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PROTOCOL

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (MPDL3280A, ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH CARBOPLATIN + PACLITAXEL WITH OR WITHOUT BEVACIZUMAB COMPARED WITH CARBOPLATIN + PACLITAXEL + BEVACIZUMAB IN CHEMOTHERAPY-NAIVE PATIENTS WITH STAGE IV NON-SQUAMOUS NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO29436
VERSION NUMBER:	7
EUDRACT NUMBER:	2014-003207-30
IND NUMBER:	117296
TEST PRODUCT:	Atezolizumab (MPDL3280A, RO5541267)
MEDICAL MONITOR:	[redacted], *R.N.*
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	21 November 2014
DATES AMENDED:	Version 2: 29 March 2015 Version 3: 14 August 2015 Version 4: 11 November 2015 Version 5: 31 May 2016 Version 6: 1 March 2017 Version 7: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	24-Oct-2018 09:49:10

PROTOCOL AMENDMENT, VERSION 7:
RATIONALE

Protocol GO29436 has been amended to reflect a change in the definition for the end of study. Changes to the protocol, along with a rationale for each change, are summarized below:

- The end of study definition has been corrected. This correction ensures that the study continues until last patient, last visit or until the Sponsor terminates the study (Section 3.2).
- The inclusion criterion that addresses female contraception has been modified to specify when women must refrain from donating eggs (Section 4.1.1).
- Instructions about patient withdrawal from the Roche Clinical Repository 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 global_rcr-withdrawal@roche.com (Section 4.5.11.6).
- The Medical Monitor has been changed, and the contact information has been revised accordingly (Section 5.4.1).
- Language has been revised to account for the fact that some sites may not allow follow-up on partner pregnancies (Section 5.4.3.2).
- Language has been updated to indicate that therapeutic or elective abortions are not considered adverse events unless performed because of an underlying maternal or embryofetal toxicity. In such cases, the underlying toxicity should be reported as a serious adverse event. Language has also been added to clarify that all abortions are to be reported on the paper Clinical Trial Pregnancy Reporting Form (Section 5.4.3.3).
- 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).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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MEDICAL MONITOR:	[redacted], *R.N.*
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.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (MPDL3280A, ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH CARBOPLATIN + PACLITAXEL WITH OR WITHOUT BEVACIZUMAB COMPARED WITH CARBOPLATIN + PACLITAXEL + BEVACIZUMAB IN CHEMOTHERAPY-NAIVE PATIENTS WITH STAGE IV NON-SQUAMOUS NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO29436
VERSION NUMBER:	7
EUDRACT NUMBER:	2014-003207-30
IND NUMBER:	117296
TEST PRODUCT:	Atezolizumab (MPDL3280A, RO5541267)
PHASE:	III
INDICATION:	Non-squamous non–small cell lung cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

Unless otherwise specified, efficacy objectives will be analyzed for the following two treatment comparisons:

- Atezolizumab + carboplatin + paclitaxel + bevacizumab (Arm B) versus carboplatin + paclitaxel + bevacizumab (Arm C)
- Atezolizumab + carboplatin + paclitaxel (Arm A) versus carboplatin + paclitaxel + bevacizumab (Arm C)

The term “wild type” (WT) refers to randomized patients who do not have a sensitizing EGFR mutation or ALK translocation.

The term “tumor gene expression” (tGE) refers to randomized patients with a defined level of expression of a PD-L1 and T-effector gene signature in tumor tissue, as analyzed through use of a centrally performed RNA-based assay.

Some efficacy endpoints will be analyzed in a population of randomized patients with a defined level of PD-L1 expression on tumor cells (TCs) and immune cells (ICs), as analyzed through use of a centrally performed IHC test.

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

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed progression-free survival (PFS) according to RECIST v1.1 in the tGE-WT population and the ITT-WT population
- To evaluate the efficacy of atezolizumab as measured by overall survival (OS) in the ITT-WT population

The secondary efficacy objectives for this study are the following:

- To evaluate the efficacy of atezolizumab as measured by OS in the tGE-WT population
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed PFS according to RECIST v1.1 and OS in the TC2/3 or IC2/3 WT population and the TC1/2/3 or IC1/2/3 WT population
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed PFS according to RECIST v1.1 and OS in the tGE population and the ITT population
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed objective response rate (ORR) according to RECIST v1.1 in the tGE-WT population and the ITT-WT population
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed duration of response (DOR) according to RECIST v1.1 in the tGE-WT population and the ITT-WT population
- To evaluate the efficacy of atezolizumab as measured by an Independent Review Facility (IRF)-assessed PFS according to RECIST v1.1 in the tGE-WT population and the ITT-WT population
- To evaluate the OS rate at 1 and 2 years in each treatment arm for the tGE-WT population and the ITT-WT population
- To compare the efficacy of the two atezolizumab-containing arms, Arm A versus Arm B, as measured by investigator-assessed PFS according to RECIST v1.1 and by OS in the tGE-WT population and the ITT-WT 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, or arm/shoulder pain, using the European Organisation 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 the tGE-WT population and the ITT-WT population
- To determine the impact of atezolizumab as measured by change in baseline (i.e., improvement or deterioration based upon presenting symptomatology) in patient-reported lung cancer symptom (chest pain, dyspnea, and cough) score using the Symptoms in Lung Cancer (SILC) scale symptom severity score for the tGE-WT population and the ITT-WT

Safety Objectives

The safety objectives for this study are the following:

- To evaluate the safety and tolerability of atezolizumab in each of the two treatment comparisons
- 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 Objectives

The pharmacokinetic (PK) objectives for this study are the following:

- To characterize the pharmacokinetics of atezolizumab when given in combination with carboplatin and paclitaxel with and without bevacizumab (Arms A and B)
- To characterize the pharmacokinetics of carboplatin when given in combination with paclitaxel with and without atezolizumab and/or bevacizumab (Arms A, B, and C)
- To characterize the pharmacokinetics of paclitaxel when given in combination with carboplatin with and without atezolizumab and/or bevacizumab (Arms A, B, and C)
- To characterize the pharmacokinetics of bevacizumab when given in combination with carboplatin and paclitaxel with and without atezolizumab (Arms B and C)

Exploratory Objectives

The exploratory objectives for this study are the following:

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed time to response (TTR) and time-in-response (TIR) according to RECIST v1.1
- To evaluate ORR and DOR according to RECIST v1.1 as assessed by the IRF
- To evaluate investigator-assessed ORR, PFS, and DOR according to modified RECIST for the atezolizumab-containing treatment arms
- To evaluate PFS at 6 months and at 1 year in each treatment arm
- To evaluate the OS rate at 3 years in each treatment arm
- To assess predictive, prognostic, and pharmacodynamic 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
- To evaluate the utility of biopsy at the time of apparent disease progression to distinguish apparent increases in tumor volume related to the immunomodulatory activity of atezolizumab (i.e., pseudoprogression/tumor-immune infiltration) from true disease progression
- To evaluate and compare patient's health status as assessed by the EuroQoL 5 Dimensions 3-Level (EQ-5D-3L) questionnaire to generate utility scores for use in economic models for reimbursement
- To determine the impact of atezolizumab as measured by change from baseline in patient-reported outcomes of health-related quality of life, lung cancer–related symptoms, and functioning as assessed by the EORTC QLQ-C30 and LC13

Study Design

Description of Study

This is a randomized, Phase III, multicenter, open-label study (IMpower150) designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin + paclitaxel with or without bevacizumab compared with treatment with carboplatin + paclitaxel + bevacizumab in approximately 1200 chemotherapy-naive patients with Stage IV non-squamous non–small cell lung cancer (NSCLC).

Tumor specimens will be prospectively tested for PD-L1 expression by a central laboratory. Eligible patients will be stratified by sex (male vs. female), presence of liver metastases at baseline (yes vs. no), and by PD-L1 tumor expression by IHC (TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1). Patients will be randomized in a 1:1:1 ratio to receive one of the following treatment regimens:

Treatment Arm A: Atezolizumab + carboplatin + paclitaxel (Induction: four or six 21-day cycles); atezolizumab (Maintenance: 21-day cycles)

Treatment Arm B: Atezolizumab + carboplatin + paclitaxel + bevacizumab (Induction: four or six 21-day cycles); atezolizumab + bevacizumab (Maintenance: 21-day cycles)

Treatment Arm C: Carboplatin + paclitaxel + bevacizumab (Induction: four or six 21-day cycles); bevacizumab (Maintenance: 21-day cycles)

The number of cycles of induction treatment (four or six) will be at the discretion of the investigator and will be determined and documented prior to randomization. Induction treatment will be administered on a 21-day cycle until the following occur (whichever occurs first): 1) administration of four or six cycles or 2) disease progression (Arm C) or loss of clinical benefit (Arms A and B) is documented.

Following the induction phase, patients will continue treatment with maintenance therapy. Patients who are randomized to Arms B and C will continue treatment with bevacizumab until progressive disease, unacceptable toxicity, or death. Patients who are randomized to Arms A or B may continue treatment with atezolizumab beyond radiographic progression according to RECIST v1.1, provided they are experiencing clinical benefit as assessed by the investigator (i.e., in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease

progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results [if available], and clinical status).

Treatment with chemotherapy (Arms A, B, and C) and bevacizumab (Arms B and C) must be discontinued in all patients who exhibit evidence of progressive disease.

Patients will undergo tumor assessments at baseline and every 6 weeks for the first 48 weeks following Cycle 1, Day 1, regardless of dose delays. After 48 weeks, tumor assessment will be required every 9 weeks. Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. Patients who discontinue treatment for reasons other than radiographic disease progression (e.g., toxicity) will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment after radiographic disease progression according to 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.

A secondary endpoint of this study is IRF-assessed PFS according to RECIST v1.1. An IRF will therefore conduct an independent review of the responses of all patients, including a blinded review of computed tomography (CT) scans. All primary imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints. These reviews will be performed prior to the final efficacy analyses.

For Treatment Arms A and B Only

At any point during treatment, patients receiving atezolizumab who show evidence of clinical benefit will be permitted to continue atezolizumab after RECIST v1.1 for progressive disease are met if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values, e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease
- No decline in Eastern Cooperative Oncology Group (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 atezolizumab at the time of initial progression

Patients in all treatment arms will undergo a mandatory tumor biopsy sample collection, unless not clinically feasible as assessed and documented by investigators, at the time of radiographic disease progression. These data will be used to explore whether radiographic findings are consistent with the presence of tumor. Additionally, these data will be analyzed to evaluate the association between changes in tumor tissue and clinical outcome and to understand further 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 in Arms A and B who are unable to undergo biopsy sample collection but who otherwise meet the criteria listed above may continue to receive atezolizumab.

Number of Patients

Approximately 270 sites globally will participate in the study, and approximately 1200 patients will be randomized.

Target Population

Inclusion Criteria

Patients may be eligible if they have chemotherapy-naive, Stage IV, non-squamous NSCLC.

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, Stage IV non-squamous NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 7th edition).

  Patients with tumors of mixed histology (i.e., squamous and non-squamous) are eligible if the major histological component appears to be non-squamous.
- No prior treatment for Stage IV non-squamous NSCLC

  Patients with a sensitizing mutation in the epidermal growth factor receptor (EGFR) gene must have experienced disease progression (during or after treatment) or intolerance to treatment with one or more EGFR TKIs, such as erlotinib, gefitinib, or another EGFR tyrosine kinase inhibitor (TKI) appropriate for the treatment of EGFR-mutant NSCLC.

  Patients with an anaplastic lymphoma kinase (ALK) fusion oncogene must have experienced disease progression (during or after treatment) or intolerance to treatment with one or more ALK inhibitors (i.e., crizotinib) appropriate for the treatment of NSCLC in patients having an ALK fusion oncogene.

  Patients with unknown EGFR and/or ALK status require test results at screening. ALK and/or EGFR may be assessed locally or at a central laboratory.
- Patients who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomization since the last chemotherapy, radiotherapy, or chemoradiotherapy.
- 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 stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomization

  No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  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.

- Known PD-L1 tumor status as determined by an IHC assay performed by a central laboratory on previously obtained archival tumor tissue or tissue obtained from a biopsy at screening

  A representative formalin-fixed paraffin-embedded (FFPE) tumor specimen in paraffin block (preferred) or 15 or more unstained, freshly cut, serial sections on slides from an FFPE tumor specimen is required for participation in this study. If fewer than 15 slides are available at baseline (but no fewer than 10), the patient may still be eligible, upon discussion with the Medical Monitor. This specimen must be accompanied by the associated pathology report.

  Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or cell smears), brushing, cell pellet specimens (e.g., from pleural effusion, and lavage samples) are not acceptable.

  Tumor tissue from bone metastases that is subject to decalcification is not acceptable.

  For core needle biopsy specimens, preferably at least three cores embedded in a single paraffin block, should be submitted for evaluation.
- 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
- For female patients of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate (< 1% per year) when used consistently and correctly, and to continue its use for 5 months after the last dose of atezolizumab and/or 6 months after the last dose of bevacizumab or paclitaxel, whichever is later). *Women must refrain from donating eggs during this same period. Highly effective contraceptive* methods include: combined (estrogen and progestogen containing) hormonal contraception, progestogen-only hormonal contraception associated with inhibition of ovulation together with another additional barrier method always containing a spermicide, intrauterine device (IUD): intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner (on the understanding that this is the only one partner during the whole study duration), and sexual abstinence.

- For male patients with female partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate [< 1% per year] when used consistently and correctly, and to continue its use for 6 months after the last dose of bevacizumab, carboplatin, or paclitaxel. Male patients should not donate sperm during this study and for at least 6 months after the last dose of bevacizumab, carboplatin, or paclitaxel.
- Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drug. The same rules are valid for male patients involved in this clinical study if they have a partner of childbirth potential. Male patients must always use a condom.
- Women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug

Exclusion Criteria

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

Cancer-Specific Exclusions

- Active or untreated CNS metastases as determined by 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 > 2 weeks prior to randomization
- Leptomeningeal disease
- Uncontrolled tumor-related pain

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to randomization. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for locoregional therapy, if appropriate, prior to randomization.
- 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.
- Uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > ULN)

  Patients who are receiving denosumab prior to randomization must be willing and eligible to receive a bisphosphonate instead while in the study.
- Malignancies other than NSCLC 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)
- Known tumor PD-L1 expression status as determined by an IHC assay from other clinical studies (e.g., patients whose PD-L1 expression status was determined during screening for entry into a study with PD-1 or anti-PD-L1 antibodies but were not eligible are excluded)

General Medical Exclusions

- Women who are pregnant, lactating, or intending to become pregnant during the study
- 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 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 a stable dose of thyroid replacement hormone are eligible for this study.

  Patients with controlled Type 1 diabetes mellitus on a stable dose of insulin regimen are eligible for this study

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

  Rash must cover less than 10% of body surface area (BSA).

  Disease is well controlled at baseline and only requiring low-potency topical steroids.

  No acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], 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 for HIV

  All patients will be tested for HIV prior to inclusion into the study; patients who test positive for HIV will be excluded from the clinical study.
- Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

  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 only if they are negative for HBV DNA.

  Patients positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV RNA.
- Active tuberculosis
- Severe infections within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received therapeutic oral or IV antibiotics within 2 weeks prior to randomization

  Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.

- 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
- 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
- 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 renders the patient at high risk from treatment complications
- Patients with illnesses or conditions that interfere with their capacity to understand, follow and/or comply with study procedures

Exclusion Criteria Related to Medications

- Any approved anti-cancer therapy, including hormonal therapy, within 3 weeks prior to initiation of study treatment; the following exceptions are allowed:

  TKIs approved for treatment of NSCLC discontinued > 7 days prior to randomization; the baseline scan must be obtained after discontinuation of prior TKIs.
- Treatment with any other investigational agent with therapeutic intent within 28 days prior to randomization
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti–PD-1, and anti–PD-L1 therapeutic antibodies

  Patients who have had prior anti–CTLA-4 treatment may be enrolled, provided the following requirements are met:

  Last dose of anti–CTLA-4 at least 6 weeks prior to randomization

  No history of severe immune-mediated adverse effects from anti–CTLA-4 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 3 and 4)
- Treatment with systemic immunostimulatory agents (including, but not limited to, IFNs, IL-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to randomization

  Prior treatment with cancer vaccines is allowed.
- Treatment with systemic immunosuppressive medications (including but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to randomization

  Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study.

  The use of corticosteroids (≤ 10 mg oral prednisone or equivalent) for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency is allowed

Exclusions Related to Bevacizumab

- Inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg)

  Anti-hypertensive therapy to achieve these parameters is allowable.
- Prior history of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to randomization
- History of hemoptysis ($\geq$ one-half teaspoon of bright red blood per episode) within 1 month prior to randomization
- Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (within 10 days of randomization) use of aspirin (>325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and clostazol
- Current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes that has not been stable for >2 weeks prior to randomization

  The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the patient has been on a stable dose of anticoagulants for at least 2 weeks prior to randomization.

  Prophylactic anticoagulation for the patency of venous access devices is allowed, provided the activity of the agent results in an INR $<1.5\times$ ULN and aPTT is within normal limits within 14 days prior to randomization.

  Prophylactic use of low-molecular-weight heparin (i.e., enoxaparin 40 mg/day) is permitted.
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to the first dose of bevacizumab
- History of abdominal or tracheosphageal fistula or gastrointestinal perforation within 6 months prior to randomization
- Clinical signs of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- Serious, non-healing wound, active ulcer, or untreated bone fracture
- Proteinuria, as demonstrated by urine dipstick or >1.0 g of protein in a 24-hour urine collection

  All patients with $\geq 2+$ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection and must demonstrate ≤ 1 g of protein in 24 hours.
- Known sensitivity to any component of bevacizumab
- Clear tumor infiltration into the thoracic great vessels is seen on imaging
- Clear cavitation of pulmonary lesions is seen on imaging

Exclusions Related to Chemotherapy

- Known history of severe allergic reactions to platinum-containing compounds or mannitol
- Known sensitivity to any component of paclitaxel
- Grade ≥ 2 peripheral neuropathy as defined by NCI CTCAE v4.0 (paclitaxel)
- Known history of severe hypersensitivity reactions to products containing Cremophor® EL (e.g., cyclosporin for injection concentrate and teniposide for injection concentrate)

Length of Study

The final PFS analysis will be conducted when both of the following criteria have been met: approximately 516 PFS events have occurred in Arms B and C combined in the ITT-WT population and the last patient has been enrolled in the study. The final PFS analysis is expected to occur approximately 29 months after the first patient is enrolled. At the time of the final PFS analysis, it is expected that approximately 249 events will have occurred in the tGE-WT population.

With a sample size of 720 patients, approximately 507 OS events are expected to occur in Arms B and C combined in the ITT-WT population for the final OS analysis. The final OS analysis is expected to occur approximately 40 months after the first patient is enrolled. This number of events corresponds to a minimum detectable difference in HR of approximately 0.83 in the ITT-WT population

End of Study

The end of study is defined as the date of the last follow-up visit of the last patient or when all patients have been enrolled into an extension study. The Sponsor may decide to terminate the study at any time. If the Sponsor decides to end the study, patients who are still receiving study treatment or are in survival follow-up may be offered enrollment in an extension study or a non-interventional study.

Outcome Measures

Efficacy Outcome Measures

The co-primary efficacy outcome measures for this study are the following:

- 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 in the tGE-WT population and the ITT-WT population
- OS, defined as the time from randomization to death from any cause in the ITT-WT population

The secondary efficacy outcome measures for this study are the following:

- OS in the tGE-WT population
- PFS, as determined by the investigator according to RECIST v1.1, and OS in the TC2/3 or IC2/3 WT population and the TC1/2/3 or IC1/2/3 WT population
- PFS, as determined by the investigator according to RECIST v1.1, and OS in the tGE population and the ITT population
- Objective response, defined as partial response (PR) or complete response (CR) as determined by the investigator according to RECIST v1.1 1 in the tGE-WT population and the ITT-WT population
- 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 occurs first 1 in the tGE-WT population and the ITT-WT population
- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the IRF using RECIST v1.1 or death from any cause, whichever occurs first 1 in the tGE-WT population and the ITT-WT population
- OS rates at 1 and 2 years 1 in the tGE-WT population and the ITT-WT population
- PFS, as determined by the investigator according to RECIST v1.1, and OS in the two atezolizumab-containing arms in the tGE-WT population and the ITT-WT population
- 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 in the tGE-WT population and the ITT-WT population
- Change from baseline in patient-reported lung cancer symptoms (chest pain, dyspnea, and cough) on the symptom severity score of the Symptoms in Lung Cancer scale in the tGE-WT population and the ITT-WT population

Safety Outcome Measures

The safety outcome measures for this study are the following:

- Incidence, nature, and severity of adverse events graded according to the NCI CTCAE v4.0
- Changes in vital signs, physical findings, and clinical laboratory results during and following atezolizumab 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 the following:

- Maximum observed serum atezolizumab concentration (C_{max}) after infusion (Arms A and B)
- 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 (Arms A and B)
- Plasma concentrations for carboplatin (Arms A, B, and C)
- Plasma concentrations for paclitaxel (Arms A, B, and C)
- Bevacizumab C_{max} and C_{min} (Arms B and C)

Exploratory Outcome Measures

The exploratory outcome measures for this study are:

- TTR, defined as the time from randomization to first occurrence of a documented objective response as determined by the investigator according to RECIST v1.1
- Time in response (TIR), defined as 1 day for non-responders and defined the same as DOR for responders, as determined by the investigator according to RECIST v1.1
- Objective response and DOR, as determined by the IRF according to RECIST v1.1
- Objective response, PFS, and DOR, in the two atezolizumab-containing arms, as determined by the investigator according to modified RECIST (Arms A and B)
- PFS at 6 months and at 1 year
- OS rate at 3 years
- Status of PD-L1–, immune- and NSCLC-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 in combination with chemotherapy
- Status of tumor-infiltrating immune cells and other exploratory biomarkers in mandatory biopsy specimens and blood collected at progression
- Utility scores of the EQ-5D-3L
- Change from baseline in patient-reported outcomes of health-related quality of life, lung cancer–related symptoms, and functioning as assessed by the EORTC QLQ-C30 and LC13

Investigational Medicinal Products

Test Product (Investigational Drug)

Atezolizumab (1200 mg IV) will be administered on Day 1 of each 21–day cycle. Atezolizumab will be administered to patients who are randomized to Arms A and B.

Comparator

Bevacizumab (15 mg/kg IV) will be administered on Day 1 of each 21-day cycle for four or six cycles during the induction phase and during the maintenance phase.

Bevacizumab will be administered to patients randomized to Arms B and C.

Non-Investigational Medicinal Products

- Carboplatin will be administered by IV infusion to achieve an initial target area under the concentration–time curve (AUC) of 6 mg/mL/min on Day 1 of each 21-day cycle for four or six cycles during the induction phase.
- Paclitaxel (200 mg/m^2 IV) will be administered on Day 1 of each 21-day cycle for four or six cycles during the induction phase.

Carboplatin and paclitaxel will be administered to patients in in all treatment arms.

Statistical Methods

Primary Analysis

The co-primary efficacy endpoints are PFS as assessed by the investigator using RECIST v1.1, and OS. The primary endpoint of PFS will be analyzed in the tGE-WT population and in the ITT-WT population, and the primary endpoint of OS will be analyzed in the ITT-WT population. 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 died 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.

OS is defined as the time between the date of randomization and death from any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.

The following analyses will be performed for both PFS endpoints described above and for OS. PFS and OS will be compared between treatment arms with the use of the stratified log-rank test. The HR for PFS and OS for each comparison (i.e., Arm A vs. Arm C, Arm B vs. Arm C) will be estimated using a stratified Cox regression model, respectively. The 95% CI for the HR will be provided.

The hypothesis testing will be done in the order described below:

Comparison of Arm B versus Arm C

To control the overall type I error rate for the one-sided test at 0.025, a one-sided type I error (α) will be allocated to PFS in the tGE-WT population, PFS in the ITT-WT population, and OS in the ITT-WT population in a 3:3:19 ratio for comparison of Arm B versus Arm C

1. PFS in the tGE-WT population will be tested at $\alpha = 0.003$ (one sided). If the estimate of the HR is <1 and the one-sided p-value corresponding to the stratified log-rank test is < 0.003, the null hypothesis will be rejected, and it will be concluded that atezolizumab + carboplatin + paclitaxel + bevacizumab prolongs the duration of PFS relative to the control arm in the tGE-WT population.
2. PFS in the ITT-WT population will be tested at $\alpha = 0.003$ (one sided).
3. α recycling from PFS to OS will be conducted as follows:
   a. If the PFS result is not statistically significant in either the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.019$ (one sided).
   b. If the PFS result is only statistically significant in the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.022$ (one sided).
   c. If the PFS result is statistically significant in both the tGE-WT population and the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.025$ (one sided).

Comparison of Arm A versus Arm C

If the difference in OS between Arm B and Arm C in the ITT-WT population is statistically significant at an α of 0.019, 0.022, or 0.025 (Step 3 above), that same α will become the overall one-sided type I error rate for the comparison of Arm A versus Arm C, with α allocated to PFS in the tGE-WT population, PFS in the ITT-WT population, and OS in the ITT-WT population at the same 3:3:19 ratio (see Figure 3 in Section 6.1). If the difference in OS between Arm B and Arm C in the ITT-WT population is not statistically significant, there will be no formal comparison of Arm A versus Arm C for the co-primary endpoints of PFS and OS.

Depending on the outcome of the PFS testing of Arm A vs. Arm C in the tGE-WT and ITT-WT populations, the α from these two PFS comparisons will be recycled back to the OS comparison in the ITT-WT population for Arm A vs. Arm C.

1. If the difference in OS between Arm B and Arm C is statistically significant at $\alpha = 0.019$ (one sided):
   a. PFS in the tGE-WT population will be tested at $\alpha = 0.00228$ (one sided). If the estimate of the HR is <1 and the one-sided p-value corresponding to the stratified log-rank test is < 0.00228, the null hypothesis will be rejected, and it will be concluded that atezolizumab + carboplatin + paclitaxel prolongs the duration of PFS relative to the control arm in the tGE-WT population.
   b. PFS in the ITT-WT population will be tested at $\alpha = 0.00228$ (one sided
   c. α recycling from PFS to OS will be conducted as follows:
      - If the PFS result is not statistically significant in either the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.01444$ (one sided)
      - If the PFS result is only statistically significant in the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.01672$ (one sided)
      - If the PFS result is statistically significant in both the tGE-WT population and the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.019$ (one sided).
2. If the difference in OS between Arm B and Arm C is statistically significant at $\alpha = 0.022$ (one sided):
   a. PFS in the tGE-WT population will be tested at $\alpha = 0.00264$ (one sided). If the estimate of the HR is <1 and the one-sided p-value corresponding to the stratified log-rank test is < 0.00264, the null hypothesis will be rejected, and it will be concluded that atezolizumab + carboplatin + paclitaxel prolongs the duration of PFS relative to the control arm in the tGE-WT population.
   b. PFS in the ITT-WT population will be tested at $\alpha = 0.00264$ (one sided
   c. α recycling from PFS to OS will be conducted as follows:
      - If the PFS result is not statistically significant in either the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.01672$ (one sided)
      - If the PFS result is only statistically significant in the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.01936$ (one sided)
      - If the PFS result is statistically significant in both the tGE-WT population and the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.022$ (one sided).
3. If the difference in OS between Arm B and Arm C is statistically significant at $\alpha = 0.025$ (one sided):
   a. PFS in the tGE-WT population will be tested at $\alpha = 0.003$ (one sided). If the estimate of the HR is <1 and the one-sided p-value corresponding to the stratified log-rank test is < 0.003, the null hypothesis will be rejected, and it will be concluded that atezolizumab + carboplatin + paclitaxel prolongs the duration of PFS relative to the control arm in the tGE-WT population.
   b. PFS in the ITT-WT population will be tested at $\alpha = 0.003$(one sided
   c. α recycling from PFS to OS will be conducted as follows:
      - If the PFS result is not statistically significant in either the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.019$ (one sided)

- If the PFS result is only statistically significant in the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.022$(one sided)
- If the PFS result is statistically significant in both the tGE-WT population and the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.025$ (one sided).

The stratification factors will be those used during randomization (i.e., sex [male vs. female], presence of liver metastases at baseline [yes vs. no], and PD-L1 tumor expression by IHC [TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1]), as recorded in the IxRS.

Results from an unstratified analysis will also be presented. Kaplan-Meier methodology will be used to estimate the median PFS and the median OS for each treatment arm, and a Kaplan-Meier curve will be constructed to provide a visual description of the difference between treatment arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS and the median OS for each treatment arm.

Determination of Sample Size

This study will enroll approximately 1200 patients. The ITT-WT population will include approximately 1080 patients, assuming a 10% prevalence for sensitizing EGFR mutations or ALK translocations. The tGE-WT population will include approximately 540 patients, assuming a 50% prevalence with the chosen tGE cutoff.

The sample size of this study is based on the number of events required to demonstrate efficacy with regard to both PFS and OS (co-primary endpoints).

The estimate of the number of events required to demonstrate efficacy with regard to PFS in the comparison of Arm A versus Arm B is based on the following assumptions:

- One-sided significance level of 0.003 for the comparison of Arm B versus Arm C in the tGE-WT population
- One-sided significance level of 0.003 for the comparison of Arm B versus Arm C in the ITT-WT population
- 98% power to detect an HR of 0.55, corresponding to an improvement in median PFS from 6 months to 10.9 months in the tGE-WT population
- 98% power to detect an HR of 0.65, corresponding to an improvement in median PFS from 6 months to 9.2 months in the ITT-WT population
- No interim analysis for PFS
- Dropout rate of 5% per 12 months

The estimate of the number of events required to demonstrate efficacy with regard to OS in the comparison of Arm A versus Arm B is based on the following assumptions:

- One-sided significance level of 0.019 for the comparison of Arm B versus Arm C in the ITT-WT population
- 87% power to detect an HR of 0.75, corresponding to an improvement in median OS from 12 months to 16 months in the ITT-WT population
- One interim OS analysis performed at the time of the final PFS analysis, at which time approximately 73% of the total number of OS events required for the final analysis are expected to have occurred as determined through use of the Lan-DeMets approximation to the O'Brien-Fleming boundary
- Dropout rate of 5% per 12 months

The estimate of the number of events required to demonstrate efficacy with regard to PFS and OS in the comparison of Arm A versus Arm C is based on assumptions similar to those outlined above for Arm B versus Arm C.

With these assumptions, approximately 1200 patients in total will be enrolled into this study, with approximately 720 patients in each comparison (i.e., Arm B vs. Arm C and Arm A vs. Arm C) in the ITT-WT population. The final PFS analysis will be conducted when both of the

following criteria have been met: approximately 516 PFS events have occurred in Arms B and C combined in the ITT-WT population and the last patient has been enrolled in the study. The final PFS analysis is expected to occur approximately 29 months after the first patient is enrolled. At the time of the final PFS analysis, it is expected that approximately 249 events will have occurred in the tGE-WT population. These numbers of events would allow for a minimum detectable difference corresponding to an HR of approximately 0.70 in the tGE-WT population and 0.78 in the ITT-WT population.

With a sample size of 720 patients, approximately 507 OS events are expected to occur in Arms B and C combined in the ITT-WT population for the final OS analysis. The final OS analysis is expected to occur approximately 40 months after the first patient is enrolled. This number of events corresponds to a minimum detectable difference in HR of approximately 0.83 in the ITT-WT population

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 Institutional Review Boards (IRBs)/Ethics Committees (ECs). A detailed plan will be included in the iDMC Charter.

If approximately 370 OS events have occurred in Arms B and C combined in the ITT-WT population at the time of the final PFS analysis (see criteria for final PFS analysis in Section 6.1), an interim OS analysis will be conducted for Arm B versus Arm C in the ITT-WT population. If there are significantly fewer than the expected 370 OS events at the time of the final PFS analysis, a nominal α of 0.01% (negligible impact on overall type I error rate) will be spent on the OS analysis at the time of the final PFS analysis and a second interim OS analysis will then be conducted after approximately 370 OS events have occurred.

The final OS analysis for the comparison of Arm B versus Arm C will be conducted when approximately 507 OS events have occurred in Arms B and C combined in the ITT-WT population. This is expected to occur approximately 40 months after the first patient is enrolled.

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
BSC	best supportive care
CL	clearance
C_{max}	maximum observed serum concentration
C_{min}	minimum observed serum concentration
CR	complete response
CRC	colorectal cancer
CRCL	creatinine clearance
CRF	Case Report Form
ctDNA	circulating-tumor DNA
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 Organisation for Research and Treatment of Cancer
ePRO	electronic PRO
EQ-5D-3L	Euro QoL5 Dimensions 3-Level Version
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FOLFOX	oxaliplatin, leucovorin, and 5-fluorouracil
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 Council for Harmonisation

Abbreviation	Definition
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IRF	Independent Review Facility
ITT	intent to treat
IV	intravenous
IxRS	interactive Web/voice response system
LFT	liver function test
MTD	maximum tolerated dose
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
PD–1	programmed death–1
PD–L1	programmed death–ligand 1
PET	positron emission tomography
PFS	progression-free survival
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PVC	polyvinylchloride
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
SILC	Symptoms in Lung Cancer
TC	tumor cell

Abbreviation	Definition
TE	thromboembolic events
tGE	tumor gene expression
TIR	time in response
TKI	tyrosine kinase inhibitor
TNF-α	tumor necrosis factor-α
TSH	thyroid-stimulating hormone
TTD	time to deterioration
TTF-1	thyroid transcription factor–1
TTP	time to progression
UBC	urothelial bladder cancer
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
V_{ss}	volume of distribution at steady state

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 both men and women and accounted for approximately 13% of all new cancers in 2008 (Jemal et al. 2011). In 2012, it was estimated that there would be 226,160 new cases of lung cancer and 160,340 lung cancer deaths in the United States alone (Siegel et al. 2012). Similar data from Europe estimate that there were 288,000 new cases of lung cancer and 253,000 deaths in 2008 (GLOBOCAN 2008).

Non–small cell lung cancer (NSCLC) is the predominant subtype of lung cancer, accounting for approximately 85% of all cases (Molina et al. 2008; Howlader et al. 2011). NSCLC can be divided into two major histologic types: adenocarcinoma and squamous cell carcinoma (Travis et al. 2011). Adenocarcinoma histology accounts for more than half of all NSCLC, while squamous cell histology accounts for approximately 25% (Langer et al. 2010). The remaining cases of NSCLC are represented by large cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma, and poorly differentiated histology.

The overall 5-year survival rate for advanced disease is 2%–4%, depending on geographic location (Cetin et al. 2011). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status, and a history of unintentional weight loss. More than half of the patients with NSCLC are diagnosed with distant disease, which directly contributes to poor survival prospects.

There are recognized differences in disease characteristics between adenocarcinoma and squamous NSCLC. First, squamous tumors commonly present in the central airways and typically remain localized in the bronchial epithelium (Hirsch et al. 2008), whereas non-squamous tumors are more commonly located in the lung parenchyma distal to the central airways. Evaluation of NSCLC tumor tissue will reveal cytological differences between the squamous cell type (keratinization, intracellular bridges, and central necrosis) and adenocarcinoma (glandular architecture). In cases where the tumor sample is poorly differentiated or there is limited tissue available, immunohistochemical markers may support the histologic diagnosis. Thyroid transcription factor–1 (TTF-1) is infrequently expressed in squamous cells and strongly expressed in adenocarcinoma. In contrast, p63, CK5/6, and 34βE12 are strongly expressed in squamous cell carcinoma and less frequently in adenocarcinoma (Travis et al. 2011).

Genetic changes that have prognostic and/or predictive significance in NSCLC include mutations in the *EGFR*, the rearrangement in the *ALK* genes, and mutations in the *KRAS* gene. The rates of these mutations differ between squamous cell carcinoma and adenocarcinoma. For example, *EGFR* kinase domain mutations have been reported in 10%–40% of patients with adenocarcinoma NSCLC but are infrequently observed in

squamous NSCLC (Herbst et al. 2008). Similarly, the *ALK* fusion oncogene, recognized as a driver of lung tumorigenesis, is observed in approximately 7% of patients with adenocarcinoma but is very rare in the squamous histology (Herbst et al. 2008; Langer et al. 2010). In addition, *KRAS* mutations are very rare in squamous NSCLC, while they can be observed in up to 30% of cases of adenocarcinoma NSCLC (Travis et al. 2011).

1.1.1 First-Line Treatment for Advanced Non–Small Cell Lung Cancer with an *EGFR* Mutation or *ALK* Rearrangement

Genotype-directed therapy has the potential to dramatically improve the balance of benefit and toxicity for selected patients with NSCLC characterized by alterations of driver oncogenes, including sensitizing *EGFR* mutations and *ALK* rearrangements. However, these mutations are more prevalent in adenocarcinoma NSCLC and are very rare in squamous NSCLC. Randomized Phase III studies of gefitinib (IPASS), erlotinib (EURTAC), and afatinib (LUX-LUNG 3) showed significant improvement of progression-free survival (PFS) and objective response rate (ORR) compared with platinum doublet chemotherapy (Fukuoka et al. 2011; Rosell et al. 2012; Sequist et al. 2013; respectively). Similarly, the *ALK* inhibitor crizotinib has demonstrated efficacy in patients with NSCLC positive for *ALK* rearrangement as defined by fluorescence in situ hybridization (Crino et al. 2011; Camidge et al. 2012; Shaw et al. 2012; XALKORI® U.S. Package Insert). Both *EGFR* tyrosine kinase inhibitors (TKIs) and crizotinib have been shown to be generally well tolerated.

1.1.2 First-Line Treatment for Advanced NSCLC without an *EGFR* Mutation or *ALK* Rearrangement

Patients with previously untreated advanced NSCLC that does not harbor a driver mutation that confers sensitivity to a targeted agent are typically treated with chemotherapy. The first evidence that chemotherapy produced a significant survival benefit in patients with advanced NSCLC came in 1995; a meta-analysis showed that platinum-based doublet chemotherapy conferred a 2-month improvement in median survival over best supportive care (BSC) (NSCLC Collaborative Group 1995). More recently, the European Big Lung Trial demonstrated the potential benefits of chemotherapy. In this study, 725 patients with advanced NSCLC were randomly assigned to BSC plus cisplatin-based chemotherapy or BSC alone (Spiro et al. 2004). Patients allocated to chemotherapy had a significantly longer median survival than did those managed with BSC (8 vs. 5.7 months; hazard ratio [HR] = 0.77, 95% CI: 0.66, 0.89).

The globally recognized standard-of-care for patients with inoperable Stage IIIB and Stage IV NSCLC is platinum-based chemotherapy for 4–6 cycles followed by maintenance treatment until progression. This standard-of-care applies to both non-squamous and squamous NSCLC (Pfister et al. 2004; D'Addario et al. 2010; De Marinis et al. 2011; National Comprehensive Cancer Network [NCCN] 2014). Agents that have been partnered with either cisplatin or carboplatin include the

taxanes (paclitaxel, docetaxel), vinorelbine, gemcitabine, and pemetrexed. Combinations of these drugs with platinum analogs are superior to single-agent therapy and have been shown to prolong survival (Azzoli et al. 2009).

The Eastern Cooperative Oncology Group (ECOG) conducted a Phase III study (Study E1594) to compare four commonly used platinum-based doublets in patients with Stage IIIB/IV NSCLC who had not previously received chemotherapy (Schiller et al. 2002). Gemcitabine + cisplatin, docetaxel + cisplatin, and paclitaxel + carboplatin were compared with paclitaxel + cisplatin. No significant clinical advantage of any one of the chemotherapy regimens over the others was observed; the median survival rates of the four treatment arms were approximately the same: approximately 8 months. The regimen of paclitaxel + carboplatin was chosen as the reference regimen for ECOG's future studies because of its more favorable toxicity profile.

Despite modest gains, the benefit conferred by platinum-based chemotherapy regimens appears to have reached a plateau in ORR (approximately 15%–25%) and median survival (7–11 months). Pemetrexed (ALIMTA® U.S. Package Insert) has recently demonstrated activity in the first-line setting where patients with non-squamous carcinoma had improved survival when treated with cisplatin and pemetrexed compared with those treated with cisplatin and gemcitabine (11.8 vs. 10.4 months; $p = 0.005$) (Scagliotti et al. 2008). In addition, cisplatin and pemetrexed was associated with better tolerability and safety and necessitated less supportive care. More recently, the addition of bevacizumab to carboplatin and paclitaxel in patients with non-squamous NSCLC resulted in an increase in response rate from 15% to 35% and an increase in median overall survival (OS) from 10 to 12 months (see Table 1).

Recently, immune checkpoint inhibitors, including PD-L1/PD-1 blocking antibodies, have emerged as a new therapeutic option for first-line treatment of metastatic NSCLC. Study KEYNOTE-024 was a Phase III, randomized, open-label study evaluating pembrolizumab given as monotherapy compared with platinum-based chemotherapy in patients who had previously untreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells. Patients with sensitizing mutation of the EGFR gene or translocation of the ALK gene were excluded from this study. In this study, median PFS was 10.3 months in the pembrolizumab group versus 6.0 months in the chemotherapy group ($HR = 0.50$; 95% CI: 0.37, 0.68; $p < 0.001$). The estimated rate of OS at 6 months was 80.2% (95% CI: 72.9%, 85.7%) in the pembrolizumab group versus 72.4% (95% CI: 64.5%, 78.9%) in the chemotherapy group; median OS was not reached in either group. OS was significantly longer in the pembrolizumab group than in the chemotherapy group ($HR = 0.60$; 95% CI: 0.41, 0.89; $p = 0.005$) (Reck et al. 2016). On the basis of this study, pembrolizumab was approved for the first-line treatment of metastatic NSCLC in patients whose tumors have high PD-L1 expression (tumor proportion score ≥50%) with no EGFR or ALK gene aberrations.

Table 1 Randomized Phase III Trials in Patients with Previously Untreated Non–Small Cell Lung Cancer

Treatment Group	ORR (%)	Median PFS (months)	Median OS (months)	OS HR 95% CI
Chemotherapy [a]				
Cisplatin and paclitaxel (n = 288)	21	3.4	7.8	
Cisplatin and gemcitabine (n = 288)	22	4.2	8.1	
Cisplatin and docetaxel (n = 289)	17	3.7	7.4	
Carboplatin and paclitaxel (n = 290)	17	3.1	8.1	
Chemotherapy + biologic [b]				
Carboplatin and paclitaxel (n = 444)	15	4.5	10.3	0.79
Carboplatin, paclitaxel, and bevacizumab (n = 434)	35	6.2	12.3	0.67–0.92
Chemotherapy [c]				
Cisplatin and pemetrexed, overall (n = 839)	31	4.8	10.3	0.94
Cisplatin and gemcitabine, overall (n = 830)	28	5.1	10.3	0.84–1.05
Cisplatin and pemetrexed, non-squamous	NR	5.3	11.8	0.81
Cisplatin and gemcitabine, non-squamous	NR	4.7	10.4	0.70–0.94
Cisplatin and pemetrexed, squamous	NR	4.4	9.4	1.23
Cisplatin and gemcitabine, squamous	NR	5.5	10.8	1.00–1.51
Chemotherapy [d]				
Carboplatin and nab-paclitaxel, overall (n = 521)	33	6.3	12.1	0.922
Carboplatin and paclitaxel, overall (n = 531)	25	5.8	11.2	0.797–1.066
Carboplatin and nab-paclitaxel, non-squamous (n = 221)	26	6.9	13.1	0.950
Carboplatin and paclitaxel, non-squamous (n = 292)	25	6.5	13.0	NR
Carboplatin and nab-paclitaxel, squamous (n = 300)	41	5.6	10.7	0.890
Carboplatin and paclitaxel, squamous (n = 229)	24	5.7	9.5	0.719–1.101

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37/Protocol GO29436, Version 7

Table 1 Randomized Phase III Trials in Patients with Previously Untreated Non–Small Cell Lung Cancer (cont.)

Treatment Group	ORR (%)	Median PFS (months)	Median OS (months)	OS HR 95% CI
Chemotherapy + biologic [e]				
Cisplatin and vinorelbine (n = 568)	29	4.8	10.1	0.871 0.762–0.996
Cisplatin, vinorelbine, and cetuximab (n = 557)	36	4.8	11.3	
Immunotherapy [f]				
Pembrolizumab, PD-L1 positive (≥ 50%) (n = 154)	45	10.3	Not reached	0.60
Platinum-based chemotherapies, PD-L1 positive (≥ 50%) (n = 151)	28	6.0	Not reached	0.41–0.89

HR = hazard ratio; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

[a] Schiller et al. 2002.
[b] Sandler et al. 2006.
[c] Scagliotti et al. 2008.
[d] Socinski et al. 2012.
[e] Pirker et al. 2009.
[f] Reck et al. 2016.

1.1.3 AVASTIN® and Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is the most important pro-angiogenic factor and a key regulator of physiological angiogenesis. It is also implicated in pathological angiogenesis such as that associated with tumor growth. Increased levels of VEGF have been found in most tumors examined to date, including tumors of the lung where, in addition, overexpression is associated with a poorer prognosis (Giatromanolaki 2001; Brattstrom et al. 2004).

AVASTIN® (bevacizumab) is a recombinant humanized monoclonal antibody to VEGF that recognizes all isoforms of VEGF. It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor environment. Additional anti-tumor activity may be on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells (Jain 2001).

Bevacizumab has been tested in Phase II and III studies in a variety of solid tumors in combination with chemotherapy. Bevacizumab is registered in over 40 countries worldwide for the first-line treatment of metastatic colorectal cancer (CRC) in combination with chemotherapy, as second-line CRC treatment, and first-line treatment of advanced NSCLC, metastatic breast cancer, advanced renal cell carcinoma (RCC), ovarian cancer, and glioblastoma (Reck and Crino 2009).

1.1.3.1 Clinical Studies of Bevacizumab and Platinum-Based Treatment in NSCLC

Two Phase III studies have demonstrated the benefit of bevacizumab in combination with platinum-based chemotherapy as first-line treatment of patients with unresectable, advanced, metastatic or recurrent non-squamous NSCLC.

Efficacy

The first study, conducted by the ECOG (Study E4599) was an open-label, randomized, Phase III study comparing the regimen of 15 mg/kg bevacizumab every 3 weeks (Q3W) in combination with carboplatin and paclitaxel versus carboplatin and paclitaxel alone as first-line treatment of patients with advanced non-squamous NSCLC. The Phase III study was based on a randomized Phase II study in patients with recurrent or advanced NSCLC that evaluated carboplatin and paclitaxel (up to six cycles) with or without bevacizumab (7.5 or 15 mg/kg) and found that the combination of bevacizumab 15 mg/kg with carboplatin/paclitaxel for up to six cycles followed by maintenance bevacizumab until disease progression resulted in increased response rates (31.5% vs. 18.8%) and prolonged time to progression (TTP) (7.4 vs. 4.2 months; $p = 0.023$) compared with chemotherapy alone (Johnson et al. 2004). There was also a non-significant improvement in OS (17.7 vs. 14.9 months) (Johnson et al. 2004). A higher incidence of bleeding was noted in the bevacizumab-treated patients. Severe pulmonary hemorrhage, which was observed in 6 patients (9.1%) and led to 4 fatalities, was more common in patients with squamous cell histology, tumor necrosis, and

cavitation, and central tumors (Johnson et al. 2004). On the basis of the results of this Phase II study, patients with squamous cell histology were excluded from this and other studies utilizing bevacizumab in NSCLC. In Study E4599, patients who received six cycles of bevacizumab plus chemotherapy without disease progression continued on single-agent bevacizumab until progression. A total of 878 patients were enrolled. Median OS was 12.3 months versus 10.3 months (HR = 0.79; $p < 0.003$); PFS was 6.2 months versus 4.5 months (HR = 0.66; $p < 0.001$), and the response rate was 35% (133 of 381) versus 15% (59 of 392) ($p < 0.001$) for patients treated with bevacizumab versus chemotherapy alone (Sandler et al. 2006).

The second study (BO17704 or AVAiL) was a randomized, double-blind, multicenter, two-stage, Phase III study of bevacizumab in combination with cisplatin and gemcitabine versus placebo, cisplatin, and gemcitabine as first-line treatment in patients with advanced or recurrent non-squamous NSCLC. A total of 1043 patients were randomized. Bevacizumab-based therapy until disease progression reduced the risk of disease progression. Bevacizumab at a dose level of 7.5 mg/kg resulted in an HR for PFS of 0.75 (median PFS, 6.7 vs. 6.1 months; $p = 0.003$), and bevacizumab at a dose level of 15 mg/kg resulted in an HR of 0.82 (median 6.5 months vs. 6.1 months, $p = 0.03$). These results were maintained with a longer follow-up. OS was a secondary endpoint, and the PFS benefit did not translate into a significant OS benefit. Nevertheless, median OS in all treatment arms of the study exceeded 13 months (Reck et al. 2009; Reck et al. 2010).

Safety

In the initial Phase II and III clinical studies, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events (TEs), and hemorrhage. Additional completed Phase II and III studies of bevacizumab and spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in Phase III studies include congestive heart failure (primarily in metastatic breast cancer), gastrointestinal perforations, wound-healing complications, and arterial TEs. Reversible posterior leukoencephalopathy syndrome and fistula have also been reported infrequently. Further details on the safety profile of bevacizumab are available in the Bevacizumab Investigator's Brochure.

In summary, platinum-based regimens remain the standard first-line option for most patients with locally advanced and metastatic NSCLC not harboring an activating *EGFR* mutation or *ALK* gene rearrangement. In particular, for newly diagnosed advanced-stage non-squamous NSCLC, the current standard-of-care is a platinum doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. However, these regimens are associated with substantial toxicities (such as febrile neutropenia, myelosuppression, nausea, alopecia, nephropathy, and neuropathy) and are generally poorly tolerated by elderly and poor performance status

patients. Therefore, novel therapies that deliver an improved therapeutic index are urgently needed for non-squamous NSCLC.

1.1.4 Targeted Therapy for NSCLC

Genotype-directed therapy has the potential to dramatically improve the balance of benefit and toxicity for selected patients with NSCLC (mainly non-squamous histology) characterized by alterations of driver oncogenes, including sensitizing *EGFR* mutations and *ALK* rearrangement. Randomized Phase III studies of gefitinib (IPASS), erlotinib (EURTAC), and afatinib (LUX-LUNG 3) showed significant improvement of PFS and objective response rate (ORR) compared with platinum doublet chemotherapy (Fukuoka et al. 2011; Rosell et al. 2012; Sequist et al. 2013). Similarly, the ALK inhibitors crizotinib and ceritinib have demonstrated efficacy in patients with NSCLC positive for *ALK* rearrangement as defined by fluorescence in situ hybridization (Crino et al. 2011; Camidge et al. 2012; Shaw et al. 2012; Shaw and Engelman 2014; XALKORI® U.S. Package Insert; ZYKADIA™ U.S. Package Insert).

Despite progress with new targeted treatments and new chemotherapy combinations, survival rates for advanced disease remain low and acquired resistance to targeted agents is a major clinical problem. Therefore, alternative treatment options that yield durable responses and enhance OS remain an important focus of research. Against this background, immunotherapeutic agents, such as cancer vaccines and 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)

Atezolizumab (MPDL3280A) is a humanized immunoglobulin (Ig) G1 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 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 locally advanced or metastatic urothelial carcinoma 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 intravenous (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 (see the Atezolizumab Investigator's Brochure for study descriptions). The single-agent safety and efficacy data available to date include data from the following 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 Q3Wto 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
- Study GO28915 (OAK): A randomized, Phase III, open-label study assessing the efficacy and safety 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

- Study GP28328: A Phase Ib study assessing the safety and pharmacology of atezolizumab in combination with bevacizumab and/or chemotherapy in patients with advanced solid tumors.

1.3.2 Clinical Safety

1.3.2.1 Single-Agent Clinical Safety in Patients with NSCLC in Study PCD4989g

Study PCD4989g, in which atezolizumab is being used as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies, provides the majority of data (with 558 safety-evaluable patients as of the data extraction 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. The most common cancer types for these patients include NSCLC, urothelial bladder cancer (UBC), melanoma, and renal cell carcinoma (RCC). Safety data for NSCLC are also derived from Studies GO28625 (FIR), GO28915 (OAK), and Study GO28753 (POPLAR).

Adverse Events

Of the 558 patients, 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

Adverse Event	All Grades n (%)	All Grades Related n (%)	Grade 3–4 n (%)	Grade 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.

Grade 3 or 4 adverse events (on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4 [NCI CTCAE v4.0]) were reported in 239 patients (42.8%), of which 66 (11.8%) were considered related. Grade 3 or 4 adverse events considered related by the investigator included dyspnea, pneumonitis, increased ALT, increased AST, increased gamma-glutamyl transferase (GGT), lymphocyte count decreased, cardiac tamponade, asthenia, autoimmune hepatitis, pneumonia, influenza, and hypoxia.

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

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 that were observed in patients treated with atezolizumab. Guidelines for the management of immune-mediated adverse events are described in Section 5.1.7.

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

As of the 1 December 2015 data cutoff date, the Phase II POPLAR study (GO28753) included data from 277 safety-evaluable patients treated with either atezolizumab as a fixed dose of 1200 mg IV every three weeks (Q3W) (n = 142) or docetaxel 75 mg/m^2 IV Q3W (n = 135). The frequency of patients in the POPLAR study who reported an adverse event regardless of attribution was 95.8% for the atezolizumab arm and 96.3% for the docetaxel arm. A higher frequency of Grade 3 or 4 adverse events was observed among patients in the docetaxel arm (52.6% vs. 40.8%), explained primarily by the difference in adverse events due to bone marrow suppression. The frequency of patients who discontinued treatment because of adverse events was higher in the docetaxel arm than in the atezolizumab arm (22.2% vs. 8.5%). Adverse events reported in at least 10% of patients in either treatment arm are listed in Table 3.

Table 3 Study GO28753 (POPLAR): Adverse Events Reported in at Least 10% of Patients

Adverse Event	No. of Patients (%)	
	Atezolizumab (n = 142)	Docetaxel (n = 135)
Fatigue	55 (38.7)	54 (40.0)
Decreased appetite	49 (34.5)	28 (20.7)
Nausea	32 (22.5)	45 (33.3)
Cough	40 (28.2)	33 (24.4)
Dyspnea	39 (27.5)	27 (20.0)
Constipation	31 (21.8)	32 (23.7)
Diarrhea	25 (17.6)	38 (28.1)
Alopecia	3 (2.1)	52 (38.5)
Anemia	25 (17.6)	27 (20.0)
Pyrexia	24 (16.9)	16 (11.9)
Vomiting	20 (14.1)	18 (13.3)
Asthenia	15 (10.6)	22 (16.3)
Arthralgia	22 (15.5)	12 (8.9)
Insomnia	22 (15.5)	11 (8.1)
Rash	16 (11.3)	16 (11.9)
Back pain	16 (11.3)	11 (8.1)
Myalgia	9 (6.3)	18 (13.3)
Musculoskeletal pain	19 (13.4)	7 (5.2)
Weight decreased	16 (11.3)	9 (6.7)
Hemoptysis	15 (10.6)	8 (5.9)
Pneumonia	17 (12.0)	4 (3.0)
Neuropathy peripheral	3 (2.1)	16 (11.9)
Neutropenia	2 (1.4)	17 (12.6)

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

1.3.2.3 Single-Agent Clinical Safety in Patients with NSCLC in Study GO28915 (OAK)

As of the 7 July 2016 data cutoff date for the primary analysis, the Phase III Study GO28915 (OAK) included data from 609 patients treated with atezolizumab as a fixed dose of 1200 mg IV Q3W and 578 patients treated with docetaxel 75 mg/m^2 IV Q3W. The frequency of patients who reported any adverse event regardless of attribution was 94.1% for the atezolizumab arm and 96.0% for the docetaxel arm. A higher frequency of Grade 3 or 4 adverse events was observed among patients in the docetaxel arm

(53.6% vs. 37.3%). The frequency of patients who discontinued treatment because of adverse events was higher in the docetaxel arm than in the atezolizumab arm (18.7% vs. 7.6%). Table 4 lists adverse events with an arm difference frequency of at least 5 percentage points.

Table 4 Adverse Events in Study GO28915 (OAK) with a Between-Arm Difference in frequency of at least 5 Percentage Points

Adverse Event	Atezolizumab	Docetaxel
Fatigue	26.8%	35.5%
Alopecia	0.5%	34.9%
Diarrhea	15.4%	24.4%
Anemia	11.5%	23.5%
Nausea	17.7%	22.7%
Myalgia	6.4%	15.7%
Neutropenia	1.6%	15.6%
Peripheral edema	8.9%	14.2%
Peripheral neuropathy	3.9%	11.2%
Stomatitis	3.1%	10.9%
Febrile neutropenia	0.2%	10.7%
Dysgeusia	3%	10%
Musculoskeletal pain	10.5%	4.3%
Pruritus	8.2%	3.1%

Source: Rittmeyer et al. 2017.

1.3.2.4 Clinical Safety in Combination with Bevacizumab or Platinum-Based Doublet Chemotherapy

Study GP28328 is a Phase Ib study of atezolizumab in combination with bevacizumab or cytotoxic chemotherapy in patients with multiple tumor types including NSCLC, triple negative breast cancer, and colorectal cancer. As of 10 February 2015, 144 patients had been enrolled in this study: 39 in Arm A (atezolizumab + bevacizumab), 36 in Arm B (atezolizumab + bevacizumab and FOLFOX), 14 in Arm C (atezolizumab + carboplatin and paclitaxel), 24 in Arm D (atezolizumab + carboplatin and pemetrexed), 20 in Arm E (atezolizumab + carboplatin and nab-paclitaxel), and 11 in Arm F (atezolizumab + nab-paclitaxel). The treatment combinations have been generally well tolerated. No DLTs have been reported during the dose-escalation stage in any study arm. Patients are being enrolled in safety and biopsy expansion cohorts in Arms A and B as well as in additional arms testing atezolizumab in combination with commonly used NSCLC chemotherapy doublets.

A total of 141 of 144 patients (97.9%) reported at least one adverse event while receiving study drug. The majority of these events were Grade 2 or 3 in severity. The five most commonly reported adverse events across the study arms (≥10% of patients) included fatigue, nausea, diarrhea, decreased appetite, and pyrexia. 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 5 Study GP28328: All Reported Adverse Events

Parameter	Arm A (n=39) No. (%)	Arm B (n=36) No. (%)	Arm C (n=14) No. (%)	Arm D (n=24) No. (%)	Arm E (n=20) No. (%)	Arm F (n=12) No. (%)	All Patients (n=145) No. (%)
Any AEs	39 (100)	36 (100)	14 (100)	24 (100)	19 (95.0)	10 (83.3)	142 (97.9)
Related AEs	29 (74.4)	28 (77.8)	12 (85.7)	19 (79.2)	19 (95.0)	6 (50.0)	113 (77.9)
Grade 3–5 AEs	20 (51.3)	29 (80.6)	12 (85.7)	17 (70.8)	18 (90.0)	6 (50.0)	102 (70.3)
Related Grade 3–5 AEs	1 (2.6)	7 (19.4)	4 (28.6)	4 (16.7)	11 (55.0)	4 (33.3)	31 (21.4)
Serious AEs	14 (35.9)	15 (41.7)	5 (35.7)	10 (41.7)	8 (40.0)	3 (25.0)	55 (37.9)
Related serious AEs	0 (0)	1 (2.8)	1 (7.1)	2 (8.3)	2 (10.0)	2 (16.7)	8 (5.5)
AEs leading to discontinuation	1 (2.6)	4 (11.1)	0 (0)	1 (4.2)	1 (5.0)	0 (0)	8 (5.6)
AEs leading to death (Grade 5)	0 (0)	2 (2.8)	1 (7.1)	2 (8.3)	2 (10.0)	1 (8.3)	7 (4.8)
Related AEs leading to death (Grade 5)	0 (0)	0 (0)	0 (0)	1 (4.2)	0 (0)	0 (0)	1 (0.7)
Immune-mediated AEs	12 (30.8)	28 (77.8)	8 (57.1)	11 (45.8)	11 (55.0)	2 (16.7)	72 (49.7)

AE = adverse event.

All 39 patients who were enrolled in Arm A reported one or more adverse event. The five most frequently reported events were consistent with the overall population and included fatigue, nausea, diarrhea, decreased appetite, and pyrexia. There were 36 patients enrolled in Arm B, and 97% of patients reported at least one adverse event. The most frequently reported adverse events (>20% of patients) included fatigue, pyrexia, peripheral neuropathy, neutropenia, anemia, diarrhea, decreased appetite, temperature intolerance, constipation, vomiting, and nausea.

All patients who were enrolled in Arms C and D experienced an adverse event; 95% of patients who were enrolled in Arm E experienced an adverse event, and 83.3 % of patients enrolled in Arm F experienced an adverse event. The adverse events commonly reported in 2 or more patients in Arms C, D, and E included anemia, decreased appetite, hypomagnesemia, nausea, neutropenia, constipation, vomiting,

fatigue, rash, cough, and diarrhea. Adverse events commonly reported in 2 or more patients in Arm F included dermatitis, upper respiratory infection, alopecia, peripheral sensory neuropathy, fever, constipation, neutrophil count decreased, anemia, diarrhea, headache, nausea, and fatigue.

1.3.3 Clinical Activity

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

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

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

As of the clinical data cutoff of 2 December 2014, the efficacy evaluable population included 88 patients with locally advanced or metastatic NSCLC. The median age was 60.5 years (range 24–84 years) and represented a heavily pre-treated patient population: 97% of the patients had received ≥2 prior systemic therapies, and 77.3% had received ≥4 prior systemic therapies.

Overall, responses were observed in 20 of 88 (22.7%) patients with NSCLC and included responses in patients with squamous and non-squamous NSCLC (4 in 21 patients and 16 in 67 patients, respectively). A total of 8 of the 20 responding patients have continued to respond at the time of the clinical data cutoff.

Table 6 displays the confirmed ORR, duration of confirmed response (DOR), and 6-month PFS rates by PD-L1 expression for patients with NSCLC. These results are based on investigator-assessed RECIST v1.1. Analyses of tumor-infiltrating immune cells (ICs) and tumor cells (TCs) for PD-L1 expression on baseline tumor tissue from NSCLC patients have been performed. Higher ORRs were associated with higher PD-L1 expression (TC3 or IC3).

Refer to the Atezolizumab Investigator's Brochure for updated details on clinical activity in patients with NSCLC treated to date.

Table 6 Patients with NSCLC in Study PCD4989g: Investigator-Assessed Confirmed Objective Response Rate by Tumor PD-L1 Expression, Duration of Response, and 6-Month Progression-Free Survival Rates (per RECIST, Version 1.1)

PD-L1 IHC Expression Category	ORR by RECIST, Version 1.1 n = 88	SD (n/N)	PD (n/N)	DOR (range in months)	6-month PFS % (95% CI)
TC3 or IC3	50.0% (11 of 22) (95%CI: 28.22%, 71.78%)	13.6% (3/22)	31.8% (7/22)	7.16–25.26	50.0 (29.1, 70.9)
TC3 or IC2/3	37.5% (15 of 40) (95% CI: 22.73%, 54.2%)	12.5% (5/40)	45.0% (18/40)	7.16–26.74+	44.9 (29.4, 60.3)
TC2/3 or IC2/3	33.3% (16 of 48) (95%CI: 20.40%, 48.41%)	22.9% (11/48)	37.5% (18/48)	7.16–26.74+	41.6 (27.6, 55.5)
TC0/1/2 and IC0/1/2	15.5% (9 of 58) (95%CI: 7.35%, 27.42%)	37.9% (22/58)	37.9% (22/58)	7.16–26.74+	41.1 (28.4, 53.8)
TC0/1/2 and IC0/1	12.5% (5 of 40) (95%CI: 4.19%, 26.8%)	37.5% (15/40)	40.0% (16/40)	9.92–24.74	42.3 (27, 57.7)
TC0/1 and IC0/1	12.5% (4 of 32) (95% CI: 3.51%, 28.99%)	43.8% (14/32)	34.4% (11/32)	9.92–24.74	46.7 (29.3, 64.0)

DOR = duration of response; IC = tumor-infiltrating immune cell; NSCLC = non–small cell lung cancer; ORR = objective response rate; PFS = progression-free survival; PR = partial response; SD = stable disease; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors; TC = tumor cell.

Notes: This table is based on a data cutoff of 02 Dec 2014 of NSCLC patients. ORR includes confirmed responses. "+" denotes a censored value.

1.3.3.2 Single-Agent Clinical Activity in Patients with NSCLC in Study GO28753 (POPLAR)

The primary OS analysis in Study GO28753 (POPLAR) was conducted when 173 deaths had occurred (clinical cutoff, 8 May 2015). Key efficacy results for the intent-to-treat (ITT) population are shown in Table 7. 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 months) for atezolizumab versus 9.7 months (95% CI: 8.6, 12.0 months) 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 months) for docetaxel (see Table 7) (Fehrenbacher et al. 2016).

Table 7 Efficacy Results in Study GO28753 (POPLAR): Intent-to-Treat Population

Efficacy Endpoint	Atezolizumab (n = 144)	Docetaxel (n = 143)
Overall survival		
No. of deaths (%)	78 (54.2)	95 (66.4)
Median (months) 95% CI	12.6 9.7, 16.4	9.7 8.6, 12.0
Stratified hazard ratio 95% CI	0.73 0.53, 0.99	
Progression-free survival		
No. of events (%)	124 (86.1)	121 (84.6)
Median (months) 95% CI	2.7 2.0, 4.1	3.0 2.8, 4.1
Stratified hazard ratio 95% CI	0.94 0.72, 1.23	
Objective response rate (confirmed)	14.6%	14.7
Duration of response		
Median (months) 95% CI	14.3 11.6, NE	7.2 5.6, 12.5

NE = not estimable.

At the time of an updated analysis representing an additional 7 months of follow-up (1 December 2015 data cutoff date), 200 of 287 randomized patients (70%) had died. Improvement in OS benefit was observed for atezolizumab compared with docetaxel in the ITT population (stratified HR = 0.69; 95% CI: 0.52, 0.92) (see Table 8). The median OS in the ITT population was 12.6 months (95% CI: 9.7, 16.0 months) in the atezolizumab arm and 9.7 months (95% CI: 8.6, 12.0 months) in the docetaxel arm. PFS was similar between groups (2.7 months with atezolizumab vs. 3.4 months with docetaxel) (Smith et al. 2016).

The updated OS and PFS analyses for the ITT population and by PD-L1 expression levels are shown in Table 8. Improvement in OS numerically increased with increasing PD-L1 expression, whereas patients with the lowest PD-L1 expression levels experienced OS similar to that in the docetaxel group (see Table 8).

Table 8 Study GO28753 (POPLAR) Efficacy Results by Combination PD-L1 Diagnostic Subgroups with Complementary Comparison Subgroupings: Intent-to-Treat Population

Population	HR (95% CI)		Total No. of Patients (Atezolizumab/ Docetaxel)
	OS	PFS	
ITT	0.69 (0.52, 0.92)	0.92 (0.71, 1.20)	287 (144/143)
TC3 or IC3	0.45 (0.22, 1.95)	0.60 (0.32, 1.13)	47 (24/23)
TC2/3 or IC2/3	0.50 (0.31, 0.80)	0.71 (0.47, 1.08)	105 (50/55)
TC1/2/3 or IC1/2/3	0.59 (0.41, 0.83)	0.86 (0.63, 1.16)	195 (93/102)
TC0 and IC0	0.88 (0.55, 1.42)	1.06 (0.68, 1.67)	92 (51/41)

HR = hazard ratio; IC = tumor-infiltrating immune cell; ITT = intent to treat; OS = overall survival; PFS = progression-free survival; TC = tumor cell.

Notes: The data cutoff date is 1 December 2015.

The HRs are stratified for the ITT population and unstratified for the PD-L1 expression subgroups.

In summary, the data from Study GO28753 (POPLAR) show that atezolizumab provides survival benefit compared with docetaxel in previously treated patients with NSCLC.

1.3.3.3 Single-Agent Clinical Activity in Patients with NSCLC in Study GO28915 (OAK)

The co-primary endpoints of the Study GO28915 (OAK) were OS in all randomized patients (ITT population) and OS in a PD-L1–selected subgroup in the primary analysis population (TC1/2/3 or IC1/2/3).

At the time of the primary analysis (7 July 2016 data cutoff date), which included data from the first 850 randomized patients (425 in the atezolizumab arm and 425 in the docetaxel arm), the median duration of survival follow-up was 21 months and 569 patients had died. In the ITT population, OS was significantly improved with atezolizumab compared with docetaxel (median OS, 13.8 vs. 9.6 months; HR = 0.73; 95% CI: 0.62, 0.87; p = 0.0003). For the TC1/2/3 or IC1/2/3 subgroup, OS was also significantly improved with atezolizumab compared with docetaxel (median OS, 15.7 vs. 10.3 months; HR = 0.74; 95% CI: 0.58, 0.93; p = 0.0102).

PFS was similar between the atezolizumab and docetaxel arms (median PFS, 2.8 vs. 4 months; HR = 0.95; 95% CI: 0.82, 1.10). Fifty-eight patients (14%) in the atezolizumab arm and 57 patients (13%) in the docetaxel arm achieved a confirmed objective response per RECIST v1.1. Objective responses with atezolizumab were durable, with a median duration of 16.3 months (95% CI: 10.0 months, not estimable) in the atezolizumab arm compared with 6.2 months (95% CI: 4.9, 7.6 months) in the docetaxel arm (Rittmeyer et al. 2017).

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

As of the 10 February 2015 data cutoff, 58 patients with NSCLC were enrolled in Arms C, D, or E of the Phase Ib Study GP28328. Patients who had received their first dose of atezolizumab by 10 November 2014 were evaluable for efficacy (n = 41). Patients who were enrolled in Arms C, D, and E received 15 mg/kg atezolizumab administered Q3W in combination with carboplatin + paclitaxel, carboplatin + pemetrexed, and carboplatin + nab-paclitaxel, respectively. All patients had histologically or cytologically documented Stage IIIB, Stage IV, or recurrent NSCLC and had not received prior chemotherapy for advanced disease. The median age was 65 years and 79% of patients had non-squamous histology. The overall confirmed ORR per RECIST v1.1 in all three arms combined was 63% (26 of 41 patients).

The ORR was 50% (95% CI: 16%, 84%) in Arm C (4 partial responses [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 (5 PRs and 4 complete responses [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), 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 (CL) and the mean volume of distribution at steady state (V_{ss}) had a range of 3.11 to 4.14 mL/kg and 48.1 to 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 to 20 mg/kg. Patients who were 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 or infusion reactions 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} 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 down-regulation 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 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.

PD-L1 expression is prevalent in many human tumors, and elevated PD-L1 expression is associated with a poor prognosis in patients with NSCLC (Mu et al. 2011).

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies and who have failed standard-of-care therapies. At the time of Study GO29436 initiation, Study PCD4989g, a Phase Ia dose-escalation and expansion study of patients treated with atezolizumab as a single agent, had the following clinical activity: 345 evaluable patients were dosed by 21 October 2013 (data cutoff date as of 21 April 2014) with a minimum of 6 months of follow-up; 62 patients experienced objective responses per RECIST v1.1 with an ORR of 18.0% (95% CI: 14.1%, 22.3%). Objective responses were observed across a broad range of malignancies, including NSCLC, RCC, melanoma, and UBC. In Studies GO28753 (POPLAR) and GO28915 (OAK), there was significant improvement in OS with atezolizumab compared with docetaxel in patients with previously treated advanced NSCLC

1.4.1 Rationale for Testing Atezolizumab in Combination with Bevacizumab

Bevacizumab is a recombinant, humanized therapeutic antibody directed against VEGF. In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. For example, experiments with activated endothelial cells suggested that in the tumor microenvironment, VEGF may reduce lymphocyte adhesion to vessel walls, thus contributing to decreased immune cell recruitment to the tumor site (Bouzin and Feron 2007). Some immunosuppressive activities of VEGF can be reversed by inhibition of VEGF signaling. Thus, mice exposed to pathophysiologic levels of VEGF exhibited impaired dendritic cell function, which could be restored by blockade of VEGFR2 (Huang et al. 2007). In a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). Synergistic effects have also been observed in a clinical study combining an immunomodulatory antibody (anti–CTLA-4; ipilimumab) and bevacizumab: Hodi et al. (2010) described increased T-cell trafficking in post-treatment biopsies, as well as marked increases in central memory cells in peripheral blood in the majority of patients. Therefore, combined treatment with PD-L1 and bevacizumab may augment the anti-tumor immune response, resulting in improved and more durable clinical benefit.

1.4.2 Rationale for Testing Atezolizumab in Combination with Carboplatin/Paclitaxel

Platinum-based regimens remain the standard first-line option for patients with locally advanced or metastatic NSCLC not harboring *EGFR* mutations or *ALK* gene rearrangements. However, the survival benefit conferred by cytotoxic chemotherapy has reached a plateau, with overall response rates of approximately 20% and 1-year survival ranging 31%–36% (Schiller et al. 2002), leaving considerable room for improvement in outcomes. Tumor cell killing by cytotoxic chemotherapy can reasonably be expected to 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). Evaluating the safety and efficacy of these treatment combinations in patients with NSCLC will enable future tests of this hypothesis.

Nivolumab, a fully human IgG4 PD-1 antibody, was evaluated in combination with platinum-based doublet therapy in PD-1–unselected, chemotherapy-naive patients with NSCLC, and interim results were presented at American Society of Clinical Oncology (ASCO) 2014 (Antonia et al. 2014). The ORR for patients treated with gemcitabine + cisplatin, pemetrexed + cisplatin, and paclitaxel + carboplatin, in addition to 10 mg nivolumab, was 33% (n = 12), 47% (n = 15), and 47% (n = 15), respectively. The median duration of response ranged from 24 weeks with nivolumab in combination with paclitaxel + carboplatin to 45 weeks with nivolumab in combination with gemcitabine + cisplatin. The 1-year OS for patients treated with gemcitabine + cisplatin, pemetrexed + cisplatin, and paclitaxel + carboplatin in addition to 10 mg nivolumab was 50%, 87%, and 60%, respectively. Grade 3/4 treatment-related adverse events were reported in 45% of patients across all treatment arms, with the most common treatment-related Grade 3/4 adverse events being pneumonitis (7%), fatigue (5%), and acute renal failure (5%) (Antonia et al. 2014).

Although the patient numbers are limited, these data along with the preliminary efficacy and safety results from Study GP28328 offer evidence of an acceptable safety profile when combining a PD-L1/PD-1 inhibitor with platinum-based doublet chemotherapy in a non–PD-L1–selected population.

In light of these observations, Study GO29436 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 + paclitaxel with or without bevacizumab compared with carboplatin + paclitaxel + bevacizumab in patients with non-squamous NSCLC. This study will allow for the evaluation of the efficacy of atezolizumab in both the ITT population, as well as in patients with PD-L1–selected tumors (defined by expression of

PD-L1 in TCs and/or ICs). A PD-L1 immunohistochemistry (IHC) assay will be used to identify patients by their tumor PD-L1 expression (see Appendix 6).

Study GO29436 will enroll patients with Stage IV non-squamous NSCLC who are naive to chemotherapy treatment and for whom the experimental arms (atezolizumab + carboplatin + paclitaxel and atezolizumab + carboplatin + paclitaxel + bevacizumab) can represent a valuable treatment option and a reasonable benefit-risk balance. Patients whose tumors are known to harbor sensitizing *EGFR* mutations or *ALK* rearrangements must have experienced disease progression or have proven intolerance during or after treatment with an EGFR tyrosine kinase or ALK inhibitor, respectively (see specific inclusion criteria in Section 4.1.1), before they can enroll in the study.

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 treated with atezolizumab to receive treatment beyond the initial apparent radiographic progression (see Section 3.3.5 and Section 4.6) and will use modified RECIST (in addition to RECIST v1.1) to evaluate clinical benefit. 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 yet continuing to receive atezolizumab may experience further progression of NSCLC and delay treatment with subsequent therapies for which they are eligible. Investigators should make every effort to fully inform patients of this risk.

Atezolizumab has been generally well tolerated (see Section 1.3.2); adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, hypothyroidism, hepatitis/transaminitis, colitis, and myasthenia gravis, have been observed in Study PCD4989g. To date, these events have been manageable with treatment.

In summary, treatment with atezolizumab offers the potential for clinical benefit in patients with NSCLC, in addition to platinum-based chemotherapy with or without bevacizumab. Patients will be fully informed of the risk of continuing study treatment in spite of apparent radiographic progression, and investigators should make a careful assessment of the potential benefit of doing so, considering radiographic data, biopsy results, and the clinical status of the patient.

2. OBJECTIVES

The following objectives will be assessed in chemotherapy-naive patients with Stage IV non-squamous NSCLC.

2.1 EFFICACY OBJECTIVES

Unless otherwise specified, efficacy objectives will be analyzed for the following two treatment comparisons:

- Atezolizumab + carboplatin + paclitaxel + bevacizumab (Arm B) versus carboplatin + paclitaxel + bevacizumab (Arm C)
- Atezolizumab + carboplatin + paclitaxel (Arm A) versus carboplatin + paclitaxel + bevacizumab (Arm C)

The term "wild type" (WT) refers to randomized patients who do not have a sensitizing EGFR mutation or ALK translocation.

The term "tumor gene expression" (tGE) refers to randomized patients with a defined level of expression of a PD-L1 and T-effector gene signature in tumor tissue, as analyzed through use of a centrally performed RNA-based assay.

Some efficacy endpoints will be analyzed in a population of randomized patients with a defined level of PD-L1 expression on TCs and ICs, as analyzed through use of a centrally performed IHC test.

2.1.1 Co-Primary Efficacy Objectives

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

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed PFS according to RECIST v1.1 in the tGE-WT population and the ITT-WT population
- To evaluate the efficacy of atezolizumab as measured by OS in the ITT-WT population

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives for this study are the following:

- To evaluate the efficacy of atezolizumab as measured by OS in the tGE-WT population
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed PFS according to RECIST v1.1 and OS in the TC2/3 or IC2/3 WT population and the TC1/2/3 or IC1/2/3 WT population
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed PFS according to RECIST v1.1 and OS in the tGE population and the ITT population

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed ORR according to RECIST v1.1 in the tGE-WT population and the ITT-WT population
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed duration of response (DOR) according to RECIST v1.1 in the tGE-WT population and the ITT-WT population
- To evaluate the efficacy of atezolizumab as measured by an Independent Review Facility (IRF)-assessed PFS according to RECIST v1.1 in the tGE-WT population and the ITT-WT population
- To evaluate the OS rate at 1 and 2 years in each treatment arm for the tGE-WT population and the ITT-WT population
- To compare the efficacy of the two atezolizumab-containing arms, Arm A versus Arm B, as measured by investigator-assessed PFS according to RECIST v1.1 and by OS in the tGE-WT population and the ITT-WT 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, or arm/shoulder pain, using the European Organisation 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 the tGE-WT population and the ITT-WT population
- To determine the impact of atezolizumab as measured by change from baseline (i.e., improvement or deterioration based upon presenting symptomatology) in patient-reported lung cancer symptom (chest pain, dyspnea, and cough) score using the Symptoms in Lung Cancer (SILC) scale symptom severity score for the tGE-WT population and the ITT-WT population

2.2 SAFETY OBJECTIVES

The safety objectives for this study are the following:

- To evaluate the safety and tolerability of atezolizumab in each of the two treatment comparisons
- 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 OBJECTIVES

The PK objectives for this study are the following:

- To characterize the pharmacokinetics of atezolizumab when given in combination with carboplatin and paclitaxel with and without bevacizumab (Arms A and B)
- To characterize the pharmacokinetics of carboplatin when given in combination with paclitaxel with and without atezolizumab and/or bevacizumab (Arms A, B, and C)

- To characterize the pharmacokinetics of paclitaxel when given in combination with carboplatin with and without atezolizumab and/ or bevacizumab (Arms A, B, and C)
- To characterize the pharmacokinetics of bevacizumab when given in combination with carboplatin and paclitaxel with and without atezolizumab (Arms B and C)

2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are the following:

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed time to response (TTR) and time-in-response (TIR) according to RECIST v1.1
- To evaluate ORR and DOR according to RECIST v1.1 as assessed by the IRF
- To evaluate investigator-assessed ORR, PFS, and DOR, according to modified RECIST for the atezolizumab-containing treatment arms
- To evaluate PFS at 6 months and at 1 year in each treatment arm
- To evaluate the OS rate at 3 years in each treatment arm
- To assess predictive, prognostic, and pharmacodynamic 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.
- To evaluate the utility of biopsy at the time of apparent disease progression to distinguish apparent increases in tumor volume related to the immunomodulatory activity of atezolizumab (i.e., pseudoprogression/tumor-immune infiltration) from true disease progression
- To evaluate and compare patient's health status as assessed by the EuroQoL 5 Dimensions 3-Level (EQ-5D-3L) questionnaire to generate utility scores for use in economic models for reimbursement
- To determine the impact of atezolizumab as measured by change from baseline in patient-reported outcomes of health-related quality of life (HRQoL), lung cancer–related symptoms, and functioning as assessed by the EORTC QLQ-C30 and QLQ-LC13

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a randomized, Phase III, multicenter, open-label study (IMpower150) designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin + paclitaxel with or without bevacizumab compared with treatment with carboplatin + paclitaxel + bevacizumab in approximately 1200 chemotherapy-naive patients with Stage IV non-squamous NSCLC. Figure 1 illustrates the study design. The schedules of assessments are provided in Appendix 1 and Appendix 2.

Tumor specimens will be prospectively tested for PD-L1 expression by a central laboratory. Eligible patients will be stratified by sex (male vs. female), presence of liver metastases at baseline (yes vs. no), and by PD-L1 tumor expression by IHC (TC3 and

any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1). Patients will be randomized in a 1:1:1 ratio to receive one of the following treatment regimens as shown in Table 9.

Table 9 Study GO29436 Treatment Arms

Treatment Arm	Induction (Four or Six 21-Day Cycles)	Maintenance (21-Day Cycles)
A	Atezolizumab + carboplatin + paclitaxel	Atezolizumab
B	Atezolizumab + carboplatin + paclitaxel + bevacizumab	Atezolizumab + bevacizumab
C	Carboplatin + paclitaxel + bevacizumab	Bevacizumab

The number of cycles of induction treatment (four or six) will be at the discretion of the investigator and will be determined and documented prior to randomization. Induction treatment will be administered on a 21-day cycle until the following occur (whichever occurs first): 1) administration of four or six cycles or 2) disease progression (Arm C) or loss of clinical benefit (Arms A and B) is documented.

Following the induction phase, patients will continue treatment with maintenance therapy as per Table 9. Patients who are randomized to Arms B and C will continue treatment with bevacizumab until progressive disease, unacceptable toxicity, or death. Patients who are randomized to Arms A or B may continue treatment with atezolizumab beyond radiographic progression by RECIST v1.1, provided they are experiencing clinical benefit as assessed by the investigator (i.e., in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results [if available], and clinical status).

Treatment with chemotherapy (Arms A, B, and C) and bevacizumab (Arms B and C) must be discontinued in all patients who exhibit evidence of disease progression according to RECIST v1.1.

Patients will undergo tumor assessments at baseline and every 6 weeks for the first 48 weeks following Cycle 1, Day 1, regardless of dose delays. After 48 weeks, tumor assessment will be required every 9 weeks. Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. Patients who discontinue treatment for reasons other than radiographic disease progression according to RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab

after radiographic disease progression according to 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.

A secondary endpoint of this study is IRF-assessed PFS according to RECIST v1.1. An IRF will therefore conduct an independent review of the responses of all patients, including a blinded review of CT scans. All primary imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints. These reviews will be performed prior to the final efficacy analyses.

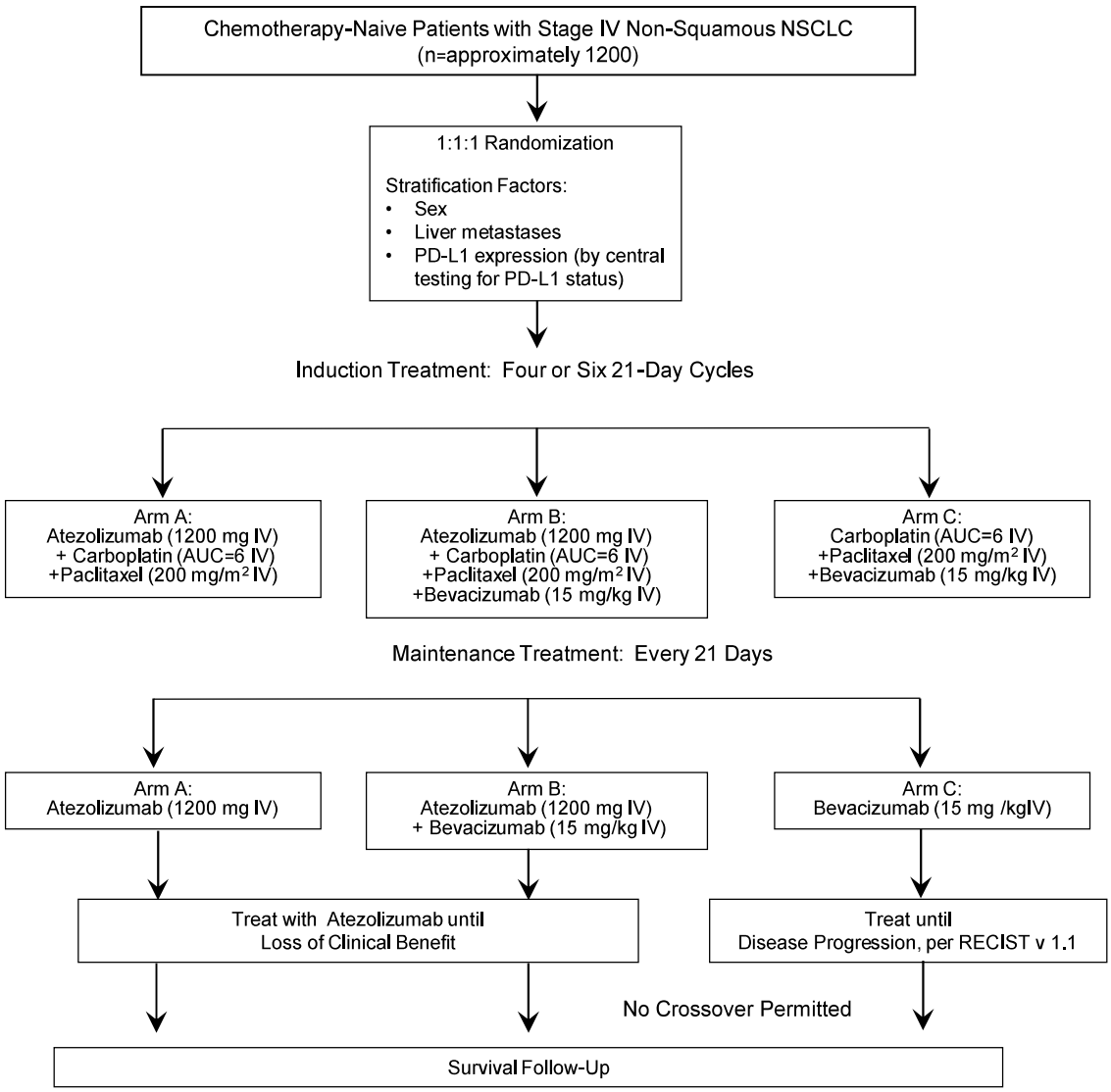
For Treatment Arms A and B Only

At any point during treatment, patients receiving atezolizumab who show evidence of clinical benefit will be permitted to continue atezolizumab after RECIST v1.1 for progressive disease are met if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values, e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease
- 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 atezolizumab at the time of initial progression

Patients in all treatment arms will undergo a mandatory tumor biopsy sample collection, unless not clinically feasible as assessed and documented by investigators, at the time of radiographic disease progression. These data will be used to explore whether radiographic findings are consistent with the presence of tumor. Additionally, these data will be analyzed to evaluate the association between changes in tumor tissue and clinical outcome and to understand further 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 in Arms A and B who are unable to undergo biopsy sample collection but who otherwise meet the criteria listed above may continue to receive atezolizumab.

Figure 1 Study Schema



AUC = area under the concentration–time curve; IV = intravenous; NSCLC = non–small cell lung cancer; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.
Patients of Asian race/ethnicity receive paclitaxel at a dose of 175 mg/m^2

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 on a periodic basis, approximately every 6 months from the point of first patient in (FPI). In addition, the iDMC will review safety data once 12 patients have been enrolled into each treatment arm and have received treatment for two cycles. The safety data will include demographic data, adverse events, serious adverse events, and relevant laboratory data.

The Sponsor will remain blinded to the efficacy results until the final PFS analysis for the primary comparisons (i.e., Arm A vs. Arm C and Arm B vs. Arm C). 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 or efficacy 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

The end of study is defined as the date of the last follow-up visit of the last patient or when all patients have been enrolled into an extension study. The Sponsor may decide to terminate the study at any time. If the Sponsor decides to end the study, patients who are still receiving study treatment or are in survival follow-up may be offered enrollment in an extension study or a non-interventional study.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Testing Atezolizumab in Patients with PD-L1–Unselected NSCLC

Despite recent improvements in treatment, the prognosis for patients with advanced NSCLC remains dismal, with a median OS of approximately 12.3 months (Sandler et al. 2006). Patients who receive second-line treatment for their disease have an even more limited prognosis, with a median survival duration of approximately 8–9 months (Stinchcombe et al. 2008). Approved therapies are associated with significant toxicities (e.g., neuropathy, febrile neutropenia, myelosuppression, and alopecia) that negatively impact quality of life. Therefore, there is a continuing need for more efficacious, better-tolerated treatments.

Inhibition of PD-L1/PD-1 signaling has been shown to produce durable responses in some patients, and expression of PD-L1 by TCs and/or ICs in several tumor types (including NSCLC) correlates with response to therapy (Topalian et al. 2012) (Fehrenbacher et al. 2016).

Atezolizumab monotherapy has demonstrated clinical efficacy and is generally well-tolerated in patients with squamous or non-squamous NSCLC (Besse et al. 2015; Horn et al. 2015; Spigel et al. 2015; Fehrenbacher et al. 2016). In the second- and third-line setting, the POPLAR study, the first randomized Phase II study of atezolizumab in advanced NSCLC, showed significant improvement in OS with atezolizumab (12.6 vs.

9.7 months; HR = 0.73; 95% CI: 0.53, 0.99, p = 0.04) versus docetaxel (Fehrenbacher et al. 2016). In the Phase III Study GO28915 (OAK) which investigated the efficacy and safety of atezolizumab compared with docetaxel in patients with previously treated locally advanced or metastatic NSCLC, OS was significantly prolonged with atezolizumab (median OS 13.8 months vs 9.6 months, HR = 0.73; 95% CI 0.62,0.87, p=0.0003). In patients with squamous and non-squamous disease, OS was 8.9 versus 7.7 months (HR = 0.73; 95% CI: 0.54, 0.98), and 15.6 versus 11.2 months (HR = 0.73; 95% CI: 0.60, 0.89), respectively, in the atezolizumab arm compared with the docetaxel arm (Rittmeyer et al. 2017).

On the basis of promising efficacy of atezolizumab as a single agent (Study GO28753 [POPLAR]; Study PCD4989g) and in combination with platinum-doublet therapy (Study GP28328) and the safety findings from Study GP28328 indicating no additive toxicity of atezolizumab in combination with platinum-based chemotherapy or bevacizumab, this study will evaluate atezolizumab in combination with platinum-based chemotherapy, with or without bevacizumab. Tumor cell 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

Standard-of-care first-line treatment for advanced stage non-squamous NSCLC is a platinum doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. In this study, all patients in the experimental arms will receive, at minimum, the platinum doublet of carboplatin with paclitaxel with atezolizumab. The control group will receive the combination of carboplatin + paclitaxel + bevacizumab. This control group is recognized as a standard of care for the first-line treatment of NSCLC based on the results of the ECOG 4599 study, which showed a significant improvement in OS (12.3 months vs. 10.3 months [HR = 0.80; p < 0.003]), PFS (6.4 months vs. 4.8 months [HR = 0.65; p < 0.0001]), and response rate (35% [133 of 381 patients] vs. 15% [59 of 392 patients]; p < 0.001) in patients treated with bevacizumab Q3W in combination with carboplatin/paclitaxel compared with carboplatin/paclitaxel alone.

In addition, as opposed to the platinum-doublet regimen with pemetrexed induction followed by pemetrexed maintenance, the platinum-doublet with bevacizumab does not require the use of corticosteroids during bevacizumab maintenance. Because the effects of corticosteroids on T-cell proliferation have the potential to ablate early atezolizumab-mediated anti-tumor immune activity, it is recommended that dexamethasone doses be minimized to the extent that is clinically feasible in patients treated with atezolizumab. Therefore, the backbone treatment of carboplatin + paclitaxel + bevacizumab in combination with atezolizumab is considered

optimal to minimize the prolonged requirement for systemic corticosteroids, and it follows that carboplatin + paclitaxel + bevacizumab would be a logical comparator. This control group will be instrumental in assessing the relative benefit and safety of atezolizumab in combination with carboplatin + paclitaxel with and without bevacizumab in the front-line treatment setting.

3.3.3 Rationale for Open-Label Study

An open-label study design was chosen for this study for the following reasons: Given the known toxicities associated with bevacizumab therapy, patients assigned to bevacizumab-containing arms (Arms B and C), as well as physicians, may be capable of identifying treatment assignment in a blinded study. In addition, a blinded study would require prolonged administration of placebo during the maintenance phase, which could pose a significant burden to patients. Furthermore, because of the potential for pseudoprogression in patients randomized to atezolizumab-containing arms, a blinded study would require the option that all patients continue treatment until loss of clinical benefit regardless of whether they were receiving atezolizumab. In the absence of pseudoprogression, this could then delay subsequent treatment with approved therapies for NSCLC in patients assigned to any treatment arm, as well as increase the complexity of treatment decisions.

Adequate steps have been taken to ensure the validity of data in an open-label study design. This includes performing a supportive analysis of efficacy on the basis of determined progression by an IRF, performing a sensitivity analysis to demonstrate the robustness of the primary endpoint, defining progression using established response evaluation criteria (RECIST v1.1), performing tumor assessments at the same frequency in all arms, adhering to protocol-defined schedules, and determining the strategy for the final analysis of the primary endpoint prior to database lock for the primary efficacy analyses, including predefined methods for handling missing data and censoring rules. Efficacy analyses will be performed only at the prespecified analysis timepoints in the protocol.

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

Investigator-assessed PFS (which will be supported by an IRF-assessed PFS analysis, one of the secondary endpoints of the study) and OS are the co-primary endpoints for this study.

The co-primary endpoint of OS has been added to the PFS primary endpoint because recent data suggest that OS may be a more sensitive endpoint for cancer immunotherapy than PFS. For example, in the randomized Phase II study GO28753 (POPLAR) in patients with advanced NSCLC, an OS benefit in the atezolizumab arm compared with the docetaxel arm was observed in the ITT population, with a stratified HR of 0.73 (95% CI: 0.53, 0.99). PFS in the ITT population was similar between both treatment arms: HR of 0.94 (95% CI: 0.72, 1.23) (Fehrenbacher et al. 2016). In

addition, OS is the most objective and best measure of clinical benefit for patients with advanced/unresectable or metastatic lung cancer.

However, given that the majority of patients in this study will likely receive subsequent anti-cancer therapies and/or palliative care (Temel et al. 2010) post-disease progression, the OS analysis may be confounded (Miller et al. 2012). Therefore, PFS is being retained as a co-primary endpoint, and crossover from the control arm to either of the experimental arms after the disease progression will not be permitted with the aim of preserving the study's ability to potentially demonstrate treatment benefit of atezolizumab on OS.

PFS as an endpoint can reflect tumor growth and can be assessed before the determination of a survival benefit. Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit of the new treatment compared with available therapies (Guidance for Industry 2007; European Medicines Agency 2012). To ensure the validity of investigator-assessed PFS as a co-primary endpoint, a number of measures have been implemented: full IRF assessment to support the analysis of the co-primary endpoint, a substantial target magnitude of benefit (target HR = 0.65 in the ITT-WT and 0.55 in the tGE-WT population), and study assessments that will allow a robust evaluation of risk-benefit (standard RECIST to define progression with fixed assessment intervals that are identical in all treatment arms and a robust definition of PFS and prospectively defined methods to assess, quantify, and analyze PFS, including sensitivity analyses).

New treatment modalities, such as targeted therapies and immunotherapy, are emerging as highly effective regimens that are providing improvements in patient outcomes far beyond what was achieved before (Ellis et al. 2014). In particular, immunotherapy has been correlated/associated with durable responses, significant prolongation of PFS, and improvement of quality of life. In addition, meta-analyses have indicated that PFS can be considered a good measure of clinical benefit for patients with locally advanced/metastatic NSCLC (Laporte et al. 2013).

3.3.5 Rationale for Allowing Patients to Continue Atezolizumab Treatment until Loss of Clinical Benefit

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 randomized to the atezolizumab treatment arms to remain on atezolizumab after apparent radiographic progression, provided the benefit-risk ratio is judged to be favorable. Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status (see Section 3.1).

In addition, while a co-primary endpoint measure of efficacy (PFS) comparing the atezolizumab-containing treatment arms with carboplatin + paclitaxel + bevacizumab will be using RECIST v1.1, exploratory analyses of PFS, ORR, and DOR, using modified RECIST (see Section 2.4) will be performed for patients randomized to receive atezolizumab. Modified RECIST allows for the incorporation of new lesions into the calculation of total tumor burden after baseline. Tumor assessments will be performed according to RECIST v1.1 and modified RECIST for patients in the atezolizumab-containing treatment arms (Arms A and B) and only according to RECIST v1.1 for patients in the control arm (Arm C).

3.3.6 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 HRQoL (Hyde and Hyde 1974; Hopwood and Stephens 1995; Sarna et al. 2004). This is especially true for studies that use 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 NSCLC. 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 3 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 and symptom severity.

In addition, the SILC scale will be used to assess the effect/impact of atezolizumab on TTD of specific lung cancer symptoms (chest pain, dyspnea, and cough) in patients with Stage IV, non-squamous NSCLC in the first-line setting.

The single-item Patient Global Impressions of Severity (PGIS) and the EQ-5D-3L instrument are included in the study to generate HRQoL and utility scores to confirm construct validity of the SILC scale and for use in economic models for reimbursement, respectively. Results from the PGIS and EQ-5D-3L are not planned to be used for market authorization.

3.3.7 Rationale for Collection of Archival and/or Fresh Tumor Specimens and Evaluation of PD-L1 and T-Effector Gene Signature

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 therapy (Topalian et al. 2012). This correlation was also observed with atezolizumab in Studies PCD4989g (Herbst et al. 2014; Horn et al. 2015), GO28625 (FIR) (Spiegel et al. 2015), GO28754 (BIRCH) (Besse et al. 2015), GO28753 (POPLAR) (Fehrenbacher et al. 2016), and GO28915 (OAK) (Rittmeyer et al. 2017). In addition, POPLAR data suggest that higher expression of genes related to PD-L1 and T-effector biology in tumor tissue is associated with improved efficacy of atezolizumab compared with docetaxel (Fehrenbacher et al. 2016). Similar observations have been reported for other PD-L1 or PD-1 inhibitors (Higgs et al. 2015; Muro et al. 2015; Seiwert et al. 2015). Furthermore, expression of PD-L1 on ICs was reported to be associated with expression of a T-effector gene signature, therefore representing a preexisting immunity (Fehrenbacher et al. 2016).

In this study, archival and/or fresh tumor specimens will be prospectively tested for PD-L1 expression by a central laboratory during the screening period. Patients will be stratified by PD-L1 expression. The primary analysis of this study will evaluate the efficacy of atezolizumab in the ITT population, as well as in patients with a defined level of expression of a PD-L1 and T-effector gene signature (tGE population). Both populations will exclude patients with a sensitizing EGFR mutation or ALK translocation. On the basis of an analysis of independent cohorts of patients with NSCLC, it is estimated that the primary tGE cutoff for this study will identify a population corresponding to approximately 50% of the first-line NSCLC patient population.

In addition to the assessment of PD-L1 status and T-effector gene signature status, other exploratory markers, such as potential predictive and prognostic markers related to the clinical benefit of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may also be analyzed. DNA and/or RNA extraction and analysis may be performed to enable identification of somatic mutations by use of NGS and to evaluate expression of genes (including but not limited to PD-L1, PD-1, T-effector and others) to assess their association with efficacy and to increase understanding of disease pathobiology.

3.3.8 Rationale for Blood Sampling for Biomarkers

An exploratory objective of this study is to evaluate surrogate biomarkers (that may include circulating-tumor DNA [ctDNA], gene expression, tumor burden biomarkers, and others) in blood samples. Evaluation of blood biomarkers may provide evidence for biologic activity of atezolizumab in patients with NSCLC and may allow for the development of blood-based biomarkers to help predict which patients may benefit from atezolizumab.

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

3.3.9 Rationale for the Collection of Mandatory 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 radiological progression. This initial apparent progression may occur as a result of either delayed anti-tumor activity and/or robust tumor-immune infiltration 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, collection of a mandatory tumor biopsy at the time of radiographic progression is required in order to evaluate the utility of the biopsy in distinguishing pseudoprogression/tumor-immune infiltration from true progression. Additionally, 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 efficacy will be evaluated. DNA and/or RNA analysis may be performed to enable identification of somatic mutations, by use of NGS, 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 Co-Primary Efficacy Outcome Measures

The co-primary efficacy outcome measures for this study are the following:

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first in the tGE-WT population and the ITT-WT population
- OS, defined as the time from randomization to death from any cause in the ITT-WT population

3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are the following:

- OS in the tGE-WT population
- PFS, as determined by the investigator according to RECIST v1.1, and OS in the TC2/3 or IC2/3 WT population and the TC1/2/3 or IC1/2/3 WT population
- PFS, as determined by the investigator according to RECIST v1.1, and OS in the tGE population and the ITT population

- Objective response, defined as partial response (PR) or complete response (CR) as determined by the investigator according to RECIST v1.1 in the tGE-WT population and the ITT-WT population
- 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 according to RECIST v1.1 or death from any cause, whichever occurs first in the tGE-WT population and the ITT-WT population
- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the IRF according to RECIST v1.1 or death from any cause, whichever occurs first, in the tGE-WT population and the ITT-WT population
- OS rates at 1 and 2 years for the tGE-WT population and the ITT-WT population
- PFS, as determined by the investigator according to RECIST v1.1, and OS in the two atezolizumab-containing arms in the tGE-WT population and the ITT-WT population
- 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 in the tGE-WT population and the ITT-WT population
- Change from baseline in patient-reported lung cancer symptoms (chest pain, dyspnea, and cough) on the symptom severity score of the SILC scale for the tGE-WT population and the ITT-WT population

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are the following:

- Incidence, nature, and severity of adverse events graded according to the NCI CTCAE v4.0
- Changes in vital signs, physical findings, and clinical laboratory results during and following atezolizumab 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 the following:

- Maximum observed serum atezolizumab concentration (C_{max}) after infusion (Arms A and B)
- 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 (Arms A and B)
- Plasma concentrations for carboplatin (Arms A, B, and C)
- Plasma concentrations for paclitaxel (Arms A, B, and C)
- Bevacizumab C_{max} and C_{min} (Arms B and C)

See Appendix 2 for specific sample collection times.

3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are:

- TTR, defined as the time from randomization to first occurrence of a documented objective response as determined by the investigator according to RECIST v1.1
- Time in response (TIR), defined as 1 day for non-responders and defined the same as DOR for responders, as determined by the investigator according to RECIST v1.1
- Objective response and DOR, as determined by the IRF according to RECIST v1.1
- Objective response, PFS, and DOR, in the two atezolizumab-containing arms, as determined by the investigator according to modified RECIST (Arms A and B)
- PFS at 6 months and at 1 year
- OS rate at 3 years
- Status of PD-L1-, immune-, and NSCLC-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 in combination with chemotherapy
- Status of tumor-infiltrating immune cells and other exploratory biomarkers in mandatory biopsy specimens and blood collected at progression
- Utility scores of the EQ-5D-3L
- Change from baseline in patient-reported outcomes of HRQoL, lung cancer–related symptoms, and functioning as assessed by the EORTC QLQ-C30 and QLQ-LC13

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients may be eligible if they have chemotherapy-naive, Stage IV, non-squamous NSCLC.

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 10)
- Histologically or cytologically confirmed, Stage IV non-squamous NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 7th edition; Detterbeck et al. 2009; see Appendix 3)

Patients with tumors of mixed histology (i.e., squamous and non-squamous) are eligible if the major histological component appears to be non-squamous.

- No prior treatment for Stage IV non-squamous NSCLC

  Patients with a sensitizing mutation in the *EGFR* gene must have experienced disease progression (during or after treatment) or intolerance to treatment with one or more *EGFR TKI*s, such as erlotinib, gefitinib, or another *EGFR TKI* appropriate for the treatment of *EGFR*-mutant NSCLC.

  Patients with an *ALK* fusion oncogene must have experienced disease progression (during or after treatment) or intolerance to treatment with one or more ALK inhibitors (i.e., crizotinib) appropriate for the treatment of NSCLC in patients having an *ALK* fusion oncogene.

  Patients with unknown *EGFR* and/or *ALK* status require test results at screening. *ALK* and/or *EGFR* may be assessed locally or at a central laboratory.

- Patients who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomization since the last chemotherapy, radiotherapy, or chemoradiotherapy.
- 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 stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomization

  No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  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.

- Known PD-L1 tumor status as determined by an IHC assay performed by a central laboratory on previously obtained archival tumor tissue or tissue obtained from a biopsy at screening. See Section 4.5.7.1.

  A representative formalin-fixed paraffin-embedded (FFPE) tumor specimen in paraffin block (preferred) or 15 or more unstained, freshly cut, serial sections on slides from an FFPE tumor specimen is required for participation in this study. If fewer than 15 slides are available at baseline (but no fewer than 10), the patient may still be eligible, upon discussion with the Medical Monitor. This specimen must be accompanied by the associated pathology report.

Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or cell smears), brushing, cell pellet specimens (e.g., from pleural effusion, and lavage samples) are not acceptable.

Tumor tissue from bone metastases that is subject to decalcification is not acceptable.

For core needle biopsy specimens, preferably at least three cores embedded in a single paraffin block, should be submitted for evaluation.

- 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

- For female patients of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate (<1% per year) when used consistently and correctly, and to continue its use for 5 months after the last dose of atezolizumab and/or 6 months after the last dose of bevacizumab or paclitaxel, whichever is later). *Women must refrain from donating eggs during this same period. Highly effective contraceptive* methods include: combined (estrogen and progestogen containing) hormonal contraception, progestogen-only hormonal contraception associated with inhibition of ovulation together with another additional barrier method always containing a spermicide, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral

tubal occlusion, vasectomized partner (on the understanding that this is the only one partner during the whole study duration), and sexual abstinence.

- For male patients with female partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate (< 1% per year) when used consistently and correctly, and to continue its use for 6 months after the last dose of bevacizumab, carboplatin, or paclitaxel. Male patients should not donate sperm during this study and for at least 6 months after the last dose of bevacizumab, carboplatin, or paclitaxel.
- Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drug. The same rules are valid for male patients involved in this clinical study if they have a partner of childbearing potential. Male patients must always use a condom.
- Women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug

4.1.2 Exclusion Criteria

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

4.1.2.1 Cancer-Specific Exclusions

- Active or untreated CNS metastases as determined by CT or 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 > 2 weeks prior to randomization
- Leptomeningeal disease
- Uncontrolled tumor-related pain

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to randomization. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for locoregional therapy, if appropriate, prior to randomization.
- 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.
- Uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > ULN)

Patients who are receiving denosumab prior to randomization must be willing and eligible to receive a bisphosphonate instead while in the study.

- Malignancies other than NSCLC 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)
- Known tumor PD-L1 expression status as determined by an IHC assay from other clinical studies (e.g., patients whose PD-L1 expression status was determined during screening for entry into a study with anti–PD-1 or anti–PD-L1 antibodies but were not eligible are excluded)

4.1.2.2 General Medical Exclusions

- Women who are pregnant, lactating, or intending to become pregnant during the study
- 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 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 12 for a more comprehensive list of autoimmune diseases)

  Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study.

  Patients with controlled Type 1 diabetes mellitus on a stable dose of insulin regimen are eligible for this study

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

  Rash must cover less than 10% of body surface area (BSA).

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

  No acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], 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 for HIV

  All patients will be tested for HIV prior to inclusion into the study; patients who test positive for HIV will be excluded from the study.

- Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

  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 only if they are negative for HBV DNA.

  Patients positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV RNA.

- Active tuberculosis
- Severe infections within 4 weeks prior to randomization, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received therapeutic oral or IV antibiotics within 2 weeks prior to randomization

  Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.

- 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
- 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
- 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 renders the patient at high risk from treatment complications
- Patients with illnesses or conditions that interfere with their capacity to understand, follow and/or comply with study procedures

4.1.2.3 Exclusion Criteria Related to Medications

- Treatment with any approved anti-cancer therapy, including hormonal therapy, within 3 weeks prior to initiation of study treatment; the following exceptions are allowed:

  TKIs approved for treatment of NSCLC discontinued >7 days prior to randomization; the baseline scan must be obtained after discontinuation of prior TKIs.

- Treatment with any other investigational agent with therapeutic intent within 28 days prior to randomization
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti–PD-1, and anti–PD-L1 therapeutic antibodies

  Patients who have had prior anti–CTLA-4 treatment may be enrolled, provided the following requirements are met:

  Last dose of anti–CTLA-4 at least 6 weeks prior to randomization

  No history of severe immune-mediated adverse effects from anti–CTLA-4 (NCI CTCAE Grade 3 or 4)

- Treatment with systemic immunostimulatory agents (including but not limited to interferons, interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to randomization

  Prior treatment with cancer vaccines is allowed.

- Treatment with systemic immunosuppressive medications (including but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to randomization

  Patients who have received acute, low-dose (≤10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study.

  The use of corticosteroids (≤10 mg oral prednisone or equivalent) for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency is allowed.

4.1.2.4 Exclusions Related to Bevacizumab

- Inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg)

  Anti-hypertensive therapy to achieve these parameters is allowable.

- Prior history of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to randomization
- History of hemoptysis (≥one-half teaspoon of bright red blood per episode) within 1 month prior to randomization

- Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (within 10 days of randomization) use of aspirin (>325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and cilostazol
- Current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes that has not been stable for >2 weeks prior to randomization

  The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the patient has been on a stable dose of anticoagulants for at least 2 weeks prior to randomization.

  Prophylactic anticoagulation for the patency of venous access devices is allowed, provided the activity of the agent results in an INR < 1.5 × ULN and aPTT is within normal limits within 14 days prior to randomization.

  Prophylactic use of low-molecular-weight heparin (i.e., enoxaparin 40 mg/day) is permitted.
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to the first dose of bevacizumab
- History of abdominal or tracheosphageal fistula or gastrointestinal perforation within 6 months prior to randomization
- Clinical signs of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- Serious, non-healing wound, active ulcer, or untreated bone fracture
- Proteinuria, as demonstrated by urine dipstick or >1.0 g of protein in a 24-hour urine collection

  All patients with ≥2+ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection and must demonstrate ≤1 g of protein in 24 hours.
- Known sensitivity to any component of bevacizumab
- Clear tumor infiltration into the thoracic great vessels is seen on imaging
- Clear cavitation of pulmonary lesions is seen on imaging

4.1.2.5 Exclusions Related to Chemotherapy

- Known history of severe allergic reactions to platinum-containing compounds or mannitol
- Known sensitivity to any component of paclitaxel
- Grade ≥2 peripheral neuropathy as defined by NCI CTCAE v4.0 (paclitaxel)
- Known history of severe hypersensitivity reactions to products containing Cremophor® EL (e.g., cyclosporin for injection concentrate and teniposide for injection concentrate)

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

- This is an open-label study.
- After written informed consent has been obtained and eligibility has been established, the study site will enter demographic and baseline characteristics in the interactive voice/Web response system (IxRS/IWRS). For patients who are eligible for enrollment, the study site will obtain the patient's randomization number and treatment assignment from the IxRS. The number of cycles of induction treatment (four or six) will be determined by the investigator and documented prior to randomization.

Randomization to one of the three treatment arms will occur in a 1:1:1 ratio. Permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm. Randomization will be stratified by the following criteria:

- Sex (male vs. female)
- Presence of liver metastases at baseline (yes vs. no)
- PD-L1 expression by IHC (TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1) (see Section 6.4.1)

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.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab (MPDL3280A)

The atezolizumab (MPDL3280A) drug product is provided as a sterile liquid in a single-use, 20-mL glass vial. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume.

For further details on the formulation and handling of atezolizumab, see the Pharmacy Manual and Atezolizumab Investigator's Brochure.

Atezolizumab (MPDL3280A) will be supplied by the Sponsor.

4.3.1.2 Carboplatin, Paclitaxel, and Bevacizumab

Carboplatin, paclitaxel, and bevacizumab will be used in commercially available formulations. For information on the formulation, packaging, and handling of carboplatin, paclitaxel, and bevacizumab, see the local prescribing information for each drug.

4.3.2 Dosage, Administration, and Compliance

The induction phase of the study will consist of four or six cycles of chemotherapy, 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 → paclitaxel → carboplatin

Arm B: Atezolizumab → bevacizumab → paclitaxel → carboplatin

Arm C: Bevacizumab → paclitaxel → carboplatin

During the induction phase, a chemotherapy cycle counts toward the prespecified number of induction chemotherapy cycles (four or six), as long as at least one chemotherapy component has been administered. Cycles in which no chemotherapy is given do not count toward the total number of induction chemotherapy cycles. Additional guidance in the event of chemotherapy interruption and reintroduction is provided in Appendix 15.

Patients who experience no further clinical benefit (for patients enrolled into Arm A or B, see Section 3.1 for definition) or disease progression (for patients enrolled into Arm C) at any time during the induction phase will discontinue all study treatment. In the absence of the above criteria, after the fourth or sixth-cycle induction phase, patients will begin maintenance therapy (atezolizumab in Arm A; atezolizumab + bevacizumab in Arm B; bevacizumab in Arm C).

During treatment (induction or maintenance), patients in Arms A and B who show evidence of clinical benefit will be permitted to continue atezolizumab after RECIST v1.1 for progressive disease are met if they meet all criteria listed in Section 3.1. Treatment with chemotherapy (Arms A, B, and C) and bevacizumab (Arms B and C) must be discontinued.

Patients should receive anti-emetic medications and IV hydration for platinum-based treatments according to the local standard of care and manufacturer's instruction. Table 10 lists the suggested premedication for induction treatment, and Table 11 lists the suggested infusion times for treatment administration during the induction and maintenance phases. Chemotherapy infusion times may be adapted in accordance with local standard of care in lieu of the suggested infusion times specified in Table 11 and Section 4.3.2.2. Chemotherapy dose modifications are allowed only to address toxicities (see Section 5.1.6.1 and Section 5.1.9 for guidelines) The investigator may use discretion in modifying or accelerating the chemotherapy dose modification, 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.

Table 10 Suggested Premedication for Induction Treatment for All Treatment Arms

Premedication	Dose/Route	Timing
Dexamethasone	20 mg PO	12 and 6 hours before paclitaxel (or per standard-of-care at treating institution)
Diphenhydramine (or equivalent)	50 mg IV	30–60 minutes before paclitaxel
Cimetidine (or ranitidine) (or equivalent)	300 mg (or 50 mg) IV (or equivalent)	30–60 minutes before paclitaxel

IV = intravenous; PO = oral.

Note: Prophylactic anti-emetics and hydration should be administered as per the local standard of care and manufacturer's instruction.

Table 11 Treatment Regimen and Order of Administration for All Treatment Arms

Agent		(1) Atezolizumab	(2) Bevacizumab	(3) Paclitaxel	(4) Carboplatin
Dose and administration route		1200 mg IV	15 mg/kg IV	200 mg/m^2 IV [a]	AUC 6 IV [b]
Infusion rate		Over 60 (±15) min (for the first infusion); 30 (±10) min for subsequent infusions if tolerated	Over 90 (±15) min (for the first infusion); shortening to 60 (±10) then 30 (±10) min for subsequent infusions if tolerated	Over 3 hours [c]	Over approximately 15–30 min
Frequency		Day 1 of every 21 days			
Induction Phase (Four or Six Cycles)	A	x		x	x
	B	x	x	x	x
	C		x	x	x
Maintenance Phase	A	x			
	B	x	x		
	C		x		

AUC = area under the concentration–time curve; IV = intravenous.

[a] Patients of Asian race/ethnicity: 175 mg/m^2 IV.

[b] See Section 4.3.2.2 for details on dose calculation of carboplatin.

[c] See Section 4.3.2.2 for more details on paclitaxel infusion times.

Guidelines for dose modification and treatment interruption or discontinuation for carboplatin, paclitaxel, and bevacizumab are provided in Sections 5.1.6.1, 5.1.8, and 5.1.9.

4.3.2.1 Atezolizumab

Patients randomized to atezolizumab will receive 1200 mg of atezolizumab administered by IV infusion every 21 days in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions.

Atezolizumab infusions will be administered per the instructions outlined in Table 12.

Table 12 Administration of First and Subsequent Infusions of Atezolizumab

First Infusion	Subsequent Infusions
• No premedication administered for atezolizumab specifically is permitted • Record patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) within 60 min before starting infusion. • Infuse atezolizumab (1200 mg in a 250 mL 0.9% NaCl IV infusion bag) over 60 (±15) min. • If clinically indicated: record patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) during the infusion at 15 min, 30 min, 45 min, and 60 min (±5 min windows are allowed for all timepoints). • If clinically indicated: record patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) at 30 min (±10 min) 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 patient experienced 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 min before starting infusion. • If the patient tolerated the first infusion well without infusion-associated adverse events, the second infusion may be delivered over 30 (±10) min. • If no reaction occurs, subsequent infusions may be delivered 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 delivered over 60 (±15) min. Record patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) every 15 (±5) minutes during the infusion if clinically indicated or patient experienced symptoms during the previous infusion. Record patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) 30 min (±10 min) after the infusion if clinically indicated or patient experienced symptoms during previous infusion.

Dose modifications to atezolizumab are not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events are provided in Sections 5.1.6.2 and 5.1.7.

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

4.3.2.2 Bevacizumab, Carboplatin, and Paclitaxel

Bevacizumab

Bevacizumab will be administered at a dose of 15 mg/kg on Day 1 of each 21-day cycle. The initial dose of bevacizumab will be based on the patient's weight at screening and will remain the same throughout the study unless the patient's weight changes by $>10\%$.

Bevacizumab will be diluted in 0.9% sodium chloride injection, USP, to a total volume of 100 mL. For patients weighing more than 110 kg, please refer to AVASTIN Pharmacy Manual for this protocol for the infusion preparation. The initial dose will be delivered over 90 ± 15 minutes. If the first infusion is tolerated without any infusion-associated adverse events (i.e., fever and/or chills), the second infusion may be delivered over 60 ± 10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 ± 10 minutes. Bevacizumab infusions may be slowed or interrupted for patients experiencing infusion-associated symptoms. If infusion-related symptoms occur, patients should be treated according to best medical practice, and patients will be monitored until adequate resolution of signs and symptoms.

Paclitaxel

In general, paclitaxel will be administered intravenously at a dose of 200 mg/m^2 over 3 hours followed by carboplatin. Patients of Asian race/ethnicity will have a lower starting dose of paclitaxel at 175 mg/m^2 intravenously over 3 hours. The lower starting dose of paclitaxel is based on a higher overall incidence of hematologic toxicities in patients from Asian countries compared with those from non-Asian countries, as observed during safety review of this study by the iDMC. The term "Asian race/ethnicity" refers to a pan-ethnic/racial group that includes diverse populations who either live or have ancestral origins in East Asia, Southeast Asia, or South Asia. The applicability of such term in a particular patient will be at the discretion of the treating investigator and should be based on the patient's clinical characteristics and country of origin.

Paclitaxel Injection must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL.

Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 μm. Use of

filter devices such as IVEX-2® filters, which incorporate short inlet and outlet PVC-coated tubing, has not resulted in significant leaching of bis(2-ethylhexyl)phthalate (DEHP).

Sites should follow their institutional standard of care for dose adjustments in the event of patient weight changes. For paclitaxel infusion, exceptions to the infusion time of 3 hours will be allowed for sites that have an institutional policy of infusing paclitaxel more quickly (over 90 minutes) or more slowly (up to 4 hours for the first infusion).

Carboplatin

Carboplatin should be administered by IV infusion, immediately after the completion of paclitaxel administration, over 15–30 minutes to achieve an initial target area under the concentration–time curve (AUC) of 6 mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines.

The carboplatin dose of AUC 6 will be calculated using the Calvert formula (Calvert et al. 1989):

Calvert Formula

$$\text{Total dose (mg)} = (\text{target AUC}) \times (\text{glomerular filtration rate [GFR]} + 25)$$

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:

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

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 GFR using 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 on the basis of 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:

$$\text{Maximum carboplatin dose (mg)} = \text{target AUC (mg} \bullet \text{min/mL)} \times (\text{GFR} + 25 \text{ mL/min})$$

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

For a target AUC = 6, the maximum dose is $6 \times 150 = 900$ mg.
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 using the following URL for more details:
http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm228974.htm.

4.3.3 Additional Required Medication

4.3.3.1 Prophylactic Measures for Carboplatin

Carboplatin is considered moderately to highly emetogenic. Therefore, appropriate anti-emetic medication should be given prior to initiation of chemotherapy according to the local practice and standard-of-care.

4.3.3.2 Premedication for Paclitaxel

All patients should be premedicated prior to paclitaxel administration to prevent severe hypersensitivity reactions. Prior to receiving paclitaxel, all patients will receive either the institutional standard-of-care or the following premedication:

- Dexamethasone 20 mg orally approximately 12 hours prior and 6 hours prior to the paclitaxel infusion

  Patients may be treated with dexamethasone 10–20 mg IV within 1 hour prior to paclitaxel infusion if the patient did not take the oral dexamethasone.
- Diphenhydramine 50 mg IV (or equivalent) 30–60 minutes prior to paclitaxel infusion
- Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent) 30–60 minutes prior to paclitaxel infusion

Because the effects of corticosteroids on T-cell proliferation have the potential to ablate early atezolizumab-mediated anti-tumor immune activity, it is recommended that dexamethasone doses be minimized to the extent that is clinically feasible. For example, if Cycle 1 is tolerated without apparent hypersensitivity reaction, a reduction in dexamethasone premedication dose should be considered for subsequent cycles if permitted by institutional standard of care.

4.3.4 Investigational Medicinal Product Accountability

The investigational medicinal products (IMPs) for this study are atezolizumab and bevacizumab. IMPs required for completion of this study will be provided by the Sponsor if required by local health authority regulations. The Sponsor or appointed designee will supply other medicinal products in accordance with local regulations.

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.

4.3.5 Post-Study Access to Atezolizumab

Patients may continue to receive atezolizumab as part of an extension study. 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, herbal 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.

4.4.1 Permitted Therapy

Premedication with antihistamines may be administered for any atezolizumab 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 during palliative radiotherapy.

- Inactive influenza vaccinations
- Megastrol administered as an appetite stimulant
- Corticosteroids (≤10 mg oral prednisone or equivalent) 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 H_2-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 11).

All concomitant medications must be recorded on the appropriate Concomitant Medications electronic Case Report Form (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 feasible, 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. Guidelines for the management of immune-mediated adverse events are described in Section 5.1.7.

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 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 while in the study.
- Any live, attenuated vaccine (e.g., FluMist®) within 4 weeks prior to randomization, during treatment, or within 5 months after the last atezolizumab dose (for patients randomized to atezolizumab).
- 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 of the chest and non-contrast CT or MRI scans 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

Flowcharts of scheduled 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 are treated with atezolizumab and who show apparent radiographic progression per RECIST v1.1at a tumor response evaluation and are eligible and willing to continue treatment with atezolizumab must sign consent at that time to have a biopsy

of the progressing lesion (if clinically feasible) and to acknowledge deferring other treatment options available to them in favor of continuing treatment with atezolizumab.

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.

NSCLC cancer history will include prior cancer therapies, procedures, and an assessment of tumor mutational status (e.g., sensitizing *EGFR* mutation, *ALK* fusion status). For patients not previously tested for tumor mutational status, testing will be required at screening. For these patients, testing can either be performed locally or submitted for central evaluation during the screening period. If *EGFR* mutations or *ALK* status testing is not performed locally, additional tumor sections may be required for central evaluation of the mutational status of these genes. Please review tissue requirements for central evaluation in the central laboratory instruction manual.

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 temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressures.

Vital signs will be measured and recorded as described in Table 13.

For all sites in Argentina, pulse oximetry to measure hypoxia will be performed at every visit. These data will not be recorded.

Table 13 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 infusion • During (every 15 [±5] minutes) the atezolizumab infusion and within 30 (±10) minutes after atezolizumab infusion, if clinically indicated • Within 30 (±10) minutes after carboplatin infusion
Arm C	• Within 60 minutes prior to bevacizumab infusion • Within 30 (±10) minutes after carboplatin infusion
Subsequent Cycles	
Treatment Arm	Timepoints
Arms A and B	• Within 60 minutes prior to atezolizumab infusion • During (every 15 [±5] minutes) the atezolizumab infusion and within 30 (±10) minutes after atezolizumab infusion if clinically indicated or if symptoms occurred during prior infusion
Arm C	• Within 60 minutes prior to bevacizumab infusion • During the bevacizumab infusion if clinically indicated or if symptoms occurred during the prior infusions • Within 30 (±10) minutes after carboplatin infusion if clinically indicated or if symptoms occurred during the prior infusion

For patients in the atezolizumab arm, also refer to Section 4.3.2.1.

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 exclude CNS metastasis. 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 4.1.2.1).

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 re-assessed at each subsequent tumor evaluation. Patients with a history of irradiated brain metastases at screening are not required to undergo imaging brain scans at subsequent tumor evaluations, unless scans are clinically indicated. 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 according to RECIST v1.1 and modified RECIST. Tumor assessments will be performed according to RECIST v1.1 and modified RECIST for patients in the atezolizumab-containing treatment arms (Arms A and B) and only according to RECIST v1.1 for patients in the control arm (Arm C). 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.

Tumor assessments should occur every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1 and then every 9 weeks (±7 days) after the completion of the Week 48 tumor assessment, regardless of treatment delays, until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. 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 until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by 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 scheduled tumor assessments until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Patients treated with atezolizumab continuing to experience clinical benefit, despite evidence of radiographic progression, will continue tumor assessments as per the schedule listed above.

Scans will be submitted for central review to an IRF.

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, 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 on Day 1 of each cycle during treatment prior to administration of study treatment. If a urine pregnancy test 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: hepatitis B surface antigen (HBsAg), antibodies against HBsAg, total hepatitis B core antibody (HBcAb)

  HBV DNA test must be performed prior to randomization if patient has a negative serology for HBsAg and a positive serology for HBcAb. HBV DNA test must be negative.
- HCV serology: hepatitis C virus antibody (anti-HCV)

  HCV RNA test must be performed prior to randomization if the 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 clinical study.

A central laboratory will coordinate the sample collection of tissue and blood samples for research-related testing at central laboratories or by 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 (all atezolizumab- and bevacizumab-treated patients)

  Serum samples will be assayed for the presence of ATAs to atezolizumab and bevacizumab with use of validated immunoassays. Accompanying PK samples will be collected at the same timepoints (See Appendix 2).

- 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 selected sites, a subset of 20 patients in each arm will undergo additional PK assessments for carboplatin, paclitaxel, and bevacizumab (bevacizumab in Arms B and C only).

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

    Plasma carboplatin and paclitaxel 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 NSCLC or tumor immune biology) from all eligible patients according to the schedule in Appendix 2. Samples will be processed to obtain plasma and serum for the determination of changes in blood-based biomarkers (e.g., ctDNA). Whole blood samples may be processed to obtain their derivatives (e.g., RNA and DNA) 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 RCR any leftover material from the above sample collection will be stored and used for exploratory analyses as indicated in Section 4.5.11. For patients who consent to RCR optional future research on their whole blood samples collected at screening but are determined to be ineligible for study participation, these samples and their derivatives (e.g., DNA, RNA, protein) may be used for future development of biomarker and/or diagnostic tests as indicated in Section 4.5.11.

4.5.7 Tumor Tissue Samples

4.5.7.1 Archival and Freshly Collected Tumor Tissue Samples for Screening

Representative tumor specimens in paraffin blocks (preferred) or 15 (or more) freshly cut, serial unstained sections, with an associated pathology report, must be submitted at screening for determination of PD-L1 status prior to study randomization. If fewer than

15 slides are available at baseline (but no fewer than 10), the patient may still be eligible, upon discussion with the Medical Monitor. In addition, expression of PD-L1 and T-effector gene signature will be evaluated. Exploratory biomarkers (including, but not limited to, markers related to immune or NSCLC biology, such as T-cell markers or non-inherited biomarkers identified through NGS on extracted DNA and/or RNA) may also be evaluated. The biomarkers will be identified by IHC, quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR), next-generation sequencing (NGS), and/or other methods.

Tumor tissue should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status).

An archival tumor specimen should be submitted if available. If an archival specimen is not available, the patient may still be eligible, with the assumption that the patient is willing to consent to and undergo a pre-treatment biopsy or resection of the tumor.

For freshly collected biopsy specimens, acceptable samples include those outlined below, provided there is a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method:

- Core-needle biopsies for deep tumor tissue; at least three cores, embedded into a single paraffin block, should be submitted for evaluation.
- Excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions
- Tumor tissue resections

Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield a cell suspension and/or cell smears), brushing, cell pellets (e.g., from pleural effusion), and lavage samples are not acceptable.

Tumor tissue from bone metastases that is subject to decalcification is not acceptable.

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 in the study will be returned no later than 6 weeks after eligibility determination.

ALK and/or *EGFR* status may be assessed locally or at a central lab if unknown.

4.5.7.2 Tumor Samples at the Time of Radiographic Progression

Patients in all treatment arms will undergo a mandatory tumor biopsy to obtain a tumor sample, unless not clinically feasible, at the time of radiographic disease progression (within 40 days of radiographic progression or prior to the start of the next anti-cancer treatment, whichever is sooner).

Acceptable samples include the following:

- Core-needle biopsies for deep tumor tissue; at least three cores, embedded into a single paraffin block, should be submitted for evaluation.
- Excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions
- Tumor tissue resection

The status of immune-related and 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. If performed by Foundation Medicine, the investigator can obtain results from the samples collected at the time of disease progression 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 the U.S. FDA; results from these investigational tests should not be used to guide future treatment decisions.

4.5.7.3 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 Roche Clinical Repository (RCR) optional consent will be requested (but not required) to also submit these optional fresh samples for central testing. Tumor tissue samples collected at the time of clinical events (e.g., clinical response) 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.

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than

5 years after the final Clinical Study Report has been completed, or earlier depending on local regulations.

- Blood and tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed, or earlier depending on local regulations.

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 and bevacizumab (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 may include an assessment of whether detected 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

A 12-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, SILC, PGIS, and EQ-5D-3L to more fully characterize the clinical profile of atezolizumab.

The questionnaires will be translated as required in the local language. 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 7) 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 and 6 months following disease progression (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1).

The EORTC QLQ-LC13 (see Appendix 8) 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 and 6 months following disease (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1).

The SILC scale will be used to assess patient-reported severity of lung cancer symptoms (chest pain, dyspnea, and cough). The SILC scale is a 9-item content validated self-report measure of lung cancer symptoms. It measures severity of cough, dyspnea, and chest pain with a symptom severity score. This questionnaire will be completed using an ePRO device at the patient's home on a weekly basis, then during survival follow-up every month for 6 months following disease progression (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1).

The EQ-5D-3L 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 9). The EQ-5D-3L 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 for at 3 months and 6 months following disease progression (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1).

The PGIS consists of a single question used to assess patient global impression of disease severity. This question will be completed on the ePRO tablet at each scheduled study visit during study treatment. The PGIS is not required during survival follow–up.

Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will complete the EORTC QLQ-C30, EORTC QLQ-LC13, PGIS, and EQ-5D-3L at each tumor assessment visit and will complete the SILC at home on a weekly basis, until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression) as determined by the investigator (unless the patient withdraws consent or the Sponsor terminates the study).

The Sponsor will not derive adverse events reports from PRO data. However, any PRO responses suggestive of a possible adverse event that are identified during site review of the PRO data should be reported as outlined in Section 5.3.5.12.

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 exempt from 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
- Whole blood samples collected at screening (for screen-fail patients only)

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. 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 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. A patient's withdrawal from Study GO29436 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 GO29436.

If a patient wishes to withdraw consent to the testing of his or her specimens after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

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, ATA, and biomarker sampling.

4.5.12.2 Assessments during Treatment

All 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 delivered 21 days from the previous dose administration: two consecutive 28 cycles are not permitted. If a dose modification is required because of toxicity, refer to Section 5.1.

Tumor assessments should occur every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1 and every 9 weeks (±7 days) after completion of the Week 48 tumor assessment, regardless of treatment delays, until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment with atezolizumab after disease progression according to RECIST v1.1 for Arms A and B only), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) should continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by Sponsor, whichever occurs first.

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 treatment for a study drug discontinuation visit. The visit at which the decision is made to discontinue treatment (e.g., loss of clinical benefit is confirmed [atezolizumab-treated patients] or 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 disease progression per RECIST v1.1, tumor assessments should continue at the same frequency as would have been followed had the patient remained on study treatment until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to 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 should 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 (SILC will be completed monthly only for the first 6 months after disease progression [or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1] using an ePRO device at the patient's home and EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-3L will be completed 3 and 6 months after disease progression [or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1] at the site using the ePRO tablet), study treatment–related adverse events (including serious adverse events), subsequent anti-cancer therapies, and date and cause of death.

Patients who discontinue study treatment for any reason other than disease progression or loss of clinical benefit will complete the EORTC QLQ-C30, EORTC QLQ-LC13, PGIS, and EQ-5D-3L at each tumor assessment visit and will complete the SILC at home on a weekly basis, until radiographic disease progression per RECIST v1.1 or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression) as determined by the investigator (unless the patient withdraws consent, death, or study termination by the Sponsor 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 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 NSCLC, 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. However, patients will not be followed for any reason after consent has been withdrawn. 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, and 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 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after disease progression according to RECIST v1.1) 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

  Exception for atezolizumab treatment: patients randomized to atezolizumab treatment will be permitted to continue atezolizumab after RECIST v1.1 criteria for progressive disease are met if they meet all of the following criteria (see Figure 2 for the schematic representation):

  Evidence of clinical benefit as assessed by the investigator

  Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease

  No decline in ECOG performance status

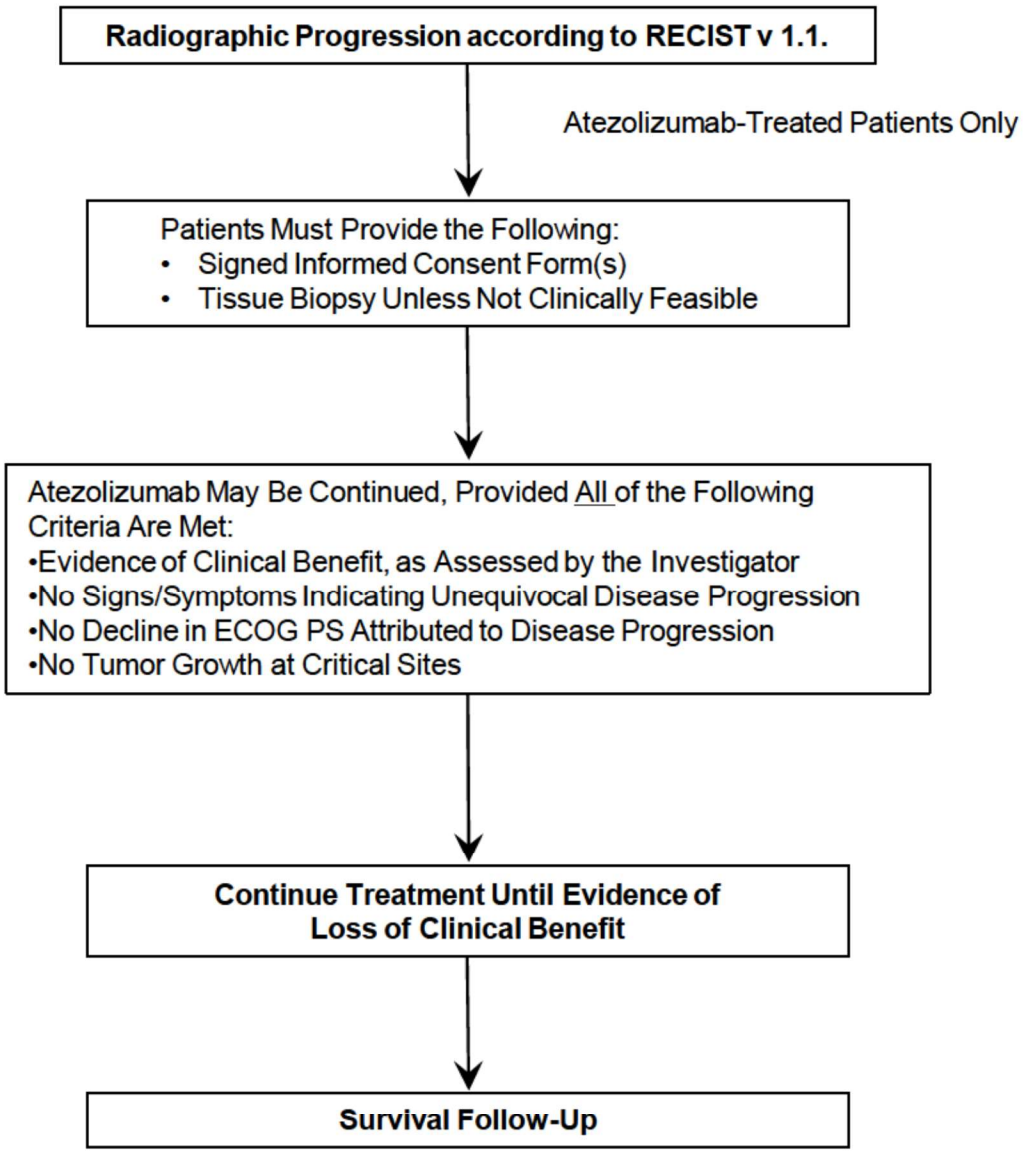
  Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing

  Patients must provide written consent to acknowledge deferring any standard treatment options that may exist in favor of continuing atezolizumab treatment at the time of initial progression.

  A mandatory biopsy sample collection, unless not clinically feasible as assessed by the investigators, at the site of local or metastatic progression

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

Figure 2 Criteria for Continuing Atezolizumab in Presence of Increased Radiographic Tumor Size (Atezolizumab Arms)



ECOG PS = Eastern Cooperative Oncology Group performance status; ICF = Informed Consent Form; 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 Council for 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 following information is based on results from nonclinical and clinical studies and published data on similar molecules.

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 5.1.5).
See Section 5.3 (Methods and Timing for Capturing and Assessing Safety Parameters) for complete details regarding safety reporting for this study.

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

5.1.1 Risks Associated with Atezolizumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events, specifically the induction or

enhancement of autoimmune conditions. Adverse events with potentially immune-mediated causes, including rash, hypothyroidism, hepatitis/transaminitis, colitis, pneumonitis, myositis, and myasthenia gravis, have been observed in the Phase Ia Study PCD4989g. For further details regarding clinical safety, including a detailed description of anticipated safety risks for atezolizumab, see the Atezolizumab Investigator's Brochure.

Although most immune-mediated 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 (Di Giacomo et al. 2010). Suggested workup procedures for suspected immune-mediated adverse events are provided in Section 5.1.7 and in Section 6 (Guidance for the Investigator) of the Atezolizumab Investigator's Brochure.

5.1.2 Risks Associated with Bevacizumab

The most common side effects associated with bevacizumab include gastrointestinal perforations, surgery and wound healing complications, hemorrhage (severe or fatal hemorrhage including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, pulmonary hemorrhage, epistaxis, and vaginal bleeding), non-gastrointestinal fistula formation, arterial thromboembolic events (including cerebral infarction, transient ischemic attacks, myocardial infarction, angina), and hypertension.

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

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 prescribing information for carboplatin.

5.1.4 Risks Associated with Paclitaxel

Paclitaxel is known to cause myelosuppression, alopecia, peripheral neuropathy, myalgia, arthralgia, nausea, and vomiting. Less commonly reported adverse events are hypersensitivity reactions, infections, bleeding, diarrhea, mucositis, liver function test (LFT) elevations, injection-site reactions, and cardiovascular effects such as hypotension, bradycardia, hypertension, arrhythmias, other ECG abnormalities, syncope, and venous thrombosis.

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

5.1.5 General Plan to Manage Safety Concerns

5.1.5.1 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. 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, 5.3.5.7, 5.5, and 5.6.

5.1.6 Dose Modification

5.1.6.1 General Notes Regarding Dose Modification

Reasons for dose modifications or 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.

- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and treated as Grade 1 toxicity for dose-modification purposes.
- 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 (i.e., atezolizumab, bevacizumab, carboplatin, or paclitaxel) and the dose of that component is delayed or modified in accordance with the guidelines below, other components may be administered if there is no contraindication.
- When treatment is temporarily interrupted because of toxicity caused by bevacizumab, atezolizumab, carboplatin and/or paclitaxel (if applicable), the treatment cycles will be restarted such that the atezolizumab and bevacizumab (if applicable) infusions remain synchronized and aligned with the chemotherapy schedule.
- If, in the opinion of the investigator, 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.

5.1.6.2 Atezolizumab Dose Modification

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment with atezolizumab for up to 105 days beyond the last dose if they experience an adverse event that requires a dose to be withheld. If atezolizumab is withheld because of adverse events for more than 105 days beyond the last dose, then the patient will be discontinued from atezolizumab treatment and will be followed for safety and efficacy as specified in Section 5.2.1. 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.

5.1.7 Management of Atezolizumab-Specific Adverse Events

Management of systemic immune activation is presented below. Refer to the Atezolizumab Investigator's Brochure for details on management of atezolizumab-specific adverse events.

Refer to Appendix 11 for precautions for anaphylaxis.

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 when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternate etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations.

5.1.8 Bevacizumab Dose Modification and Management of Specific Adverse Events

No reductions in bevacizumab dose are allowed in this study. Criteria for treatment modification and guidelines for the management of toxicities are summarized in Table 14. If adverse events occur that necessitate withholding bevacizumab, the dose will remain unchanged once treatment resumes.

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 non-serious adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤1, bevacizumab may be restarted at the same dose level. If bevacizumab is delayed because of toxicity for

>42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab.

The appropriate interval between the last dose of bevacizumab and major surgery is unknown. Because bevacizumab has a half-life of approximately 21 days, elective surgery should be delayed whenever possible, but if necessary, bevacizumab should be withheld for ≥28 days prior to the procedure. Re-initiation of bevacizumab following surgery should not occur for ≥28 days and until wounds have fully healed. Re-initiation of bevacizumab after surgery requires documented approval from the Medical Monitor.

Infusion of bevacizumab should be interrupted in patients who develop dyspnea or clinically significant hypotension. Patients who experience an NCI CTCAE Grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment. If possible, a sample for ATA assessment will be collected at the time of discontinuation.

Bevacizumab infusion should be slowed to ≤50% or interrupted for patients who experience any infusion-associated symptoms not specified above. If the infusion is interrupted, it may be resumed at ≤50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.

All patients receiving bevacizumab should have their baseline scans reviewed with a radiologist at the investigational site.

If the patient is found to have the features of cavitation and/or tumor invasion of thoracic vessels at baseline, the subsequent scans should also be reviewed and the decision to withdraw patients from bevacizumab should be based on the appearances of the scan.

- If the high-risk features are still apparent on the later scans, the investigator should consider withdrawing the patient from bevacizumab
- If the high-risk features are no longer visible on post-baseline scans, the investigator should make a benefit-risk assessment in consultation with a radiologist whether or not to continue treatment with bevacizumab
- If the patient did not have features of cavitation or tumor invasion of thoracic vessels at baseline, but develops cavitation during treatment, the investigator should make a benefit-risk assessment in consultation with a radiologist whether or not to continue treatment with bevacizumab.

For guidelines on the dosing of other study drugs when bevacizumab is withheld, see Section 5.1.6.1.

Table 14 Bevacizumab Dose Management for Adverse Events

Event	Action to Be Taken
Hypertension	
Grade 1 (asymptomatic, transient [<24 hr] blood pressure increase by >20 mmHg (diastolic) or to >150/100 mmHg if previously within normal limits)	No bevacizumab dose modifications
Grade 2 (recurrent or persistent [>24 hr] or symptomatic increase by >20 mmHg (diastolic) or to >150/100 mmHg if previously within normal limits)	Withhold bevacizumab. Start antihypertensive therapy. Once blood pressure is <150/100 mmHg, patient may continue bevacizumab therapy.
Grade 3	Requires more than one antihypertensive drug or more intensive therapy than previously: If not controlled to 150/100 mmHg with medication, discontinue bevacizumab.
Grade 4 (including hypertensive encephalopathy)	Discontinue bevacizumab.
Hemorrhage	
Grade 1 or 2 non-pulmonary or non-CNS events	No bevacizumab modifications
Grade 3 non-pulmonary or non-brain or non-spinal cord hemorrhage	Withhold bevacizumab until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from bevacizumab.
Grade 4 non-pulmonary or non-brain or non-spinal cord hemorrhage	Discontinue bevacizumab.

Table 14 Bevacizumab Dose Management for Adverse Events (cont.)

Event	Action to Be Taken
Hemorrhage (cont.)	
Grade 1 pulmonary or brain or spinal cord hemorrhage	Withhold bevacizumab until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
Grade 2, 3, or 4 pulmonary or brain or spinal cord hemorrhage	Discontinue bevacizumab.
Venous thromboembolic event	
Grade 1 or 2	No bevacizumab modifications.
Grade 3 or asymptomatic Grade 4	If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be withheld until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed after 2 weeks of full-dose anticoagulation if all of the following criteria are met: • The patient must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting study treatment. • The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Symptomatic Grade 4	Discontinue bevacizumab.
Arterial thromboembolic event (new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	Discontinue bevacizumab.
Congestive heart failure (left ventricular systolic dysfunction)	
Grade 1 or 2	No bevacizumab modifications.
Grade 3	Withhold bevacizumab until resolution to Grade ≤ 1.
Grade 4	Discontinue bevacizumab.
Proteinuria	
Grade 1 (urine dipstick 1+ or urine collection 0.15 to 1.0 g/24 hr)	No bevacizumab modifications
Grade 2 (urine dipstick 2+ to 3+ or urine collection >1.0 to 3.5 g/24 hr)	For 2+ dipstick, may administer bevacizumab and obtain 24-hour urine prior to next dose. For 3+ dipstick, obtain 24-hour urine prior to administration of bevacizumab. Withhold bevacizumab for proteinuria >2 g/24 hr and resume when proteinuria is ≤ 2 g/24 hr.[a]

Table 14 Bevacizumab Dose Management for Adverse Events (cont.)

Event	Action to Be Taken
Proteinuria (cont.)	
Grade 3 (urine dipstick 4+ or urine collection >3.5 g/24 hr)	Withhold bevacizumab. Resume when proteinuria is ≤2 g/24 hr. [a]
Grade 4 (nephrotic syndrome)	Discontinue bevacizumab.
GI perforation	
Any grade	Discontinue bevacizumab.
Fistula	
Any grade tracheoesophageal fistula	Discontinue bevacizumab.
Grade 4 fistula (other than tracheoesophageal)	Discontinue bevacizumab.
Bowel obstruction	
Grade 1	Continue patient on study for partial obstruction not requiring medical intervention.
Grade ≥2	Discontinue bevacizumab.
Wound dehiscence	
Any grade (requiring medical or surgical therapy)	Discontinue bevacizumab.
Reversible posterior leukoencephalopathy	
Any grade (confirmed by MRI)	Discontinue bevacizumab.

GI = gastrointestinal; LMWH = low molecular weight heparin.

[a] All proteinuria values are from 24-hour urine collection.

5.1.9 Carboplatin and Paclitaxel Dose Modification and Management of Specific Adverse Events

Dose reductions, holds, and discontinuations for each study drug may be made as outlined below. 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.

When a treatment cycle is delayed or interrupted because of toxicity resulting from either component of the regimen, all study drugs should generally be withheld and resumed together to remain synchronized. However, if it is anticipated that chemotherapy will be delayed by ≥2 weeks, then atezolizumab should be given without the chemotherapy if

there is no contraindication; this should be discussed with the Medical Monitor prior to re-initiating therapy.

Investigators should be vigilant and alert to early and overt signs of myelosuppression/infection/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.

Dose modifications of carboplatin and paclitaxel are allowed as described in the following sections.

5.1.9.1 Hematologic Toxicity

At the start of each cycle, the ANC must be ≥1500/μL and the platelet count must be ≥100,000 cells/μL. Treatment may be delayed for up to 63 days from the last dose to allow sufficient time for recovery. Growth factors may be used in lieu of a dose reduction for neutropenic fever or Grade 4 neutropenia in accordance with ASCO and NCCN guidelines (Smith et al. 2006; NCCN 2014). Upon recovery, dose adjustments at the start of a subsequent cycle will be based on the lowest platelet and neutrophil values from the previous cycle (see Table 15 and Table 16).

Table 15 Dosing Based on ANC and Febrile Neutropenia—Paclitaxel and Carboplatin

	Dose of Paclitaxel and Carboplatin ANC (Day 1 of each cycle)	
	<1500/μL	≥1500/μL
Febrile neutropenia (regardless of duration)	0	Paclitaxel 150 mg/m^2 Carboplatin AUC 4.5

AUC = area under the concentration–time curve.

Table 16 summarizes dose modifications based on platelet count.

Table 16 Dosing Based on Nadir Platelet Count—Paclitaxel and Carboplatin

	Dose of Paclitaxel and Carboplatin Platelets (Day 1 of each cycle)	
Nadir of Last Course	<100,000/μL	≥100,000/μL
<25,000/μL or <50,000/μL with bleeding or requiring transfusion	0	Paclitaxel = 150 mg/m^2 Carboplatin = AUC 4.5

AUC = area under the concentration–time curve.

All dose reductions for the first episode of neutropenic fever or thrombocytopenia (platelet count < 25,000 or < 50,000 with bleeding or that requires transfusion) are permanent. If a second episode of neutropenic fever or thrombocytopenia requiring dose reduction occurs, another 25% dose reduction of carboplatin and paclitaxel is recommended. Patients who require a third dose reduction will immediately discontinue chemotherapy.

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

Treatment should be delayed for up to 3 weeks until the Day 1 ANC is ≥ 1500/μL and the platelet count is ≥ 100,000/μL. However, if the counts have not recovered in 3 weeks, the patient's chemotherapy will be dose reduced, withheld until adequate neutrophil recovery, or discontinued, according to physician judgment and local standard practice. If chemotherapy is withheld longer than 63 days from the last dose, all chemotherapy should be discontinued.

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 must be 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 schedule will then proceed in the usual sequence.

No dose reductions will be made for anemia. Patients should be supported per the treating physician's institution's guidelines.

5.1.9.2 Gastrointestinal Toxicity

For Grade 3 or 4 gastrointestinal toxicities, treatment should be delayed until resolution to less than or equal to the patient's baseline value. Dose reductions at the start of the subsequent cycle will be based on gastrointestinal toxicities from the dose administered in the preceding cycle. Table 17 provides the relevant dose adjustments for gastrointestinal toxicities.

Table 17 Carboplatin and Paclitaxel Dose Modification Based on Gastrointestinal Toxicities in the Preceding Cycle

Toxicity		Adjusted Carboplatin Dose as % of Previous Dose [a]	Adjusted Paclitaxel Dose as % of Previous Dose [a]
Diarrhea	Grade 3 or 4 [b]	75%	75%
Oral mucositis/stomatitis	Grade 3 or 4	75%	75%
Nausea/vomiting	Grade 3 or 4	75%	75%

AUC = area under the concentration–time curve.

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

[b] And per investigator discretion.

Nausea and/or vomiting should be controlled with adequate anti-emetics. If Grade 3 or 4 nausea/vomiting occurs despite the use of anti-emetics, the dose should be reduced by 25% for the next course. If tolerated, the dose should be increased back to 100% as soon as possible.

If, on Day 1 of any treatment cycle, the patient has oral mucositis/stomatitis, the treatment should be withheld until the oral mucositis/stomatitis is cleared. If the oral mucositis/stomatitis has not cleared in 3 weeks, the patient's chemotherapy will be discontinued. If acute Grade 3 oral mucositis occurs at any time, a 75% dose should be given when the oral mucositis is completely cleared. This is a permanent dose reduction.

5.1.9.3 Hepatic Toxicity (Paclitaxel Only)

No dose adjustment is required in patients with mild hepatic impairment. For patients who develop hepatic toxicity, paclitaxel dose should be withheld until LFTs resolve to Grade $\leq$ 1 prior to subsequent dosing. If paclitaxel is withheld because of hepatic toxicity, carboplatin should also be withheld and administered when the paclitaxel is resumed.

The recommendations for paclitaxel dose reduction based on elevated liver function tests are provided in Table 18.

Table 18 Dose Modifications for Paclitaxel for Hepatic Toxicity

SGOT (AST) Levels		Bilirubin Levels	Paclitaxel Reduction from Starting Dose
$<10\times$ ULN	AND	$\leq 1.25\times$ ULN	No change
$<10\times$ ULN	AND	1.26–2.0 $\times$ ULN	25%
$<10\times$ ULN	AND	2.01–5.0 $\times$ ULN	50%
$>10\times$ ULN	OR	$>5.0\times$ ULN	Discontinue paclitaxel [a]

ULN = upper limit of normal.

Note: Recommendations for paclitaxel dose adjustments are extrapolated from dose adjustments for patients with hepatic impairment at baseline.

[a] Patients with AST $>10\times$ ULN or bilirubin $>5.0\times$ ULN were excluded from clinical studies for lung cancer.

If paclitaxel is withheld, hepatic values must recover to Grade ≤ 1 within 3 weeks or the patient's paclitaxel treatment will be discontinued. No dose reductions for carboplatin will be made for hepatic toxicity.

The investigator should make all efforts to exclude malignant disease progression as a cause of liver enzyme derangement. All study treatment must be discontinued if the disease under investigation has progressed.

5.1.9.4 Cardiovascular Toxicity (Paclitaxel Only)

Cardiac rhythm disturbances have occurred infrequently in patients treated with paclitaxel in clinical studies; however, most patients were asymptomatic, and cardiac monitoring is not required. Transient asymptomatic bradycardia has been noted in as many as 29% of patients. More significant atrioventricular block has rarely been noted. Cardiac events should be managed as follows:

- Asymptomatic bradycardia: no treatment required
- Symptomatic arrhythmia during infusion: Stop paclitaxel infusion, manage arrhythmia according to standard practice. Paclitaxel treatment will be discontinued.
- Chest pain and/or symptomatic hypotension ($<90/60$ mmHg or requires fluid replacement): Stop paclitaxel infusion. Perform an ECG. Give IV diphenhydramine and dexamethasone if hypersensitivity is considered. Also consider epinephrine or bronchodilators if chest pain is not thought to be cardiac. Paclitaxel treatment will be discontinued, and cardiovascular support should be given as appropriate. If appropriate, the advice of a cardiologist should also be sought.

5.1.9.5 Neurologic Toxicity (Paclitaxel Only)

The dose of paclitaxel should be modified as follows for sensory neuropathy.

Table 19 Paclitaxel Dose Modification for Neurologic Toxicity

Toxicity	Paclitaxel Dose Modification
Grade 0	None
Grade 1	None
Grade 2	Withhold treatment until patient recovers to Grade 1 toxicity, then resume treatment at a 25% reduction.
Grade 3 or worse	Withhold treatment until patient recovers to Grade 1 toxicity, then resume treatment at a 50% reduction.

Dose modifications made for neurotoxicity are permanent. If recovery to Grade 1 toxicity does not occur within 3 weeks, the patient's paclitaxel treatment will be discontinued.

5.1.9.6 Allergic Reaction/Hypersensitivity (Paclitaxel Only)

CAUTION: Patients who had a mild to moderate hypersensitivity reaction have been successfully rechallenged, but the administration of prophylactic medication (see below) and intensive monitoring of vital signs is recommended.

- Mild symptoms: Complete paclitaxel infusion. Supervise at bedside. No treatment required.
- Moderate symptoms: Stop paclitaxel infusion. Give IV diphenhydramine 25–50 mg and IV dexamethasone 10 mg. Resume paclitaxel infusion after recovery of symptoms at a low rate, 20 mL/hr for 15 minutes, then 40 mL/hr for 15 minutes, then if no further symptoms, at full-dose rate until infusion is complete. If symptoms recur, stop paclitaxel infusion. Paclitaxel treatment will be discontinued.
- Severe life-threatening symptoms: Stop paclitaxel infusion. Give IV diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. Paclitaxel treatment will be discontinued.

Moderate or severe hypersensitivity reactions should be recorded as an adverse event.

5.1.9.7 Other Toxicities

For any Grade 3 or 4 toxicities not mentioned above, carboplatin or paclitaxel should be withheld until the patient recovers completely or to Grade 1 toxicity. The treatment should then be resumed at 75% dose (permanent dose reduction) for Grade 3 toxicities and 50% of dose (permanent dose reduction) for Grade 4 toxicities. If recovery to Grade 1 toxicity does not occur within 3 weeks, the patient's chemotherapy will be discontinued. For Grade 1 and 2 toxicities, no dose reduction should be made.

For guidelines on the dosing of other study drugs when carboplatin or paclitaxel are withheld, see Section 5.1.6.1.

5.1.10 Potential Overlapping Toxicities

The risk of overlapping toxicities between atezolizumab, bevacizumab, carboplatin, and paclitaxel 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 not be unambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with bevacizumab and these chemotherapeutic agents (e.g., hepatotoxicity) could be exacerbated by the immunostimulatory activity of atezolizumab.

Toxicities should initially be managed according to the recommendations in Section 5.1.7, Section 5.1.8, Section 5.1.9, and the Atezolizumab Investigator's Brochure 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 withheld for a maximum of 105 days beyond the last dose (see Section 5.1.6.2). 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 topical corticosteroids, 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 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 5.3.5.9

- 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 5.3.5.10)
- 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)
- Results in 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:

- Confirmed treatment-emergent autoimmune conditions:

  Pneumonitis

  Hypoxia or dyspnea Grade ≥ 3

  Colitis

  Endocrinopathies: diabetes mellitus, pancreatitis, or adrenal insufficiency

  Vasculitis

  Hepatitis

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

  Systemic lupus erythematosus

  Guillain-Barré syndrome

  Skin reactions: vitiligo, pemphigoid

- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response system, 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 5.3.5.6)
- 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 who was 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 5.4–5.7.

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 treatment, 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 treatment, all serious adverse events and adverse events of special interest, regardless of relationship to study treatment, will be reported until 90 days after the last dose of study treatment or until 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 treatment, 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 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 20 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 20 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

[a] Instrumental activities of daily living refer 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.

[d] Grade 4 and 5 events must be reported as serious adverse events (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 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

For patients receiving combination therapy, 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 Diagnosis versus Signs and Symptoms

For all 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.

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

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

5.3.5.3 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.

5.3.5.4 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.

5.3.5.5 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.

5.3.5.6 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. 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 5.3.5.1) 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 an adverse event of special interest (see Section 5.4.2).

5.3.5.7 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 NSCLC should be recorded only on the StudyDiscontinuation 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, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

During survival follow-up, deaths attributed to progression of NSCLC should be recorded only on the StudyDiscontinuation eCRF.

5.3.5.8 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").

5.3.5.9 Worsening of NSCLC

Events that are clearly consistent with the expected pattern of progression of the underlying disease 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. 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.

5.3.5.10 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

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

Study 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 Study Drug Administration eCRF.

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).

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will

determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

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
- Adverse events of special interest
- Pregnancies

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], *R.N.* (Primary)
Telephone No.: [redacted]
Mobile Telephone No.: [redacted]

Medical Monitor: [redacted], M.D., Ph.D. (Secondary)
Telephone No.: [redacted]
Mobile 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 Treatment 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 emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the 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, regardless of relationship to study treatment, 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 treatment, 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 electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the 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 emailing the form using the fax number or email 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 atezolizumab and/or 6 months after the last dose of bevacizumab or paclitaxel, whichever is later. 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 emailing 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 partner becomes pregnant during the study or within 6 months after the last dose of bevacizumab, paclitaxel, or carboplatin. 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 emailing 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 treatment. *When permitted by the site, the* pregnant partner *would* need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. *If* the authorization has been signed, the investigator *should* submit a Clinical Trial Pregnancy Reporting Form 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 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 should be reported through use of the Study Discontinuation 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 emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email 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 non-serious 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 following reference documents:

- Atezolizumab Investigator's Brochure
- AVASTIN (bevacizumab) Investigator's Brochure

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

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

An 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 III, global, multicenter, open-label study designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin + paclitaxel with and without bevacizumab compared with treatment with carboplatin + paclitaxel + bevacizumab in approximately 1200 patients with Stage IV non-squamous NSCLC in the first-line setting.

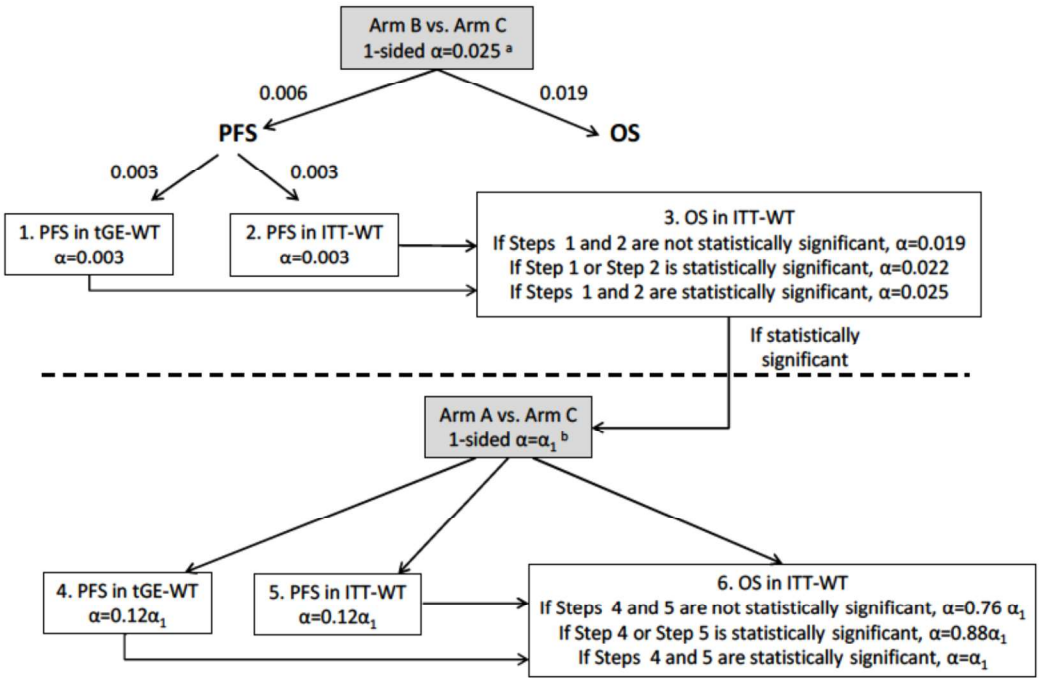
Efficacy analyses will be performed in one or more populations (tGE-WT, ITT-WT, tGE, ITT, TC2/3 or IC2/3 WT, or TC1/2/3 or IC1/2/3 WT) with patients grouped according to the treatment assigned at randomization, regardless of whether they received any assigned study treatment

Safety analyses will be performed on all randomized patients who received any amount of any components of protocol treatment, with patients grouped according to whether any full or partial dose of atezolizumab was received. Specifically, for patients randomized to Arm C, if atezolizumab was received by mistake, the patients would be grouped under Arm B for safety analyses.

6.1 DETERMINATION OF SAMPLE SIZE

The primary endpoint of PFS will be analyzed in the tGE-WT population and in the ITT-WT population, and the primary endpoint of OS will be analyzed in the ITT-WT population. Treatment comparisons will be tested by first comparing Arm B versus Arm C and then comparing Arm A versus Arm C as shown in the α-spending algorithm (see Figure 3). For each comparison, analyses will be conducted according to the α-spending algorithm to control for the type I error rate (see Figure 3) and to account for an interim OS analysis (see Section 6.8.1).The PFS and OS analysis hierarchy and α allocation (Burman et al. 2009), including possibleα recycling, are shown below in Figure 3. A detailed description of the hypothesis testing is provided in Section 6.4.1.

Figure 3 Progression-Free Survival and Overall Survival Analysis Hierarchy, Alpha Allocation, and Alpha Recycling



α_1=type I error passed down to the comparison of Arm A vs. Arm C (i.e., 0.019, 0.022, or 0.025); ITT=intent to treat; OS=overall survival; PFS=progression-free survival; tGE= tumor gene expression; WT=wild type.

[a] To control the overall type I error rate for the one-sided test at 0.025, a one-sided type I error (α) will be allocated to PFS in the tGE-WT population, PFS in the ITT-WT population, and OS in the ITT-WT population in a 3:3:19 ratio for comparison of Arm B versus Arm C.

[b] If the difference in OS between Arm B and Arm C in the ITT-WT population is statistically significant at an α of 0.019, 0.022, or 0.025 (Step 3), that same α will become the overall one-sided type I error rate for the comparison of Arm A versus Arm C, with α allocated to PFS in the tGE-WT population, PFS in the ITT-WT population, and OS in the ITT-WT population at the same 3:3:19 ratio.

This study will enroll approximately 1200 patients. The ITT-WT population will include approximately 1080 patients, assuming a 10% prevalence for sensitizing EGFR mutations or ALK translocations. The tGE-WT population will include approximately 540 patients, assuming a 50% prevalence with the chosen tGE cutoff.

The sample size of this study is based on the number of events required to demonstrate efficacy with regard to both PFS and OS (co-primary endpoints) for the comparison of Arm B versus Arm C.

The estimate of the number of events required to demonstrate efficacy with regard to PFS in the comparison of Arm B versus Arm C is based on the following assumptions:

- One-sided significance level of 0.003 for the comparison of Arm B versus Arm C in the tGE-WT population
- One-sided significance level of 0.003 for the comparison of Arm B versus Arm C in the ITT-WT population
- 98% power to detect an HR of 0.55, corresponding to an improvement in median PFS from 6 months to 10.9 months in the tGE-WT population
- 98% power to detect an HR of 0.65, corresponding to an improvement in median PFS from 6 months to 9.2 months in the ITT-WT population
- No interim analysis for PFS
- Dropout rate of 5% per 12 months

The estimate of the number of events required to demonstrate efficacy with regard to OS in the comparison of Arm B versus Arm C is based on the following assumptions:

- One-sided significance level of 0.019 for the comparison of Arm B versus Arm C in the ITT-WT population
- 87% power to detect an HR of 0.75, corresponding to an improvement in median OS from 12 months to 16 months in the ITT-WT population
- One interim OS analysis performed at the time of the final PFS analysis, at which time approximately 73% of the total number of OS events required for the final analysis are expected to have occurred as determined through use of the Lan-DeMets approximation to the O'Brien-Fleming boundary
- Dropout rate of 5% per 24 months

The estimate of the number of events required to demonstrate efficacy with regard to PFS and OS in the comparison of Arm A versus Arm C is based on assumptions similar to those outlined above for Arm B versus Arm C.

With these assumptions, approximately 1200 patients in total will be enrolled into this study, with approximately 720 patients in each comparison (i.e., Arm B vs. Arm C and Arm A vs. Arm C) in the ITT-WT population. The final PFS analysis will be conducted when both of the following criteria have been met: approximately 516 PFS events have occurred in Arms B and C combined in the ITT-WT population and the last patient has been enrolled in the study. The final PFS analysis is expected to occur approximately 29 months after the first patient is enrolled. At the time of the final PFS analysis, it is expected that approximately 249 events will have occurred in the tGE-WT population. These numbers of events would allow for a minimum detectable difference corresponding to an HR of approximately 0.70 in the tGE-WT population and 0.78 in the ITT-WT population.

With a sample size of 720 patients, approximately 507 OS events are expected to occur in Arms B and C combined in the ITT-WT population for the final OS analysis. The final OS analysis is expected to occur approximately 40 months after the first patient is enrolled. This number of events corresponds to a minimum detectable difference in HR of approximately 0.83 in the ITT-WT population.

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 tGE population, the tGE-WT population, the ITT population, and the ITT-WT population. Major protocol deviations, including major deviations with regard to inclusion/exclusion criteria, will be reported and summarized by treatment arm for the ITT-WT 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 arms for each population (tGE-WT and ITT-WT). Descriptive statistics (mean, median, standard deviation, 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

6.4.1 Co-Primary Efficacy Endpoints

The co-primary efficacy endpoints are PFS as assessed by the investigator according to RECIST v1.1, and OS. PFS will be analyzed in the tGE-WT population and the ITT-WT population. OS will be analyzed in the ITT-WT population. The timing of the final PFS

and OS analyses is described in Section 6.1. At least one interim OS analysis will be performed (see Section 6.8.1).

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 died 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.

OS is defined as the time between the date of randomization and death from any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.

The following analyses will be performed for both PFS endpoints described above and for OS. PFS and OS will be compared between treatment arms with the use of the stratified log-rank test. The HR for PFS and OS for each comparison (i.e., Arm B vs. Arm C and Arm A vs. Arm C) will be estimated using a stratified Cox regression model, respectively. The 95% CI for the HR will be provided.

The stratification factors will be those used during randomization (i.e., sex [male vs. female], presence of liver metastases at baseline [yes vs. no], and PD-L1 tumor expression by IHC [TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1]), as recorded in the IxRS.

Results from an unstratified analysis will also be presented. Kaplan-Meier methodology will be used to estimate the median PFS and the median OS for each treatment arm, and a Kaplan-Meier curve will be constructed to provide a visual description of the difference between treatment arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS and the median OS for each treatment arm (Brookmeyer and Crowley 1982).

Treatment comparisons will be conducted sequentially by first comparing Arm B versus Arm C and then comparing Arm A versus Arm C. For each comparison, analyses will be conducted according to an analysis hierarchy and an α-spending algorithm to control for the type I error rate (see Figure 3 in Section 6.1) and to account for an interim analysis (see Section 6.8.1).

The hypothesis testing will be done in the order described below:

Comparison of Arm B versus Arm C

To control the overall type I error rate for the one-sided test at 0.025, a one-sided type I error (α) will be allocated to PFS in the tGE-WT population, PFS in the ITT-WT

population, and OS in the ITT-WT population in a 3:3:19 ratio for comparison of Arm B versus Arm C

1. PFS in the tGE-WT population will be tested at $\alpha = 0.003$ (one sided). If the estimate of the HR is <1 and the one-sided p-value corresponding to the stratified log-rank test is < 0.003, the null hypothesis will be rejected, and it will be concluded that atezolizumab + carboplatin + paclitaxel + bevacizumab prolongs the duration of PFS relative to the control arm in the tGE-WT population.
2. PFS in the ITT-WT population will be tested at $\alpha = 0.003$ (one sided).
3. α recycling from PFS to OS will be conducted as follows:
    a. If the PFS result is not statistically significant in either the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.019$ (one sided).
    b. If the PFS result is only statistically significant in the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.022$ (one sided).
    c. If the PFS result is statistically significant in both the tGE-WT population and the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.025$ (one sided).

Comparison of Arm A versus Arm C

If the difference in OS between Arm B and Arm C in the ITT-WT population is statistically significant at an α of 0.019, 0.022, or 0.025 (Step 3 above), that same α will become the overall one-sided type I error rate for the comparison of Arm A versus Arm C, with α allocated to PFS in the tGE-WT population, PFS in the ITT-WT population, and OS in the ITT-WT population at the same 3:3:19 ratio (see Figure 3 in Section 6.1). If the difference in OS between Arm B and Arm C in the ITT-WT population is not statistically significant, there will be no formal comparison of Arm A versus Arm C for the co-primary endpoints of PFS and OS.

Depending on the outcome of the PFS testing of Arm A vs. Arm C in the tGE-WT and ITT-WT populations, the α from these two PFS comparisons will be recycled back to the OS comparison in the ITT-WT population for Arm A vs. Arm C.

1. If the difference in OS between Arm B and Arm C is statistically significant at $\alpha = 0.019$ (one sided):
    a. PFS in the tGE-WT population will be tested at $\alpha = 0.00228$ (one sided). If the estimate of the HR is <1 and the one-sided p-value corresponding to the stratified log-rank test is < 0.00228, the null hypothesis will be rejected, and it will be concluded that atezolizumab + carboplatin + paclitaxel prolongs the duration of PFS relative to the control arm in the tGE-WT population.
    b. PFS in the ITT-WT population will be tested at $\alpha = 0.00228$ (one sided)
    c. α recycling from PFS to OS will be conducted as follows:

- If the PFS result is not statistically significant in either the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.01444$ (one sided).
- If the PFS result is only statistically significant in the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.01672$ (one sided).
- If the PFS result is statistically significant in both the tGE-WT population and the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.019$ (one sided).

2. If the difference in OS between Arm B and Arm C is statistically significant at $\alpha = 0.022$ (one sided):
   a. PFS in the tGE-WT population will be tested at $\alpha = 0.00264$ (one sided). If the estimate of the HR is <1 and the one-sided p-value corresponding to the stratified log-rank test is < 0.00264, the null hypothesis will be rejected, and it will be concluded that atezolizumab + carboplatin + paclitaxel prolongs the duration of PFS relative to the control arm in the tGE-WT population.
   b. PFS in the ITT-WT population will be tested at $\alpha = 0.00264$ (one sided).
   c. α recycling from PFS to OS will be conducted as follows:
      - If the PFS result is not statistically significant in either the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.01672$ (one sided).
      - If the PFS result is only statistically significant in the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.01936$ (one sided).
      - If the PFS result is statistically significant in both the tGE-WT population and the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.022$ (one sided).
3. If the difference in OS between Arm B and Arm C is statistically significant at $\alpha = 0.025$ (one sided):
   a. PFS in the tGE-WT population will be tested at $\alpha = 0.003$ (one sided). If the estimate of the HR is <1 and the one-sided p-value corresponding to the stratified log-rank test is < 0.003, the null hypothesis will be rejected, and it will be concluded that atezolizumab + carboplatin + paclitaxel prolongs the duration of PFS relative to the control arm in the tGE-WT population.
   b. PFS in the ITT-WT population will be tested at $\alpha = 0.003$ (one sided).
   c. α recycling from PFS to OS will be conducted as follows:
      - If the PFS result is not statistically significant in either the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.019$ (one sided).

- If the PFS result is only statistically significant in the tGE-WT population or the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.022$ (one sided).
- If the PFS result is statistically significant in both the tGE-WT population and the ITT-WT population, OS in the ITT-WT population will be tested at $\alpha = 0.025$ (one sided).

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Progression-Free Survival and Overall Survival in Secondary Populations

PFS will be analyzed in the TC2/3 or IC2/3 WT population, the TC1/2/3 or IC1/2/3 WT population, the tGE population, and the ITT population, through use of the same methods described for the primary PFS analysis (see Section 6.4.1).

OS will be analyzed in the tGE-WT population, the TC2/3 or IC2/3 WT population, the TC1/2/3 or IC1/2/3 WT population, the tGE population, and the ITT population, through use of the same methods described for the primary OS analysis (see Section 6.4.1).

If the difference in OS between Arm A and Arm C in the ITT-WT population is statistically significant, a comparison of Arm B versus Arm C and a comparison of Arm A versus Arm C will be conducted in the tGE population and the ITT population. The α allocation will follow the same α-spending algorithm and allocation ratio described for analysis of the co-primary efficacy endpoints (see Section 6.4.1).

6.4.2.2 Objective Response Rate

An objective response is defined as either an unconfirmed CR or a PR, as determined by the investigator according to 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 achieved an objective response. ORR will be analyzed in the tGE-WT population and the ITT-WT population. Patients must have measurable disease at baseline to be included in the analysis. 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. The ORR will be compared between the two treatment arms using the stratified Mantel-Haenszel test. The stratification factors of this analysis will be the same as those described in Section 6.4.1.

6.4.2.3 Duration of Response

DOR will be analyzed in the tGE-WT population and the ITT-WT population. DOR will be assessed in patients who achieved an objective response as determined by the investigator according to RECIST v1.1. DOR is defined as the time interval from the

date of the first occurrence of a complete or partial response (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 complete or partial response, DOR will be censored at the date of the first occurrence of a complete or partial response 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.

6.4.2.4 Progression-Free Survival as Assessed by the Independent Review Facility

To support the primary analysis of investigator-assessed PFS, the analysis of PFS as assessed by the IRF will be performed in the tGE-WT population and the ITT-WT population. The methodologies outlined for the primary analysis of PFS per the investigator will be used for the analyses of PFS based on IRF assessment.

6.4.2.5 Overall Survival Rate at Landmark Timepoints

OS rate at 1 and 2 years will be analyzed in the tGE-WT population and the ITT-WT population. The OS rates at 1 and 2 years 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 OS rates between the two treatment arms will be estimated using the normal approximation method.

6.4.2.6 Progression-Free Survival and Overall Survival in the Atezolizumab-Containing Arms

PFS and OS analyses will be performed in the tGE-WT population and the ITT-WT population through use of the same methods described for the primary PFS and OS analyses (see Section 6.4.1.)

6.4.2.7 Patient-Reported Outcomes

TTD in lung cancer symptoms as determined by EORTC and change from baseline in lung cancer symptoms as determined by SILC will be analyzed in the tGE-WT population and the ITT-WT population.

TTD with use of the EORTC is defined as the time from baseline to the first time the patient's score shows a ≥ 10-point increase above baseline in any of the following EORTC-transformed symptom subscale scores (whichever comes first): 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. IA ≥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 with use of the EORTC scale will be analyzed through use of the same methods described for the PFS analysis (See Section 6.4.1).

Change from baseline per SILC scale will be analyzed in patients with a baseline and a post-baseline PRO assessment.

Further details regarding all PRO analyses will be described in the Statistical Analysis Plan (SAP).

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. Data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be handled as described in the sensitivity analysis in Section 6.7.5.4.

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 complete or partial response plus 1 day.

For TTD using 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 include all treated patients, defined as randomized patients who received any amount of any component of study treatment. Safety data will be summarized by treatment arm for treated patients in a primary safety-evaluable population consisting of the ITT-WT population and/or the tGE-WT population (depending on the results of the primary endpoint analyses). Safety data will also be summarized by treatment arm for treated patients not included in the primary safety-

evaluable population. For the safety analyses, patients will be grouped according to whether any amount of atezolizumab was received, including when atezolizumab was received in error. Specifically, patients who were randomized to Arm C but received atezolizumab in error will be grouped under Arm B in the safety analyses.

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

Verbatim description of adverse events will be mapped to MedDRA 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 $\geq$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 treatment period and those reported during the follow-up period after treatment completion/discontinuation will be summarized by treatment arm.

6.6 PHARMACOKINETIC ANALYSES

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

Plasma concentrations of carboplatin and paclitaxel will be collected in this study as outlined in Appendix 2. The concentrations of carboplatin and paclitaxel 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 Time to Response

TTR will be assessed in patients who had an objective response as determined by the investigator according to RECIST v1.1. TTR is defined as the time between the date of randomization and the date of first occurrence of a CR or PR (whichever status is recorded first). No censoring observation will occur by definition. TTR 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. TTR will be analyzed through use of the same methods described for the primary PFS analysis (see Section 6.4.1).

6.7.2 Time in Response

The two treatment arms will be compared with respect to time in response (TIR). Non-responders will be considered as having an event and TIR will be defined as 1 day; for responders, TIR will be same as DOR. TIR will be analyzed through use of the same methods described for the primary PFS analysis (see Section 6.4.1).

6.7.3 Objective Response Rate , and Duration of Response by Independent Review Facility Assessment per RECIST v1.1

The methodologies outlined for the primary and secondary efficacy endpoint analyses will be used for the analyses of ORR and DOR based on IRF assessment.

6.7.4 Objective Response Rate, Progression-Free Survival, and Duration of Responseper Modified RECIST

Analyses using modified RECIST (see Appendix 5) for ORR, PFS, and DOR, as determined by the investigator will also be conducted (Arms A and B only). Comparisons between the two experimental arms (i.e., Arm A vs. B) will be made. The methods outlined for the primary and secondary efficacy endpoint analyses will be used for these analyses.

6.7.5 Exploratory Analyses of Progression-Free Survival

6.7.5.1 Progression-Free Survival Rate at Landmark Timepoints

The PFS rates (e.g., 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 Greenwood's formula. The 95% CIs for the difference in PFS rates between the two treatment arms (i.e., Arm A vs. Arm C and Arm B vs. Arm C) will be estimated using the normal approximation method.

6.7.5.2 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 two treatment arms (i.e., Arm A vs. Arm C and Arm B vs. Arm C) in which data from 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.

6.7.5.3 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, presence of liver metastases at baseline), 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 two treatment arms (i.e., Arm A vs. Arm C and Arm B vs. Arm C).

6.7.5.4 Sensitivity Analyses

Sensitivity analyses 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. The following two imputation rules will be considered:

- If a patient missed two or more scheduled tumor assessments immediately prior to the date of the PFS event according to RECIST v1.1, the patient will be censored at the last tumor assessment prior to the first of these missed visits.
- If a patient missed two or more tumor assessments scheduled immediately prior to the date of the PFS event according to RECIST v1.1, the patient 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 all treatment arms. Statistical methodologies analogous to those used in the primary analysis of PFS as specified in Section 6.4.1 will be used for this sensitivity analysis.

6.7.6 Exploratory Analyses of Overall Survival

6.7.6.1 Loss 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 (i.e., Arm A vs. Arm C and Arm B vs. Arm C) 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.

6.7.6.2 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, presence of liver 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 two treatment arms (i.e., Arm A vs. Arm C and Arm B vs. Arm C).

6.7.6.3 Overall Survival Rate at Three-Year Landmark

The methodologies for landmark OS analysis outlined in Section 6.4.2.5 will be used.

6.7.6.4 Milestone Overall Survival Analysis

To assess the effect of long-term survival and delayed clinical effects, a milestone OS analysis will be conducted (Chen 2015). The milestone OS is an OS endpoint with cross-sectional assessment at a pre-specified timepoint. The milestone OS analysis will be performed using the same methods as those specified for the primary OS analysis and the specific definition of milestone will be documented in the SAP.

6.7.7 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.

6.7.8 EQ-5D-3L Health Status Data

The EQ-5D-3L health status data will be used for obtaining utility measures for economic modeling. These analyses will not be analyzed as an endpoint for the Clinical Study Report.

6.7.9 Patient-Reported Outcome Analyses

Change from baseline with use of the EORTC will be analyzed for patients in the exploratory efficacy analysis populations with a baseline and a post-baseline PRO assessment.

Compliance rates will be summarized by listing the numbers and proportions of patients who completed the PRO assessments at each timepoint by treatment arm. Reasons for non-completion will be summarized if available.

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.

If approximately 370 OS events have occurred in Arms B and C combined in the ITT-WT population at the time of the final PFS analysis (see criteria for final PFS analysis in Section 6.1), an interim OS analysis will be conducted for Arm B versus Arm C in the

ITT-WT population. If there are significantly fewer than the expected 370 OS events at the time of the final PFS analysis, a nominal α of 0.01% (negligible impact on overall type I error rate) will be spent on the OS analysis at the time of the final PFS analysis and a second interim OS analysis will then be conducted after approximately 370 OS events have occurred.

The final OS analysis for the comparison of Arm B versus Arm C will be conducted when approximately 507 OS events have occurred in Arms B and C combined in the ITT-WT population. This is expected to occur approximately 40 months after the first patient is enrolled.

Stopping boundaries for the interim and final OS analyses will be computed through use of the Lan-DeMets approximation to the O'Brien-Fleming boundary. The stopping boundaries for the interim and final OS analyses for the comparison of Arm B versus Arm C in the ITT-WT population, assuming the specified observed number of events (370 and 507, respectively), are provided in Table 21.

Table 21 Analysis Timing and Stopping Boundaries for Overall Survival in the ITT-WT Population: Arm B vs Arm C

Analysis Timing	Stopping Boundary: HR (p-value)		
	If $\alpha = 0.019$	If $\alpha = 0.022$	If $\alpha = 0.025$
Interim OS analysis	HR $\leq$ 0.770 ($p \leq 0.0064$)	HR $\leq$ 0.776 ($p \leq 0.0073$)	HR $\leq$ 0.781 ($p \leq 0.0087$)
Final OS analysis	HR $\leq$ 0.829 ($p \leq 0.0172$)	HR $\leq$ 0.833 ($p \leq 0.0198$)	HR $\leq$ 0.837 ($p \leq 0.0224$)

HR = hazard ratio; ITT = intent to treat; OS = overall survival.

Note: α values and p-values are one-sided. The p-value will be used to claim crossing of a boundary.

If the difference in OS between Arm B and Arm C in the ITT-WT population is statistically significant at an α of 0.019, 0.022, or 0.025, that same α will become the overall one-sided type I error rate for the comparison of Arm A versus Arm C, as described in Section 6.4.1. Stopping boundaries for the interim and final OS analyses will be computed through use of the Lan-DeMets approximation to the O'Brien Fleming boundary. The stopping boundaries for the interim and final OS analyses for the comparison of Arm A versus Arm C in the ITT-WT population, assuming the specified observed number of events (370 and 507, respectively), are provided for the three scenarios ($\alpha = 0.019$, 0.022, or $\alpha = 0.025$) in Table 22.

Table 22 Analysis Timing and Stopping Boundaries for Overall Survival in the ITT-WT Population: Arm A vs Arm C

A. Boundaries if difference in OS between Arm B and Arm C in the ITT-WT population was statistically significant at $\alpha = 0.019$.

Analysis Timing	Stopping Boundary: HR (p-value)		
	If $\alpha = 0.01444$	If $\alpha = 0.01672$	If $\alpha = 0.019$
Interim OS analysis	HR $\leq$ 0.760 ($p \leq 0.0042$)	HR $\leq$ 0.766 ($p \leq 0.0051$)	HR $\leq$ 0.770 ($p \leq 0.006$)
Final OS analysis	HR $\leq$ 0.821 ($p \leq 0.0132$)	HR $\leq$ 0.825 ($p \leq 0.0152$)	HR $\leq$ 0.829 ($p \leq 0.0172$)

B. Boundaries if difference in OS between Arm B and Arm C in the ITT-WT population was statistically significant at $\alpha = 0.022$.

Analysis Timing	Stopping Boundary: HR (p-value)		
	If $\alpha = 0.01672$	If $\alpha = 0.01936$	If $\alpha = 0.022$
Interim OS analysis	HR $\leq$ 0.766 ($p \leq 0.0051$)	HR $\leq$ 0.771 ($p \leq 0.0062$)	HR $\leq$ 0.776 ($p \leq 0.0073$)
Final OS analysis	HR $\leq$ 0.825 ($p \leq 0.0152$)	HR $\leq$ 0.829 ($p \leq 0.0175$)	HR $\leq$ 0.833 ($p \leq 0.0198$)

C. Boundaries if difference in OS between Arm B and Arm C in the ITT-WT population was statistically significant at $\alpha = 0.025$.

Analysis Timing	Stopping Boundary: HR (p-value)		
	If $\alpha = 0.019$	If $\alpha = 0.022$	If $\alpha = 0.025$
Interim OS analysis	HR $\leq$ 0.770 ($p \leq 0.006$)	HR $\leq$ 0.776 ($p \leq 0.0073$)	HR $\leq$ 0.781 ($p \leq 0.0087$)
Final OS analysis	HR $\leq$ 0.829 ($p \leq 0.0172$)	HR $\leq$ 0.833 ($p \leq 0.0198$)	HR $\leq$ 0.837 ($p \leq 0.0224$)

HR = hazard ratio; ITT = intent to treat; OS = overall survival

Note: α values and p-values are one-sided. The p-value will be used to claim crossing of the boundaries.

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.

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 Statistical Analysis Plan (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.

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 U.S. 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. The data from the ePRO devices are available for view access only via secure access to a Web portal provided by 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 ePRO data, audit trail, and study and system documentation will be archived. The Sponsor will receive all data entered by patients on the e-diary and tablet device and all study documentation.

Details regarding patient reported data and the electronic device are available in the Study Reference Manual. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.4 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, patient-reported outcomes, 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, the 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 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. Investigational New Drug (IND) Application will comply with U.S. 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).

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 Forms 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 receiving atezolizumab who wish, if approved by the treating physician, to continue treatment beyond initial radiographic disease progression per RECIST v1.1 and meet criteria specified in Section 4.6.2. This separate consent is to be signed after initial radiographic disease progression per RECIST v1.1 has occurred and patients have discussed other available treatment options and the potential risks of continuing treatment.

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 (HIPAA) of 1996. 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 U.S. 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 or a designee 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 270 sites globally will participate in the study, and approximately 1200 patients will be randomized.

Randomization will occur through 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 Web site:

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 trials 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 trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials 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 to 4 or 6)	Maintenance Phase		Every 3 Months after Disease Progression or Loss of Clinical Benefit
	Days –28 to –1	Every 21 days (± 3 Days) [b]	Every 21 days (± 3 Days)	≤ 30 Days after Last Dose	
Informed consent	x				
Tumor tissue specimen for PD-L1 testing (15 FFPE slides required; blocks preferred) [c] Fresh or archival tissue can be used.	x				
ALK and/or *EGFR* assessment if status is unknown (may be done locally or centrally)	x				
Demographic data	x				
Medical history and baseline conditions	x				
NSCLC cancer history	x				
Vital signs [d]	x	x [d]	x [d]	x [d]	
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	x	x	x	

Appendix 1
Schedule of Assessments (cont.)

Procedure	Screening	All Treatment Cycles [a]		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1 to 4 or 6)	Maintenance Phase		Every 3 Months after Disease Progression or Loss of Clinical Benefit
	Days –28 to –1	Every 21 days (± 3 Days) [b]	Every 21 days (± 3 Days)	≤ 30 Days after Last Dose	
Serum chemistry [h]	x	x	x	x	
Coagulation test (aPTT or INR)	x			x	
Pregnancy test (women of childbearing-potential ONLY)	x [i]	x [j]	x [j]	x [j]	x [x]
TSH, free T3, free T4 [k]	x	x [k]	x [k]	x	
HIV, HBV, HCV serology [l]	x				
Urinalysis [m]	x	x	x	x	
Determination of duration of induction treatment	x				
Induction treatment administration Arm A: Atezolizumab + carboplatin + paclitaxel Arm B: Atezolizumab + carboplatin + paclitaxel + bevacizumab Arm C: Carboplatin + paclitaxel + bevacizumab		x [n]			
Maintenance treatment administration Arm A: Atezolizumab Arm B: Atezolizumab + bevacizumab Arm C: Bevacizumab			x [n]		
Tumor response assessment	x [o]	x [p]	x [p]		x [q]

Appendix 1
Schedule of Assessments (cont.)

Procedure	Screening	All Treatment Cycles [a]		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1 to 4 or 6)	Maintenance Phase		Every 3 Months after Disease Progression or Loss of Clinical Benefit
	Days –28 to –1	Every 21 days (± 3 Days) [b]	Every 21 days (± 3 Days)	≤ 30 Days after Last Dose	
Serum sample for atezolizumab ATA assessment (atezolizumab patients only) [r]		x	x	x	120 (±30) days after last dose of atezolizumab
Serum sample for PK sampling (atezolizumab-treated patients only) [r]		x	x	x	120 (±30) days after last dose of atezolizumab
Carboplatin, paclitaxel, and bevacizumab (Arms B and C) PK sampling (20 patients per arm) [r]		x		x	
Bevacizumab ATA and PK sampling (Arms B and C patients) [r]		x		x	
Blood samples for PD biomarkers [r]	x	x	x	x	120 (±30) days after last dose of atezolizumab
Optional blood for DNA extraction (RCR only) [r, s]		x			
Informed consent to continue treatment beyond radiographic progression (atezolizumab-treated patients)		At time of radiographic progression			
Tumor biopsy		At time of radiographic progression [y]			

Appendix 1
Schedule of Assessments (cont.)

Procedure	Screening	All Treatment Cycles [a]		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1 to 4 or 6)	Maintenance Phase		Every 3 Months after Disease Progression or Loss of Clinical Benefit
	Days –28 to –1	Every 21 days (± 3 Days) [b]	Every 21 days (± 3 Days)	≤ 30 Days after Last Dose	
Optional tumor biopsy at other timepoints (RCR only)		Any time during study treatment or during survival follow-up			
Adverse events	x	x	x	x [t]	x [t]
Concomitant medications	x [u]	x	x	x	
Patient-reported outcomes (EORTC QLQ-C30, EORTC QLQ-LC13, SILC, PGIS, and EQ-5D-3L) [v]		x [v]	x [v]		x [v]
Survival and anti-cancer therapy follow-up					x [w]

ATA = anti-therapeutic antibody; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; ePRO = electronic Patient-Reported Outcome; EQ-5D-3L = Euro QoL5 Dimensions 3-Level Version; FFPE = formalin fixed paraffin embedded; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; IV = intravenous; LC13 = Lung Cancer module; MRI = magnetic resonance imaging; NSCLC = non–small cell lung cancer; PD = pharmacodynamic; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; QLQ-C30 = Quality-of-Life Questionnaire Core 30; RCR = Roche Clinical Repository; SILC = Symptoms in Lung Cancer; TSH = thyroid-stimulating hormone.

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

[b] Cycle 1, Day 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.

Appendix 1
Schedule of Assessments (cont.)

[c] If a representative FFPE tumor specimen in paraffin block (preferred) or 15 or more unstained, freshly cut, serial sections on slides from an FFPE tumor specimen is not available for PD-L1 testing, contact the Medical Monitor to discuss to determine if the patient may participate in the study. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield a cell suspension and/or cell smears), brushing, cell pellets from pleural effusion, and lavage samples are NOT acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation. Retrieval of archival tumor sample can occur outside the 28-day screening period prior to enrollment. Section 4.5.7.1 and Section 4.1.1.

[d] Vital signs include pulse rate, respiratory rate, blood pressures, and temperature. Vital signs should be recorded as described in Section 4.5.4. For all sites in Argentina, pulse oximetry will be performed at every visit and these data will not be recorded.

[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] Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total CO_2, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.

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

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

[k] Thyroid function testing (thyroid-stimulating hormone, free T3, free T4) collected at Cycle 1, Day 1 and every fourth cycle thereafter. Total T3 will be tested only at sites where free T3 is not performed.

[l] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical 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 only if their HBV DNA test is negative. Patients with HCV will be excluded from the study; patients who test positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

[m] Urinalysis by dipstick (specific gravity, pH, glucose, protein, ketones, and blood).

[n] For atezolizumab, the initial dose will be delivered over 60 (±15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes until disease progression per RECIST v1.1 or loss of clinical benefit. For bevacizumab, carboplatin, and paclitaxel, study drug will be administered according to the local prescribing information, including premedication with steroids (see Section 4.3.2).

[o] CT scans (with oral/IV contrast unless contraindicated) or MRI 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.

[p] Perform every 6 weeks (±7 days) (approximately every two cycles) 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 (or loss of clinical benefit for patients assigned to atezolizumab who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. See Section 4.5.5 for details.

[q] If a patient discontinues 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 until radiographic disease progression (or loss of clinical benefit for patients treated with atezolizumab who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first, even if patient starts another anti-cancer therapy after study treatment discontinuation.

[r] See Appendix 2 for the detailed schedule.

[s] 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.

[t] All serious adverse events and adverse events of special interest, regardless of relationship to study treatment, will be reported until 90 days after the last dose of study treatment or initiation of new non-protocol systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. All other adverse events, regardless of relationship to study treatment, will be reported until 30 days after the last dose of study treatment or initiation of new non-protocol systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. After this period, all deaths will 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).

[u] From 7 days before screening.

Appendix 1
Schedule of Assessments (cont.)

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[v] EORTC QLQ-C30, EORTC QLQ-LC13, PGIS, and EQ-5D-3L 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). SILC will be completed using an electronic device at the patient's home on a weekly basis. During survival follow-up, the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-3L will be completed at 3 and 6 months following disease progression (or loss of clinical benefit for atezolizumab-treated patients). The SILC will be completed monthly during survival follow-up for 6 months following disease progression (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1). The PGIS is not required during survival follow-up. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will complete the EORTC QLQ-C30, EORTC QLQ-LC13, PGIS, and EQ-5D-3L at each tumor assessment visit and will complete the SILC at home on a weekly basis, until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression) as determined by the investigator (unless the patient withdraws consent or the Sponsor terminates the study). Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. 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 exempt from all ePRO assessments.

[w] 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.

[x] For Argentina sites only: A urine pregnancy test is required monthly until 6 months after the last dose of study treatment

[y] Mandatory biopsy, if clinically feasible, within 40 days of radiographic progression or prior to the start of the next anti-cancer therapy, whichever is sooner (see Section 4.5.7.2).

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

Study Visit	Time	Arm A (Atezolizumab + Carboplatin + Paclitaxel)	Arm B (Atezolizumab + Carboplatin + Paclitaxel + Bevacizumab)	Arm C (Carboplatin + Paclitaxel + Bevacizumab)
Screening	N/A	• Biomarkers [b]	• Biomarkers [b]	• Biomarkers [b]
Cycle 1, Day 1 [f]	Pre-dose (same day as treatment administration)	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Carboplatin pharmacokinetics [a] • Paclitaxel pharmacokinetics [a] • Biomarkers [d]	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Carboplatin pharmacokinetics [a] • Paclitaxel pharmacokinetics [a] • Bevacizumab pharmacokinetics • Bevacizumab ATA • Biomarkers [d]	• Carboplatin pharmacokinetics[a] • Paclitaxel pharmacokinetics[a] • Bevacizumab pharmacokinetics • Bevacizumab ATA • Biomarkers [d]
	30 min (±10 min) after end of atezolizumab infusion	• Atezolizumab pharmacokinetic	• Atezolizumab pharmacokinetics	
	30 min (±10 min) after end of bevacizumab infusion [a]		• Bevacizumab pharmacokinetics[a]	• Bevacizumab pharmacokinetics[a]
	5–10 min before the end of carboplatin infusion [a]	• Carboplatin pharmacokinetics [a]	• Carboplatin pharmacokinetics[a]	• Carboplatin pharmacokinetics[a]
	1 hr after end of carboplatin infusion [a]	• Carboplatin pharmacokinetics [a]	• Carboplatin pharmacokinetics[a]	• Carboplatin pharmacokinetics[a]
	5–10 min before the end of paclitaxel infusion [a]	• Paclitaxel pharmacokinetics [a]	• Paclitaxel pharmacokinetics[a]	• Paclitaxel pharmacokinetics[a]
	1 hr after end of paclitaxel infusion [a]	• Paclitaxel pharmacokinetics [a]	• Paclitaxel pharmacokinetics[a]	• Paclitaxel pharmacokinetics[a]

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

Study Visit	Time	Arm A (Atezolizumab + Carboplatin + Paclitaxel)	Arm B (Atezolizumab + Carboplatin + Paclitaxel + Bevacizumab)	Arm C (Carboplatin + Paclitaxel + Bevacizumab)
Cycle 2, Day 1 (±3 days)	Pre-dose (same day as treatment administration)	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Biomarkers [d]	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Biomarkers [d]	• Biomarkers [d]
Cycle 3, Day 1 (±3 days)	Pre-dose (same day as treatment administration)	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Carboplatin pharmacokinetics [a] • Paclitaxel pharmacokinetics [a] • Biomarkers [d]	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Carboplatin pharmacokinetics [a] • Paclitaxel pharmacokinetics [a] • Bevacizumab pharmacokinetics • Bevacizumab ATA • Biomarkers [d]	• Carboplatin pharmacokinetics [a] • Paclitaxel pharmacokinetics [a] • Bevacizumab pharmacokinetics • Bevacizumab ATA • Biomarkers [d]
	30 min (±10 min) after end of atezolizumab infusion	• Atezolizumab pharmacokinetic	• Atezolizumab pharmacokinetics	
	30 min (±10 min) after end of bevacizumab infusion [a]		• Bevacizumab pharmacokinetics [a]	• Bevacizumab pharmacokinetics [a]
	5–10 min before the end of carboplatin infusion [a]	• Carboplatin pharmacokinetics [a]	• Carboplatin pharmacokinetics [a]	• Carboplatin pharmacokinetics [a]

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

Study Visit	Time	Arm A (Atezolizumab + Carboplatin + Paclitaxel)	Arm B (Atezolizumab + Carboplatin + Paclitaxel + Bevacizumab)	Arm C (Carboplatin + Paclitaxel + Bevacizumab)
Cycle 3, Day 1 (±3 days) (cont.)	1 hr after end of carboplatin infusion [a]	• Carboplatin pharmacokinetics[a]	• Carboplatin pharmacokinetics[a]	• Carboplatin pharmacokinetics[a]
	5–10 min before the end of paclitaxel infusion [a]	• Paclitaxel pharmacokinetics[a]	• Paclitaxel pharmacokinetics[a]	• Paclitaxel pharmacokinetics[a]
	1 hr after end of paclitaxel infusion [a]	• Paclitaxel pharmacokinetic [a]	• Paclitaxel pharmacokinetics[a]	• Paclitaxel pharmacokinetics[a]
Cycles 4, 8, and 16, Day 1 (±3 days)	Pre-dose (same day as treatment administration)	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Biomarkers [d]	• Atezolizumab ATA • Atezolizumab pharmacokinetic • Biomarkers [d]	• Biomarkers [d]
After Cycle 16 and every eighth cycle, Day 1 (±3 days)	Pre-dose (same day as treatment administration)	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Biomarkers [d]	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Biomarkers [d]	• Biomarkers [d]
At time of fresh biopsy (on-treatment or at progression, including during follow-up)	At visit	• Biomarkers [d]	• Biomarkers [d]	• Biomarkers [d]

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

Study Visit	Time	Arm A (Atezolizumab + Carboplatin + Paclitaxel)	Arm B (Atezolizumab + Carboplatin + Paclitaxel + Bevacizumab)	Arm C (Carboplatin + Paclitaxel + Bevacizumab)
Treatment discontinuation visit	At visit	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Biomarkers [d]	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Bevacizumab pharmacokinetics[e] • Bevacizumab ATA[e] • Biomarkers [d]	• Bevacizumab pharmacokinetics[e] • Bevacizumab ATA[e] • Biomarkers [d]
120 (±30 days) after last dose of atezolizumab	At visit	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Biomarkers [d]	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Biomarkers [d]	
Any time point during study (RCR consent required)		• Optional RCR blood (DNA extraction) [c]	• Optional RCR blood (DNA extraction) [c]	Optional RCR blood (DNA extraction) [c]

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

Notes: Serum PK samples for atezolizumab and bevacizumab; plasma PK samples for carboplatin, and paclitaxel.

All patients in Arm B and C will undergo the additional ATA and PK assessments for bevacizumab at Cycle 1 pre-dose, Cycle 3 pre-dose, and at the time of bevacizumab discontinuation.

[a] At selected centers, 20 patients in each treatment arm will undergo additional PK assessments for carboplatin, paclitaxel, and bevacizumab where applicable.

[b] Whole blood for biomarkers.

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

[d] Plasma and serum for biomarkers.

[e] Bevacizumab PK and ATA are required at time of bevacizumab discontinuation.

f Biomarker sampling before Cycle 1, Day 1 should be performed before patients are treated with the first dose of steroids.

Appendix 3
American Joint Committee on Cancer
Non–Small Cell Lung Cancer Staging, 7th Edition

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS	PATHOLOGIC *Extent of disease through completion of definitive surgery*
☐ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	TUMOR SIZE: _____ LATERALITY: ☐ left ☐ right ☐ bilateral	☐ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)	
☐ TX	Primary tumor cannot be assessed	☐ TX
☐ T0	No evidence of primary tumor	☐ T0
☐ Tis	Tis Carcinoma *in situ*	☐ Tis
☐ T1	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*	☐ T1
☐ T1a	Tumor ≤2 cm in greatest dimension	☐ T1a
☐ T1b	Tumor > 2 cm but ≤3 cm in greatest dimension	☐ T1b
☐ T2	Tumor > 3 cm but ≤7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤ 5 cm) Involves main bronchus, ≥2 cm distal to the carina Invades visceral pleura (PL1 or PL2) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung	☐ T2
☐ T2a	Tumor > 3 cm but ≤5 cm in greatest dimension	☐ T2a
☐ T2b	Tumor > 5 cm but ≤7 cm in greatest dimension	☐ T2b
☐ T3	Tumor > 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (< 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe	☐ T3
☐ T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe	☐ T4
	* The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.	
	REGIONAL LYMPH NODES (N)	
☐ NX	Regional lymph nodes cannot be assessed	☐ NX
☐ N0	No regional lymph node metastasis	☐ N0
☐ N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	☐ N1
☐ N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)	☐ N2
☐ N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)	☐ N3
	DISTANT METASTASIS (M)	
☐ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
☐ M1	Distant metastasis	☐ M1
☐ M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion**	☐ M1a
☐ M1b	Distant metastasis (in extrathoracic organs)	☐ M1b
	**Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.	

Appendix 3
American Joint Committee on Cancer
Non–Small Cell Lung Cancer Staging, 7th Edition (cont.)

ANATOMIC STAGE • PROGNOSTIC GROUPS

	CLINICAL				PATHOLOGIC			
	GROUP	T	N	M	GROUP	T	N	M
❑	Occult	TX	N0	M0	Occult	TX	N0	M0
❑	0	Tis	N0	M0	0	Tis	N0	M0
❑	IA	T1a	N0	M0	IA	T1a	N0	M0
		T1b	N0	M0		T1b	N0	M0
❑	IB	T2a	N0	M0	IB	T2a	N0	M0
❑	IIA	T2b	N0	M0	IIA	T2b	N0	M0
		T1a	N1	M0		T1a	N1	M0
		T1b	N1	M0		T1b	N1	M0
		T2a	N1	M0		T2a	N1	M0
❑	IIB	T2b	N1	M0	IIB	T2b	N1	M0
		T3	N0	M0		T3	N0	M0
❑	IIIA	T1a	N2	M0	IIIA	T1a	N2	M0
		T1b	N2	M0		T1b	N2	M0
		T2a	N2	M0		T2a	N2	M0
		T2b	N2	M0		T2b	N2	M0
		T3	N1	M0		T3	N1	M0
		T3	N2	M0		T3	N2	M0
		T4	N0	M0		T4	N0	M0
		T4	N1	M0		T4	N1	M0
❑	IIIB	T1a	N3	M0	IIIB	T1a	N3	M0
		T1b	N3	M0		T1b	N3	M0
		T2a	N3	M0		T2a	N3	M0
		T2b	N3	M0		T2b	N3	M0
		T3	N3	M0		T3	N3	M0
		T4	N2	M0		T4	N2	M0
		T4	N3	M0		T4	N3	M0
❑	IV	Any T	Any N	M1a	IV	Any T	Any N	M1a
		Any T	Any N	M1b		Any T	Any N	M1b
❑	Stage unknown				Stage unknown			

Reference: Lung. In: Edge S, Byrd DR, Compton CC, et al., editors. AJCC Cancer Staging Manual, Seventh Edition. Chicago: Springer, 2010:267–70.

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 CT or 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 ≥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 ≥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).

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, 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 or MRI (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 baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. 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.

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 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.

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.

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

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).
- 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

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

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.

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.

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

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 Tables 1–3.

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] and immune-related response criteria[4] (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.

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.

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[3] Eisenhauer et al. Eur J Cancer 2009;45: 228–47; Topalian et al. N Engl J Med 2012;366:2443–54; and Wolchok et al., Clin Can Res 2009;15:7412–20.
[4] Wolchok et al. Clin Can Res 2009;15:7412–20; Nishino et al. J Immunother Can 2014;2:17; Nishino et al. Clin Can Res 2013;19:3936–43.

Appendix 5
Modified Response Evaluation Criteria in Solid Tumors (cont.)

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-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 in addition, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance, the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$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 × 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 complete response (i.e., a complete response 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.

Appendix 5
Modified Response Evaluation Criteria in Solid Tumors (cont.)

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 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 $\geq$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 $\geq$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 $\geq$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 complete response criteria are met, because 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
Anti–PD-L1 Immunohistochemistry

OVERVIEW

The Ventana anti–PD-L1 (SP142) rabbit monoclonal primary antibody immunohistochemistry (IHC) assay will be used to determine (PD-L1) IHC status. The anti–PD-L1 (SP142) rabbit monoclonal antibody IHC assay is currently being developed by Ventana Medical Systems as a companion diagnostic to atezolizumab. For Study GO29436, the anti□PD-L1 (SP142) IHC assay will be used for investigational purposes only.

The Ventana anti–PD-L1 (SP142) rabbit monoclonal primary antibody is intended for laboratory use in the semi-quantitative immunohistochemical assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded non–small cell lung carcinoma (NSCLC) tissue stained on a Ventana BenchMark ULTRA automated slide stainer. It is indicated as an aid in the selection of patients with NSCLC with locally advanced or metastatic disease who might benefit from treatment with atezolizumab.

This assay is for investigational use only. The performance characteristics of this product have not been established.

DEVICE DESCRIPTION

The Ventana anti–PD-L1 (SP142) rabbit monoclonal primary antibody is a pre-dilute, ready-to-use antibody product optimized for use with the Ventana Medical Systems OptiView DAB IHC Detection Kit and the OptiView Amplification Kit on Ventana Medical Systems automated BenchMark ULTRA platforms. One 5-mL dispenser of anti–PD-L1 (SP142) rabbit monoclonal primary antibody contains approximately 36 μg of rabbit monoclonal antibody directed against the PD-L1 protein and contains sufficient reagent for 50 tests. The reagents and the IHC procedure are optimized for use on the BenchMark ULTRA automated slide stainer, utilizing Ventana System Software (VSS).

SCORING SYSTEM

PD-L1 staining with anti–PD-L1 (SP142) rabbit monoclonal primary antibody in NSCLC can be observed in both tumor cells and tumor-infiltrating immune cells.

Details of the criteria for PD-L1 diagnostic assessment are described in the IDI document.

Appendix 7
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): 31 ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

Appendix 7
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 8
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 9
EQ-5D-3L

Health Questionnaire

(English version for the US)

Appendix 9
EQ-5D-3L (cont.)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some 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 with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

Appendix 9
EQ-5D-3L (cont.)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

Appendix 10
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 11
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Tourniquet
- 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:

- Stop the study drug infusion.
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
- Maintain an adequate airway.
- Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations

Appendix 12
Preexisting Autoimmune Diseases

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients 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 patients 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 a stable dose of thyroid-replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

Acute disseminated encephalomyelitis	Dermatomyositis	Neuromyotonia
Addison's disease	Diabetes mellitus type 1	Opsoclonus myoclonus syndrome
Ankylosing spondylitis	Dysautonomia	Optic neuritis
Antiphospholipid antibody syndrome	Epidermolysis bullosa acquista	Ord's thyroiditis
Aplastic anemia	Gestational pemphigoid	Pemphigus
Autoimmune hemolytic anemia	Giant cell arteritis	Pernicious anemia
Autoimmune hepatitis	Goodpasture's syndrome	Polyarteritis nodusa
Autoimmune hypoparathyroidism	Graves' disease	Polyarthritis
Autoimmune hypophysitis	Guillain-Barré syndrome	Polyglandular autoimmune syndrome
Autoimmune myocarditis	Hashimoto's disease	Primary biliary cirrhosis
Autoimmune oophoritis	IgA nephropathy	Psoriasis
Autoimmune orchitis	Inflammatory bowel disease	Reiter's syndrome
Autoimmune thrombocytopenic purpura	Interstitial cystitis	Rheumatoid arthritis
Behcet's disease	Kawasaki's disease	Sarcoidosis
Bullous pemphigold	Lambert-Eaton myasthenia syndrome	Scleroderma
Chronic fatigue syndrome	Lupus erythematosus	Sjögren's syndrome
Chronic inflammatory demyelinating polyneuropathy	Lyme disease - chronic	Stiff-Person syndrome
Chung-Strauss syndrome	Meniere's syndrome	Takayasu's arteritis
Crohn's disease	Mooren's ulcer	Ulcerative colitis
	Morphea	Vitiligo
	Multiple sclerosis	Vogt-Kovanagi-Harada disease
	Myasthenia gravis	Wegener's granulomatosis

Appendix 13
Symptoms in Lung Cancer

Symptoms in Lung Cancer (SILC)

Instructions: Please answer the following questions thinking about your lung cancer symptoms over the **past week.**

Item #	Question
1	Over the past week, how would you rate your chest pain at its worst?

- ☐$_0$ No pain at all
- ☐$_1$ Mild pain
- ☐$_2$ Moderate pain
- ☐$_3$ Severe pain
- ☐$_4$ Very severe pain

2 Over the past week, how often did you have chest pain?

- ☐$_0$ Never
- ☐$_1$ Rarely
- ☐$_2$ Sometimes
- ☐$_3$ Often
- ☐$_4$ Always

3 Over the past week, how would you rate your coughing at its worst?

- ☐$_0$ No coughing at all
- ☐$_1$ Mild coughing
- ☐$_2$ Moderate coughing
- ☐$_3$ Severe coughing
- ☐$_4$ Very severe coughing

4 Over the past week, how often did you cough?

- ☐$_0$ Never
- ☐$_1$ Rarely
- ☐$_2$ Sometimes
- ☐$_3$ Often
- ☐$_4$ Always

Appendix 13
Symptoms in Lung Cancer (cont.)

Item #	Question
5	Over the past week, how often did you feel short of breath when lying down or sitting? ☐$_0$ Never ☐$_1$ Rarely ☐$_2$ Sometimes ☐$_3$ Often ☐$_4$ Always
6	Over the past week, how often did you feel short of breath when standing for less than 5 minutes? ☐$_0$ Never ☐$_1$ Rarely ☐$_2$ Sometimes ☐$_3$ Often ☐$_4$ Always
7	Over the past week, how often did you feel short of breath when walking for 2-5 minutes? ☐$_0$ Never ☐$_1$ Rarely ☐$_2$ Sometimes ☐$_3$ Often ☐$_4$ Always
8	Over the past week, how often did you feel short of breath when lifting and carrying a light load? ☐$_0$ Never ☐$_1$ Rarely ☐$_2$ Sometimes ☐$_3$ Often ☐$_4$ Always

Appendix 13
Symptoms in Lung Cancer (cont.)

Item #	Question
9	Over the past week, how often did you feel short of breath when walking up a flight of stairs or hill? ☐$_0$ Never ☐$_1$ Rarely ☐$_2$ Sometimes ☐$_3$ Often ☐$_4$ Always

Appendix 14
Patient Global Impression of Severity

Patient Global Impression of Severity (PGIS)

How would you rate your non-small cell lung cancer at this time?

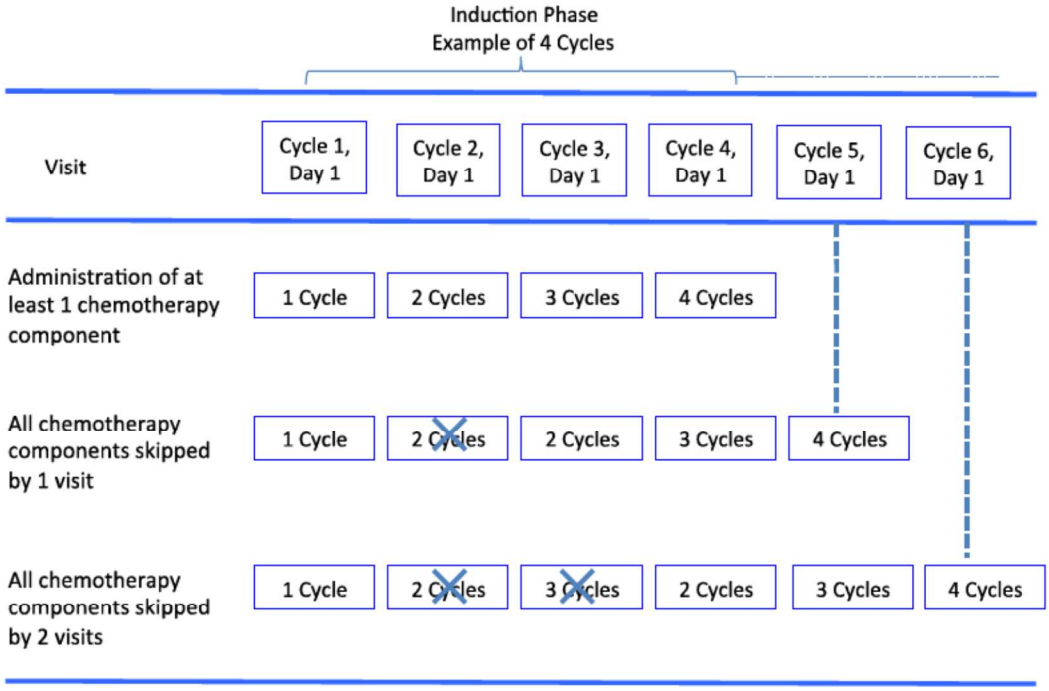
1 ☐ Not severe
2 ☐ Mildly severe
3 ☐ Moderately severe
4 ☐ Very severe
5 ☐ Extremely severe

Appendix 15
Additional Guidance on Chemotherapy Administration

For the purposes of this protocol, the Sponsor defines a chemotherapy cycle as the administration of at least one chemotherapy component. Cycles in which no chemotherapy component is given do not count toward the total number of induction chemotherapy cycles.

In the event that chemotherapy cannot be given, owing to toxicity, atezolizumab and/or bevacizumab should be given if there is no contraindication.

If only atezolizumab and/or bevacizumab but no chemotherapeutic partner has been administered during a cycle in the induction phase, the cycle does not count toward the total number of induction chemotherapy cycles. For example, if four cycles of induction chemotherapy were planned, but no component of chemotherapy could be administered during Cycle 4, Cycle 5 counts as the fourth cycle of induction chemotherapy (as shown



total of two consecutive or a total of three non-consecutive cycles before chemotherapy should be permanently discontinued.

The recommended time window for administration of all study treatment components within a cycle is 3 days. If atezolizumab was given but chemotherapy could not be administered on the same day, and the delay between the first and last component of study treatment would be more than 3 days, the remaining components should be delayed until the next cycle and the chemotherapy induction cycle considered not done.

If it is anticipated that a component of study treatment cannot be administered, it is recommended to delay all study treatment for up to 2 weeks. However, if it is anticipated that chemotherapy will be delayed by more than 2 weeks, then atezolizumab should be a given without chemotherapy, which will be delayed until the next cycle, provided there is no contraindication.

eCRF Data Entry for Recording Interruption and Re-Introduction of Chemotherapy

Because of the complex nature and possible permutations of such dosage interruptions and reintroductions, site personnel should contact the Monitor, and the Monitor will instruct the site on how to open the appropriate visits and electronic Case Report Form (eCRF) so that the site can then record the interruption and reintroduction accordingly on the eCRF.