5.4.

[e] Symptom-directed physical examinations; see Section 4.5.3 for details.

[f] ECG recordings will be obtained when clinically indicated.

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

[h] At screening, the patient must have adequate hematologic and end-organ function defined by laboratory test results obtained within 14 days prior to

randomization. See Section 4.1.1 for details.

[l] Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total CO_2 *if considered standard of care in the region*, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.

[j] Serum pregnancy test within 14 days before Cycle 1, Day 1.

[k] Urine pregnancy tests; if a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

[l] Total T3 will be tested only at sites where free T3 is not performed.

[m] Thyroid function testing (TSH, free T3, free T4) collected *on Day 1 of Cycles 1, 4, 8, and 12,* and every fourth cycle thereafter.

[n] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the study. Patients with active hepatitis B (chronic or acute; defined as having a positive HBsAg test result at screening) will be excluded from the study. Patients 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 patients *prior to randomization*. Patients with HCV will be excluded from the study; patients who test positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

[o] Urinalysis by dipstick (specific gravity, pH, glucose, protein, ketones, and blood). Urinalysis is required at screening and will be obtained when clinically indicated.

[p] For atezolizumab/placebo, 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. For carboplatin and etoposide, study drug *will* be administered as described in Section 4.3.2.

[q] During the maintenance phase, PCI is permitted as per local standard-of-care and *will* be reported on the Prophylactic Cranial Irradiation eCRF.

[r] CT scans (with oral/IV contrast unless contraindicated) or MRI scans of the chest and abdomen. A CT or MRI scan of the pelvis is required at screening and as clinically indicated or as per local standard-of-care at subsequent response evaluations. A CT (with contrast) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients. See Section 4.5.5 for details.

[s] Perform every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1 and then every 9 weeks (±7 days) thereafter, after completion of the Week 48 tumor assessment, 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. Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will continue to undergo tumor assessments every 6 weeks (±7 days) or sooner if symptomatic deterioration occurs. For these patients, tumor assessments *will* continue every 6 weeks (±7 days), regardless of time on study, until study treatment is discontinued. See Section 4.5.5 for details.

[t] If the patient discontinued study treatment for any reason other than *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 patient had remained on study treatment (i.e., every 6 weeks [± 7 days] for 48 weeks following Cycle 1, Day 1 and then every 9 weeks [± 7 days] thereafter) until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first, even if the patient starts another anti-cancer therapy after study treatment discontinuation, unless consent is withdrawn. See Section 4.5.5 for details.

[u] See Appendix 2 for detailed schedule.

[v] Optional tumor biopsy at radiographic disease progression, if clinically feasible, preferably within 40 days of radiographic progression or prior to start of the next anti-cancer therapy, whichever occurs is sooner.

[w] The optional RCR whole blood sample requires an additional informed consent and the sample can be collected at any time during the course of the study.

[x] All serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study drug, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study drug, whichever occurs first. After this period, *all deaths should continue to be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment (see Section 5.6). These events should be reported through use of the Adverse Event eCRF.*

[y] From 7 days before screening *until the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.*

[z] EORTC QLQ-C30, EORTC QLQ-LC13, and the EQ-5D-5L questionnaires will be completed by the patients on the ePRO tablet at each scheduled study visit prior to administration of study drug and prior to any other study assessment(s). During survival follow-up, the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L questionnaires will be completed at 3 *months (±30 days)* and 6 months *(±30 days)* following radiographic disease progression per RECIST v1.1 (or at 3 *months [±30 days]* and 6 months *[±30 days]* after treatment is discontinued for patients who continue treatment after disease progression per RECIST v1.1). Patients who discontinue study treatment for any reason other than *radiographic* disease progression per RECIST v1.1 (e.g., toxicity*, symptomatic deterioration*) will complete EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L at each tumor assessment visit until *radiographic* disease progression per RECIST v1.1, unless the patient withdraws consent or the Sponsor terminates the study, whichever occurs first. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. Patients whose native language is not available in the ePRO device or who are deemed by the investigator incapable of inputting their ePRO assessment after undergoing appropriate training are exempt from all ePRO assessments.

[aa] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits *every 3 months or more frequently until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up (this request must be documented in the source documents and signed by the investigator). If the patient 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.

Appendix 3
Schedule of Pharmacokinetic, Pharmacodynamic, Biomarker, and Anti-Therapeutic Antibody Assessments

Study Visit	Time	Atezolizumab/Placebo + Carboplatin + Etoposide
Cycle 1, Day 1 [a]	Predose (same day as treatment administration) (for biomarker sampling, prior to first dose of steroids)	• Atezolizumab ADA • Atezolizumab PK • Carboplatin PK [b] • Etoposide PK [b] • Biomarkers [c]
	30 (± 10) minutes after end of atezolizumab infusion	Atezolizumab PK
	5–10 minutes before the end of carboplatin infusion [b]	Carboplatin PK [b]
	1 hour (± 15 minutes) after end of carboplatin infusion [b]	Carboplatin PK [b]
	5–10 minutes before the end of etoposide infusion [b]	Etoposide PK [b]
	1 hour (± 15 minutes) after end of etoposide infusion [b]	Etoposide PK [b]
	4 hours (± 30 minutes) after end of etoposide infusion [b]	Etoposide PK [b]
Cycle 2, Day 1	Predose (same day as treatment administration)	• Atezolizumab ADA • Atezolizumab PK • Biomarkers [d]
Cycle 3, Day 1	Predose (same day as treatment administration)	• Atezolizumab ADA • Atezolizumab PK • Carboplatin PK [b] • Etoposide PK [b] • Biomarkers [c]

Appendix 3
Schedule of Pharmacokinetic, Pharmacodynamic, Biomarker, and Anti-Therapeutic Antibody Assessments (cont.)

Study Visit	Time	Atezolizumab/Placebo + Carboplatin + Etoposide
Cycle 3, Day 1	5–10 minutes before the end of carboplatin infusion [b]	Carboplatin PK [b]
	1 hour (± 15 minutes) after end of carboplatin infusion [b]	Carboplatin PK [b]
	5–10 minutes before the end of etoposide infusion [b]	Etoposide PK [b]
	1 hour (± 15 minutes) after end of etoposide infusion [b]	Etoposide PK [b]
	4 hours (± 30 minutes) after end of etoposide infusion [b]	Etoposide PK [b]
Cycles 4, 8, and 16, Day 1	Predose (same day as treatment administration)	• Atezolizumab ADA • Atezolizumab PK • Biomarkers [d]
After Cycle 16, every 8th cycle, Day 1	Predose (same day as treatment administration)	• Atezolizumab ADA • Atezolizumab PK • Biomarkers [d]
At time of fresh biopsy (on-treatment including during follow-up)	At visit	• Biomarkers [d]
Treatment discontinuation visit	At visit	• Atezolizumab ADA • Atezolizumab PK • Biomarkers [d]
120 (±30 days) after last dose of atezolizumab/placebo	At visit	• Atezolizumab ADA • Atezolizumab PK • Biomarkers [d]
Any time point during the study (RCR consent required)		Optional RCR blood (DNA extraction) [e]

ADA = anti-drug antibody; PK = pharmacokinetic; RCR = Roche Clinical Repository.

Note: Serum PK samples for atezolizumab; plasma PK samples for carboplatin and etoposide.

[a] Biomarker sampling before Cycle 1, Day 1 should be performed before patients are treated with first dose of steroids.

[b] At select sites, a subset of approximately 40 patients will undergo the additional PK assessments for carboplatin and etoposide. The additional PK assessments should be taken only if the patient is receiving both carboplatin and etoposide at the cycle.

[c] Plasma, serum, whole blood for biomarkers.

[d] Plasma and serum for biomarkers.

[e] The optional RCR blood sample (for DNA extraction) requires an additional informed consent and can be collected at any time during the course of the study.