PROTOCOL

TITLE: **A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) COMPARED WITH A PLATINUM AGENT (CISPLATIN OR CARBOPLATIN) IN COMBINATION WITH EITHER PEMETREXED OR GEMCITABINE FOR PD-L1–SELECTED, CHEMOTHERAPY-NAIVE PATIENTS WITH STAGE IV NON-SQUAMOUS OR SQUAMOUS NON–SMALL CELL LUNG CANCER**

PROTOCOL NUMBER: GO29431

VERSION NUMBER: 10

EUDRACT NUMBER: 2014-003083-21

IND NUMBER: 117296

NCT NUMBER: NCT02409342

TEST PRODUCT: Atezolizumab (MPDL3280A, RO5541267)

MEDICAL MONITOR: [redacted], M.D., Ph.D.

SPONSOR: F. Hoffmann-La Roche Ltd

DATE FINAL: Version 1: 23 December 2014

DATES AMENDED: Version 2: 24 April 2015
Version 3: 5 October 2015
Version 4: 16 December 2015
Version 5: 29 June 2016
Version 6: 14 March 2017
Version 7: 16 April 2018
Version 8: 29 August 2018
Version 9: 14 March 2019
Version 10: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
08-Feb-2020 00:08:16	Company Signatory	[redacted]

CONFIDENTIAL

PROTOCOL AMENDMENT, VERSION 10:
RATIONALE

Protocol GO29431 has been amended to update risks and management guidelines for atezolizumab to align with the latest Atezolizumab Investigator's Brochure (Version 15). Changes to the protocol, along with a rationale for each change, are summarized below:

- The list of atezolizumab risks has been updated to include myositis for consistency with the list of identified risks in the Atezolizumab Investigator's Brochure (Section 5.1.1).
- To align with the Atezolizumab Investigator's Brochure, Version 15, "immune-related" has been changed to "immune-mediated" when describing events associated with atezolizumab (Section 5.1.1 and Appendix 14).
- To address requests by the [redacted], the medical terminology of systemic immune activation has been replaced by hemophagocytic lymphohistiocytosis and macrophage activation syndrome in the list of potential risks for atezolizumab (Section 5.1.1) and management guidelines for hemophagocytic lymphohistiocytosis and macrophage activation syndrome have been added (Appendix 14).
- To address a request by the [redacted], the atezolizumab adverse event management guidelines have been revised to add laboratory (e.g., B-type natriuretic peptide) and cardiac imaging abnormalities as signs or symptoms that are suggestive of myocarditis (Appendix 14).
- The management guidelines for infusion-related reactions associated with atezolizumab have been updated to include guidelines for management of cytokine-release syndrome (Appendix 14).

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

TITLE: **A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) COMPARED WITH A PLATINUM AGENT (CISPLATIN OR CARBOPLATIN) IN COMBINATION WITH EITHER PEMETREXED OR GEMCITABINE FOR PD-L1–SELECTED, CHEMOTHERAPY-NAIVE PATIENTS WITH STAGE IV NON-SQUAMOUS OR SQUAMOUS NON–SMALL CELL LUNG CANCER**

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy to the Sponsor or their designee. Contact details will be provided to the investigator prior to study start.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) COMPARED WITH A PLATINUM AGENT (CISPLATIN OR CARBOPLATIN) IN COMBINATION WITH EITHER PEMETREXED OR GEMCITABINE FOR PD-L1–SELECTED, CHEMOTHERAPY-NAIVE PATIENTS WITH STAGE IV NON-SQUAMOUS OR SQUAMOUS NON–SMALL CELL LUNG CANCER**
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NCT NUMBER:	NCT02409342
TEST PRODUCT:	Atezolizumab (MPDL3280A, RO5541267)
PHASE:	III
INDICATION:	Non–Small Cell Lung Cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

For the primary and secondary efficacy objectives, a comparison of the treatment arms will be performed in randomized patients who are selected on the basis of a minimum level of PD-L1 expression on tumor cells (TCs) and/or immune cells (ICs) (TC1/2/3 or IC1/2/3; corresponding to ≥1% PD-L1 expressing TCs and ≥1% of tumor area occupied by PD-L1 expressing ICs) using a centrally performed immunohistochemistry (IHC) test, with populations excluding patients with a sensitizing EGFR mutation or ALK translocation *(i.e., wild type [WT])*.

Efficacy Objectives

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy consisting of a platinum agent (carboplatin or cisplatin) in combination with either pemetrexed (non-squamous disease) or gemcitabine (squamous disease) in chemotherapy-naive patients with Stage IV non–small cell lung cancer (NSCLC), as measured by overall survival (OS).

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy as measured by investigator-assessed progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors Version 1.1, Version 1.1 (RECIST v1.1)
- To evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy as measured by objective response rate (ORR) according to RECIST v1.1 assessed by investigator
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed duration of response (DOR) according to RECIST v1.1
- To evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy as measured by OS and investigator-assessed PFS according to RECIST v1.1 in patients with PD-L1 expression defined by the SP263 IHC assay

- To evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy as measured by OS and investigator-assessed PFS according to RECIST v1.1 in patients with blood tumor mutational burden (bTMB)
- To evaluate the OS rate at 1- and 2- year landmark timepoints in each treatment arm
- To determine the impact of atezolizumab compared with platinum-based chemotherapy as measured by time to deterioration (TTD) and change from baseline (i.e., improvement or deterioration based on presenting symptomatology) in each of the patient-reported lung cancer symptom (cough, dyspnea, chest pain) score as assessed by the Symptoms in Lung Cancer (SILC) scale
- To determine the impact of atezolizumab compared with platinum-based chemotherapy as measured by TTD in patient-reported lung cancer symptoms of cough, dyspnea (multi-item subscale), and chest pain as measured by the European Organisation for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core (QLQ-C30) and supplementary Quality-of-Life Questionnaire Lung Cancer Module (QLQ-LC13)

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab compared with platinum-based chemotherapy
- 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, pharmacodynamics, safety, and efficacy

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the pharmacokinetics of atezolizumab in chemotherapy-naive patients with Stage IV NSCLC.

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy as measured by OS and investigator-assessed PFS according to RECIST v1.1 in patients with PD-L1 expression measured using the 22c3 PD-L1 IHC assay, but excluding patients with a sensitizing EGFR mutation or ALK translocation
- To evaluate the efficacy of atezolizumab as measured by PFS rates at 6-month and 1-year landmark timepoints
- To evaluate the efficacy of atezolizumab as measured by OS rate at 3-year landmark timepoint in each treatment arm
- To evaluate the efficacy of atezolizumab as measured by OS and investigator-assessed PFS according to RECIST v1.1 in subgroups based on demographic and baseline characteristics
- 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 atezolizumab
- 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 Dimension, 3 Level (EQ-5D-3L) questionnaire to generate utility scores for use in economic models for reimbursement.
- To determine the impact of atezolizumab compared with platinum-based chemotherapy as measured by change from baseline in patient-reported outcomes (PROs) of health-related quality of life, lung cancer related symptoms, and functioning as assessed by the EORTC QLQ-C30 and QLQ-LC13.

Study Design

Description of Study

This is a randomized, Phase III, global, multicenter, open-label study designed to evaluate the safety and efficacy of atezolizumab compared with chemotherapy consisting of a platinum agent (carboplatin *or cisplatin* per investigator discretion) combined with either pemetrexed (non-squamous disease) or gemcitabine (squamous disease) in PD-L1–selected, chemotherapy-naive patients with Stage IV NSCLC.

At screening, tumor specimens from each potentially eligible patient will be tested for PD-L1 expression by a central laboratory using an IHC assay. Only patients who are PD-L1–selected (tumor cell [TC]1/2/3 or tumor-infiltrating immune cell [IC]1/2/3; corresponding to ≥ 1% PD-L1 expressing TCs and ≥ 1% of tumor area occupied by PD-L1 expressing ICs) will be enrolled. Patients with non-squamous disease will be randomized 1:1 to receive either atezolizumab alone or pemetrexed in combination with cisplatin or carboplatin. Patients with squamous disease will be randomized 1:1 to receive either atezolizumab alone or gemcitabine in combination with cisplatin or carboplatin. Randomization will be stratified by sex (male vs. female), Eastern Cooperative Oncology Group (ECOG) Performance Status (0 vs. 1), histology (non-squamous vs. squamous), and PD-L1 tumor expression by IHC (TC1/2/3 and any IC vs. TC0 and IC1/2/3).

Given the toxicities associated with platinum-based chemotherapies (e.g., neutropenia, anemia) and the requirement for pre-medications, this will be an open-label study. No crossover will be allowed from the control arm (platinum-based chemotherapy) to the experimental arm (atezolizumab).

Atezolizumab (fixed dose of 1200 mg) will be administered intravenously on Day 1 of each 21-day cycle. Atezolizumab treatment may continue as long as patients 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) or until unacceptable toxicity or death.

During treatment, patients who are treated with atezolizumab and who show evidence of clinical benefit will be permitted to continue atezolizumab treatment after RECIST v1.1 criteria 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 study treatment at the time of initial radiographic progression per RECIST v1.1

All patients will undergo a mandatory tumor biopsy sample collection, unless not clinically feasible as assessed and documented by investigators, at the first evidence of radiographic disease progression (within 40 days of radiographic progression or prior to the start of the next anti-cancer treatment, whichever is sooner). These data will be used to explore if the radiographic findings are consistent with the presence of tumor or if the appearance of progression was caused by pseudoprogression. In addition, these data will be analyzed for the association between changes in tumor tissue and clinical outcome and to understand further the potential mechanisms of resistance and progression to atezolizumab when compared to such mechanisms after treatment with chemotherapy. This exploratory biomarker evaluation will not be used for any treatment-related decisions. Patients who are unable to undergo biopsy sample collection but otherwise meet criteria listed above may continue to receive atezolizumab.

Patients randomized to receive pemetrexed in combination with either cisplatin or carboplatin (non-squamous disease) will receive chemotherapy intravenously on Day 1 of each 21-day

cycle for four or six cycles, followed by maintenance therapy with pemetrexed. Patients randomized to receive gemcitabine in combination with either cisplatin or carboplatin (squamous disease) will receive cisplatin or carboplatin intravenously on Day 1 and gemcitabine intravenously on Days 1 and 8 of each 21-day cycle for four or six cycles, followed by best supportive care. The intended number of cycles planned for the platinum-based induction chemotherapy (i.e., four or six cycles) will be specified by the investigator prior to study randomization. Treatment will continue until disease progression, unacceptable toxicity, or death.

All patients will undergo tumor assessment at baseline and every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1 regardless of treatment delays. After the completion of the Week 48 tumor assessment, tumor assessment will be required every 9 weeks (± 7 days) 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 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 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 after disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by Sponsor, whichever occurs first. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments should continue regardless of whether patients start a new anti-cancer therapy.

Number of Patients

Approximately 150 sites globally will participate in the study, and approximately 555 PD-L1–selected chemotherapy-naive patients with Stage IV NSCLC will be enrolled.

Target Population

Inclusion Criteria

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

- *Signed Informed Consent Form*
- *Age ≥18 years*
- *ECOG Performance Status of 0 or 1*
- Histologically or cytologically confirmed, Stage IV non-squamous or squamous NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system)

  Patients with tumors of mixed histology must be classified as non-squamous or squamous based on the major histological component.
- No prior treatment for Stage IV non-squamous or squamous NSCLC

  Patients known to have a sensitizing mutation in the EGFR gene or an ALK fusion oncogene are excluded from the study.

  Patients with non-squamous NSCLC who have an unknown EGFR or ALK status will be required to be tested at prescreening/screening. Patients with squamous NSCLC who have an unknown EGFR or ALK status will not be required to be tested at prescreening/screening.

  EGFR and/or *ALK* may be assessed locally or at a central lab. Additional tissue will be required for central testing of *EGFR* and/or *ALK*.
- 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 cycle.

- 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.

- Tumor PD-L1 expression (TC1/2/3 or IC1/2/3; corresponding to $\geq 1\%$ PD-L1 expressing TCs and $\geq 1\%$ of tumor area occupied by PD-L1 expressing ICs), 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. This specimen must be accompanied by the associated pathology report.

    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.

  For freshly collected specimens, resections, core needle biopsies, excisional, incisional, punch, or forceps biopsies are acceptable.

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

  Tumor tissue from bone metastases that have been decalcified is not acceptable.

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

  For patients whose initial archival tumor tissue sample is PD-L1 negative, a biopsy can be performed at screening to submit fresh tissue for the purposes of testing PD-L1 status. A positive test result in any tumor tissue sample will satisfy this eligibility criterion.

- Measurable disease, as defined by RECIST v1.1

  Previously irradiated lesions can only be considered 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 measureable disease

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

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

  Lymphocyte count ≥ 500 cells/μL

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

  Hemoglobin ≥ 9.0 g/dL

    Patients may be transfused to meet this criterion.

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

    This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation must have an INR or aPTT within therapeutic limits for at least 1 week prior to randomization.

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 $\leq 1.5 \times$ ULN

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

Calculated creatinine clearance (CrCl) ≥ 45 mL/min, or if using cisplatin, calculated CrCl ≥ 60 mL/min

- For female patients of childbearing potential and male patients with partners of childbearing potential, agreement to use a highly effective form(s) of contraception during study treatment that results in a low failure rate of <1% per year when used consistently and correctly. Female patients should continue contraception use for 5 months after the last dose of atezolizumab and for 6 months after the last dose of cisplatin. Women must refrain from donating eggs during this same period. Male patients treated with chemotherapy (cisplatin or carboplatin plus pemetrexed or gemcitabine) should continue contraception use for 6 months after the last dose of chemotherapy. Men must refrain from donating sperm during this same period. Such 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 or vasectomized partner (on the understanding that this is the only one partner during the entire study duration), and sexual abstinence.
- 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 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.

Exclusion Criteria

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

Cancer-Specific Exclusions

- Known sensitizing mutation in the EGFR gene or ALK fusion oncogene
- Active or untreated CNS metastases as determined by CT or magnetic resonance imaging 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 loco-regional therapy if appropriate prior to enrollment.

- 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 calcium > 12 mg/dL or corrected serum calcium > ULN)

  Patients who are receiving denosumab prior to randomization must be willing and eligible to discontinue its use and replace it with 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)

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 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 thyroid-replacement therapy are eligible for this study.

  Patients with controlled Type I diabetes mellitus on an 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

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

  No acute exacerbations of underlying condition within the last 12 months requiring treatment with either PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or 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 HIV test

  All patients must be tested for HIV; patients who test positive for HIV will be excluded.
- Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test 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 and absence of HBsAg) are eligible. HBV DNA test must be performed in these patients prior to randomization.

  Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction 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
- 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 transplantation
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk 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

- Treatment with any approved anti-cancer therapy, including hormonal therapy, within 3 weeks prior to initiation of study treatment
- Treatment with any other investigational agent with therapeutic intent within 28 days prior to randomization
- Received therapeutic oral or intravenous (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.
- 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
- 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–cytotoxic T lymphocyte–associated antigen 4 (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-related adverse effects from anti–CTLA-4 (CTCAE Grade 3 or 4)
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons or 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 corticosteroids or other systemic immunosuppressive medications (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor 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 are allowed.

Exclusion Criteria Related to Chemotherapy

- History of allergic reactions to cisplatin, carboplatin, or other platinum-containing compounds
- Patients with hearing impairment (cisplatin)
- Grade ≥2 peripheral neuropathy as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 criteria (cisplatin)
- CrCl <60 mL/min (cisplatin)
- Known hypersensitivity to gemcitabine
- History of radiation therapy within 7 days prior to initiating gemcitabine

Length of Study

The length of the study, from enrollment of the first patient to final analysis, is expected to be approximately 55 months.

End of Study

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

- The required number of deaths for the final analysis of OS has been observed.
- The last patient, last visit has occurred.

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

Outcome Measures

Efficacy Outcome Measures

The primary efficacy outcome measure for this study is OS, defined as the time from randomization to death from any cause.

The secondary efficacy outcome measures for this study are as follows:

- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator with use of RECIST v1.1, or death from any cause, whichever occurs first
- Objective response (partial response plus complete response) as determined by the investigator according to RECIST v1.1
- DOR, defined as the time from the first occurrence of a documented objective response to the time of disease progression, as determined by the investigator with use of RECIST v1.1, or death from any cause, whichever occurs first
- OS at 1- and 2-year landmark timepoints
- TTD and change from baseline (i.e., improvement or deterioration based on presenting symptomatology) in each of the patient-reported lung cancer symptoms (cough, dyspnea, or chest pain) with use of the SILC scale.
- TTD in patient-reported lung cancer symptoms, defined as time from randomization to deterioration (10-point change) in any of the following symptom subscales (cough, dyspnea [multi-item scale], and chest pain), whichever occurs first, as measured by the EORTC QLQ-LC13
- OS and investigator-assessed PFS according to RECIST v1.1 in the PD-L1 (defined with SP263 IHC assay) and bTMB subpopulations

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- 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 as follows:

- Maximum serum atezolizumab concentration observed (C_{max}) after infusion on Day 1 of Cycle 1
- Minimum serum atezolizumab concentration observed (C_{min}) prior to infusion on Day 1 of Cycles 2, 3, 4, 8, 16, and every eighth cycle thereafter, at treatment discontinuation, and at 120 ($\pm$30) days after the last dose of atezolizumab

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- OS and investigator-assessed PFS according to RECIST v1.1 in the PD-L1 (defined with 22c3 assay) subpopulation
- PFS at 6-month and at 1-year landmark timepoints
- OS at 3-year landmark timepoint
- OS and investigator-assessed PFS according to RECIST v1.1 in subgroups based on demographic and baseline characteristics
- Status of immune cell infiltrate and other exploratory biomarkers in mandatory biopsy specimens collected at progression
- 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
- Utility scores of the EQ-5D-3L questionnaire
- Change from baseline in PROs of health-related quality of life, lung cancer-related symptoms, and functioning as assessed by the EORTC QLQ-C30 and QLQ-LC13

Investigational Medicinal Products

Test Product (Investigational Drug)

Atezolizumab, at a dose of 1200 mg, will be administered by IV infusion every 21 days.

Comparator

Non-squamous

The comparator arm includes pemetrexed+cisplatin or carboplatin to be administered every 21 days for four or six cycles at the doses and the suggested infusion times indicated in the table below. Pemetrexed will continue to be administered as maintenance regimen every 21 days.

Pemetrexed plus cisplatin or carboplatin regimen

Study Drug	Dose/Route	Induction Period (Four or Six Cycles)	Maintenance Period (Until PD)
Pemetrexed	500 mg/m^2 IV	Over ~10 minutes on Day 1 q21d	Over approximately 10 minutes on Day 1 q21d
Carboplatin	AUC 6 IV	Over ~30–60 minutes on Day 1 q21d	Not applicable
		OR	
Cisplatin	75 mg/m^2	Over 1–2 hours on Day 1 q21d	Not applicable

AUC = area under the concentration–time curve; IV = intravenous; PD = progressive disease; q21d = every 21 days.

Squamous

The comparator arm includes gemcitabine plus cisplatin or carboplatin to be administered every 21 days for four or six cycles at the doses and the suggested infusion times indicated in the table below.

Gemcitabine plus Cisplatin or Carboplatin Regimen

Chemotherapy	Dose/Route	Treatment (Four or Six Cycles)
Gemcitabine	1250 mg/m^2 IV	Over 30 minutes on Days 1 & 8 q21d
Cisplatin	75 mg/ m^2 IV	Over 1–2 hours on Day 1 q21d
Gemcitabine	1000 mg/m^2 IV	Over 30 minutes on Days 1 & 8 q21d
Carboplatin	AUC 5 IV	Over ~30–60 minutes on Day 1 q21d

AUC = area under the concentration curve; IV = intravenous; q21d = every 21 days.

Statistical Methods

Primary Analysis

The primary efficacy analysis is the comparison of OS between the two treatment arms (atezolizumab arm and chemotherapy control arm).

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

The primary efficacy analysis will be performed for the TC3 or IC3-WT subpopulation, the TC2/3 or IC2/3-WT subpopulation, and the TC1/2/3 or IC1/2/3-WT population.

The null and alternative hypotheses for the OS analysis can be phrased in terms of the survival functions SA(t) and SB(t) in the atezolizumab arm (Arm A) and the control arm (Arm B), respectively:

H0: SA(t) = SB(t) versus H1: SA(t) ≠ SB(t)

The stratification factors will be: sex (male vs. female), ECOG Performance Status (0 vs. 1), histology (non-squamous vs. squamous), and PD-L1 tumor expression status (TC1/2/3 and any IC vs. TC0 and IC1/2/3). Both stratified and unstratified analysis will be performed. Due to the potential risk of over-stratification, if at least 1 stratum (i.e., for the TC1/2/3 or IC1/2/3 population, a combination of stratification factor levels across sex, ECOG performance status, histology, and PD-L1 tumor expression status per IxRS; for the TC3 or IC3 population and the TC2/3 or IC2/3 population, a combination of stratification factor levels across sex, ECOG performance status, and histology per IxRS) has less than 10 OS events, the stratification factor

(1 of 4 stratification factors for the TC1/2/3 or IC1/2/3 population: sex, ECOG performance status, histology, and PD-L1 tumor expression by IHC per IxRS; 1 of 3 stratification factors for the TC3 or IC3 population and the TC2/3 or IC2/3 population: sex, ECOG performance status, and histology per IxRS) which contains the level with the smallest number of patients will be removed from the stratified analyses. The removal of the stratification factor will continue until there is no stratum with less than 10 OS events in the analysis population. The final set of stratification factors used in the stratified analyses of OS for a specific analysis population (e.g., TC2/3 or IC2/3) will be applied to all other efficacy endpoints where stratified analyses are planned for the same analysis population.

The hazard ratio (HR) will be estimated using a stratified Cox regression model at the time of both the interim and final analyses.

The unstratified HR will also be presented. Kaplan-Meier methodology will be used to estimate the median OS for each treatment arm and to construct survival curves for the visual description of the difference between the treatment arms. The Brookmeyer-Crowley methodology will be used to construct a 95% CI for the median OS for each treatment arm.

A group sequential design will be used for testing OS to account for the conduct of the interim analysis, which is expected to occur approximately 40 months after the first patient is enrolled in the study. Details on the hypothesis testing will be provided in the Statistical Analysis Plan (SAP). On the basis of emerging external data, the testing strategy may be modified to improve the efficiency of the design. Should this occur, modifications to the testing strategy will be documented in the SAP prior to any unblinding of the data.

Determination of Sample Size

A total enrollment of approximately 555 patients was planned for this study such that approximately 64% of those enrolled would be PD-L1 TC2/3 or IC2/3 patients.

The overall type I error rate will be controlled at a two-sided alpha-level of 0.05. Comparisons with respect to the primary endpoint of OS between treatment arms will be tested in a hierarchical fashion for the following populations: TC3 or IC3-WT, TC2/3 or IC2/3-WT, and TC1/2/3 or IC1/2/3-WT.

Estimates of the number of events required to demonstrate efficacy in terms of OS are based on the following assumptions:

- 1:1 randomization ratio
- One interim analysis of OS in the TC3 or IC3-WT, TC2/3 or IC2/3-WT, and TC1/2/3 or IC1/2/3-WT populations, with stopping boundaries determined by the Lan-DeMets approximation to the Pocock boundaries
- Two-sided significance level of 0.05
- 99% power to detect a HR of 0.45 for OS in the TC3 or IC3-WT subpopulation, 85% power to detect a HR of 0.65 for OS in the TC2/3 or IC2/3-WT subpopulation, and 77% power to detect a HR of 0.75 for OS in the TC1/2/3 or IC1/2/3-WT population
- Median survival of 14 months in the control arm (platinum-based chemotherapy)
- Event times exponentially distributed
- Dropout rate assumed for all treatment arms of 5% per 24 months
- [redacted]

With these assumptions, the final OS analysis will be conducted when approximately 135 deaths have occurred in the TC3 or IC3-WT subpopulation.

Interim Analyses

Because of a lack of the final PD-L1 prevalence, an interim analysis of OS in the TC3 or IC3-WT population will be conducted when both of the following criteria have been met:

- An approximately 45% event–patient ratio has been observed in the TC3 or IC3-*WT* subpopulation
- Approximately 96 deaths have occurred in the TC3 or IC3-*WT* subpopulation

At this timepoint, it is expected that approximately 154 OS events will have occurred in the TC2/3 or IC2/3-WT population. If the OS interim analysis in the TC3 or IC3-WT population is claimed as statistically significant, the OS analysis in the TC2/3 or IC2/3 WT population will be conducted with the stopping boundaries for the interim and final analyses calculated using the Lan-DeMets approximation to the Pocock boundaries. If there are significantly fewer than 154 OS events (i.e., <135 events) at the TC3 or IC3 WT interim analysis, a nominal two-sided alpha of 0.0001 (negligible impact on overall type I error rate) will be spent on the OS analysis in the TC2/3 or IC2/3-WT population at the time of the TC3 or IC3-WT interim analysis. The next interim and final OS analysis in the TC2/3 or IC2/3-WT population will be conducted when approximately 154 and 216 events are observed, respectively, with the stopping boundaries calculated in the same manner as above. The interim and final analyses of OS in the TC1/2/3 or IC1/2/3-WT population would be conducted at the same time as those for the TC2/3 or IC2/3-WT population.

The interim analysis is expected to occur approximately 40 months after the first patient is enrolled in the study.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
anti-HBc	antibody to hepatitis B core antigen
ASCO	American Society of Clinical Oncology
ATA	anti-therapeutic antibody
AUC	area under the concentration–time curve
BSC	best supportive care
bTMB	blood tumor mutational burden
C_{max}	maximum serum concentration observed
C_{min}	minimum serum concentration observed
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form
CT	computed tomography
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T lymphocyte–associated antigen 4
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	EuroQoL 5 Dimension, 3 Level
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GFR	glomerular filtration rate
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
HRQoL	health-related quality of life

Abbreviation	Definition
IC	tumor-infiltrating immune cell
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug application
IRB	Institutional Review Board
IRF	Independent Review Facility
ITT	intent to treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IxRS	interactive Web/voice response system
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PUVA	psoralen plus ultraviolet A radiation
q21d	every 21 days
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
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SILC	Symptoms in Lung Cancer

Abbreviation	Definition
TC	tumor cell
TMB	tumor mutational burden
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
TTD	time to deterioration
TTF-1	thyroid transcription factor−1
ULN	upper limit of normal
WT	wild type

1. BACKGROUND

1.1 NON–SMALL CELL 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. 2014). 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) of NSCLC. 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 biomarkers 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* gene, the rearrangement in the *ALK* gene, 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). The *ALK* fusion oncogene, recognized as a driver of lung tumorigenesis, is very rare in the squamous histology but observed in approximately 7% of patients with adenocarcinoma (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).

1.2 FIRST-LINE TREATMENT FOR NON–SMALL CELL LUNG CANCER WITHOUT AN *EGFR* MUTATION OR *ALK* REARRANGEMENT

Patients with previously untreated 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 trial, 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).

The benefit conferred by platinum-based chemotherapy regimens appears to have reached a plateau in objective response rate (approximately 15%–22%) and median survival (7–10 months). More recently, the addition of bevacizumab to carboplatin and paclitaxel 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).

Despite the limited survival benefit conferred by cytotoxic chemotherapy, 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, standard of care is a platinum doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. However, well-designed clinical trials conducted over the last decade have demonstrated that pemetrexed and bevacizumab are not appropriate agents for the treatment of patients with squamous-cell carcinoma of the lung (Johnson et al. 2004; Scagliotti et al. 2008; Sandler et al. 2009). The combination of gemcitabine and a platinum analog (either cisplatin or carboplatin) has demonstrated efficacy as first-line treatment for squamous NSCLC and, as a result, is often a reference arm in clinical trials to evaluate new therapeutics (Schiller et al. 2002; Treat et al. 2010).

Overall, 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 NSCLC.

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. In this study, median progression-free survival (PFS) was 10.3 months in the pembrolizumab group versus 6.0 months in the chemotherapy group (hazard ratio [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. Although the median OS was not reached in either group, OS benefit was observed with the treatment of pembrolizumab (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 as a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression (tumor proportion score $\geq 50\%$) with no EGFR or ALK genomic tumor 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

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.

1.2.1 Platinum-Based Regimen for First-Line Non–Small Cell Lung Cancer

Several meta-analyses have compared the use of cisplatin and carboplatin as treatments for NSCLC. In general, although the objective response rate (ORR) was higher in patients treated with cisplatin than in those treated with carboplatin, the 1-year and OS rates were comparable. When given in combination with a third-generation chemotherapy, cisplatin may result in longer survival than carboplatin, but overall benefit was quite marginal (Hotta et al. 2004; Ardizzoni et al. 2007), and subgroup analyses including additional, more recent trials indicate that there may be no difference between the two agents (Azzoli et al. 2009; Jiang et al. 2007).

Cisplatin-based chemotherapy has been associated with more severe nausea and vomiting and nephrotoxicity, while severe thrombocytopenia has been more frequent during carboplatin-based chemotherapy (Hotta et al. 2004; Ardizzoni et al. 2007). The risk of treatment-related deaths was greater in the cisplatin arm, but this increase was not statistically significant (Jiang et al. 2007).

Currently, the standard of care for newly diagnosed advanced stage non-squamous NSCLC is a platinum doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. In particular, the combination of platinum doublet with pemetrexed has been used more widely because of a better tolerability and safety profile. Currently, the standard of care for newly diagnosed advanced–stage squamous NSCLC includes gemcitabine in combination with a platinum agent.

1.2.2 Pemetrexed plus Platinum Compounds in First-Line Non-Squamous Non–Small Cell Lung Cancer

Two Phase II studies demonstrated that the combination of pemetrexed and carboplatin is tolerable and that its activity in first-line treatment of advanced-stage NSCLC is comparable with other standard platinum doublets commonly used in clinical practice (Kelly et al. 2001; Scagliotti et al. 2002; Fossella et al. 2003; Reck et al. 2010). The toxicity profile of the pemetrexed plus carboplatin combination appears to be more favorable than that seen with other standard regimens in first-line NSCLC.

A Phase III non-inferiority study compared the efficacy of cisplatin/pemetrexed (n = 862) versus cisplatin/gemcitabine (n = 863) in patients with incurable Stage IIIB or IV NSCLC who had received no prior chemotherapy. Median OS, PFS, and time to progression were comparable between the two treatment groups. However, among patients who had adenocarcinoma or large-cell carcinoma, patients treated with cisplatin/pemetrexed had significantly better median OS than patients treated with cisplatin/gemcitabine (12.6 vs. 10.9 months for adenocarcinoma; [HR = 0.84; 95% CI: 0.71, 0.99; p = 0.03]); 10.4 vs. 6.7 months for large-cell carcinoma [HR = 0.67; 95% CI: 0.48, 0.96; p = 0.03]) (Scagliotti et al. 2008). Therefore, in this study, patients with non-squamous NSCLC

randomized to the control arm will receive pemetrexed in combination with a platinum agent.

1.2.2.1 Pemetrexed Maintenance Therapy in Non–Squamous Non–Small Cell Lung Cancer

A Phase III randomized, double-blind, placebo-controlled study explored the use of pemetrexed as switch maintenance in first-line patients with NSCLC after four cycles of induction therapy using one of six standard platinum doublets (gemcitabine, paclitaxel, or docetaxel with either carboplatin or cisplatin). Patients who achieved a complete response (CR), partial response (PR), or stable disease were then randomized to maintenance therapy with pemetrexed plus BSC or placebo plus BSC until progression (Ciuleanu et al. 2009). A significant improvement in PFS was reported for patients who received pemetrexed maintenance therapy compared with those who received placebo (4.04 vs. 1.97 months; unadjusted HR = 0.50; 95% CI: 0.42, 0.61; $p < 0.00001$). In patients with non-squamous histology, the median PFS for patients receiving pemetrexed versus placebo was 4.5 months versus 2.6 months (unadjusted HR = 0.44; 95% CI: 0.36, 0.55; $p < 0.00001$). The median follow-up for OS was 11.2 months for patients in the pemetrexed group and 10.2 months for those receiving placebo. The median OS following induction chemotherapy in the overall study population was 13.4 months with pemetrexed and 10.6 months with placebo (unadjusted HR = 0.798; 95% CI: 0.65, 0.95; p = 0.012). In the non-squamous population, the median OS was 15.5 months for pemetrexed-treated patients and 10.3 months for patients who received placebo (unadjusted HR = 0.70; 95% CI: 0.56, 0.88; p = 0.002).

A second study also explored the value of pemetrexed in the continuous maintenance setting. In this study, patients who had not received prior treatment for lung cancer received four cycles of pemetrexed + cisplatin. Maintenance therapy was continued if stable disease, a PR, or a CR was documented. Patients were then randomized in a 2:1 fashion to either pemetrexed plus BSC or placebo plus BSC. The median PFS in patients who received pemetrexed was 4.1 months (range 3.2–4.6 months) compared with a median PFS of 2.8 months (range 2.6–3.1 months) in patients who received placebo. The HR for PFS as assessed by the investigator was 0.62 (95% CI: 0.49, 0.79; p = 0.00006). The PFS benefit was internally consistent, and benefit was seen across all clinically important subgroups. OS data from this trial are pending (Paz-Ares et al. 2012).

1.2.3 Gemcitabine plus Platinum Compounds in First-Line Squamous Non-Small Cell Lung Cancer

Although median OS, PFS, and time to progression were comparable between the cisplatin/pemetrexed versus cisplatin/gemcitabine treatment groups in the Phase III non-inferiority study referenced above (Scagliotti et al. 2008) in patients with incurable Stage IIIB or IV NSCLC who had received no prior chemotherapy, there was an improvement in survival with cisplatin/gemcitabine compared with cisplatin/pemetrexed in patients with squamous-cell carcinoma (10.8 vs. 9.4 months; HR = 1.23; 95% CI: 1.00,

1.51; p = 0.05). Therefore, in this study, patients with squamous NSCLC randomized to the control arm will receive gemcitabine in combination with a platinum agent.

1.3 FIRST-LINE TREATMENT FOR 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 (mainly non-squamous histology) 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 trials of gefitinib (IPASS), erlotinib (EURTAC), and afatinib (Lux-Lung 3) showed significant improvement of PFS and ORR compared with platinum doublet chemotherapy (Fukuoka et al. 2011; Rosell et al. 2012; Yang et al. 2012; 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; Shaw and Engelman 2014; Xalkori® U.S. Package Insert).

In the Phase III GO28915 (OAK) study evaluating the efficacy and safety of atezolizumab versus docetaxel in patients with previously treated locally advanced or metastatic NSCLC, OS was similar between the atezolizumab and docetaxel arms in patients with an EGFR mutation (HR = 1.24; 95% CI: 0.71, 2.18) (Rittmeyer et al. 2017). Consistent results were observed with the PD-1 inhibitors nivolumab and pembrolizumab (Borghaei et al. 2015; Herbst et al. 2016).

1.4 BACKGROUND ON ATEZOLIZUMAB (MPDL3280A)

Atezolizumab (MPDL3280A) is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human PD-L1 and inhibits its interaction with its receptors, PD-1 and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells.

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

1.4.1 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 trials in patients.

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

1.5 CLINICAL EXPERIENCE WITH ATEZOLIZUMAB

Refer to the Atezolizumab Investigator's Brochure for details on all clinical studies conducted to date.

1.5.1 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 include, but are not limited to, 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 every 21 days (q21d) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies
- Study GO28753 (POPLAR): A randomized, Phase II, open-label study assessing the clinical benefit of atezolizumab as a single agent versus docetaxel in patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen

- 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 GO28754 (BIRCH): A Phase II, open-label study assessing the clinical benefit of atezolizumab as a single agent in patients with PD-L1–selected (i.e., selected on the basis of a predefined level of PD-L1) locally advanced or metastatic NSCLC representing all lines of therapy (previously untreated to heavily pretreated patients with exposure to multiple prior regimens) level

1.5.2 Clinical Safety

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

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

The safety profile of atezolizumab as a single agent is observed to be consistent across different indications. The most common cancer types for these patients include NSCLC, urinary bladder cancer, melanoma, and renal cell carcinoma. Safety data for NSCLC are also derived from Studies GO28753 (POPLAR), GO28915 (OAK), and GO28754 (BIRCH).

1.5.2.1 Single-Agent Clinical Safety in Patients with Non–Small Cell Lung Cancer in Study PCD4989g

Of the 558 patients in Study PCD4989g, 520 patients (93.2%) experienced at least one adverse event, including 376 patients (67.4%) who experienced one treatment-related adverse event. Commonly reported events (reported in ≥ 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 4.0 [NCI CTCAE v4.0]), were reported in 239 patients (42.8%), with 66 patients (11.8%) experiencing treatment-related adverse events. Grade 3 or 4 adverse events considered related by the investigator included dyspnea, pneumonitis, increased ALT, increased AST, increased γ-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 the adverse events observed in patients treated with atezolizumab.

1.5.2.2 Single-Agent Clinical Safety in Patients with Non–Small Cell Lung Cancer 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 3 weeks (Q3W) (n = 142) or docetaxel 75 mg/m^2 IV Q3W (n = 135). The frequency of patients in Study GO28753 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 Adverse Events Reported in at Least 10% of Patients in Study GO28753 (POPLAR)

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.

1.5.2.3 Single-Agent Clinical Safety in Patients with Non–Small Cell Lung Cancer in Study GO28915 (OAK)

As of the 7 July 2016 data cutoff date for the primary analysis, 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 a between-arm difference in 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	3.0%	10.0%
Musculoskeletal pain	10.5%	4.3%
Pruritus	8.2%	3.1%

Source: Rittmeyer et al. 2017.

1.5.2.4 Single-Agent Clinical Safety in Patients with Non–Small Cell Lung Cancer in Study GO28754 (BIRCH)

As of the 28 May 2015 data cutoff date for the primary analysis, 659 patients were evaluable for safety. Table 5 shows the overall safety findings in Study GO28754.

Table 5 Adverse Events Reported in Study GO28754 (BIRCH)

Parameter	No. of Patients (%)			
	Cohort 1 1L (n = 139)	Cohort 2 2L (n = 267)	Cohort 3 3L+ (n = 253)	All Patients (n = 659)
All-cause AEs	91%	92%	96%	94%
All-cause Grade 3–4 AEs	40%	37%	39%	38%
Related adverse event	57%	63%	69%	64%
Related Grade 3–4 AEs	9%	12%	11%	11%
AE leading to withdrawal from treatment	6%	6%	4%	5%
Related Grade 5 (fatal) AE	0	0	0.4%[a]	0.2%

1L = first line; 2L = second line; 3L = third line; AE = adverse event.

[a] One Grade 5 treatment-related event (pneumonia).

Adapted from Besse et al. 2015.

The most commonly reported adverse events (all grade) were fatigue, diarrhea, and nausea. The adverse event profile observed in Study GO28754 is consistent with that observed in Study PCD4989g (overall and NSCLC populations), as well as with the atezolizumab arm in Studies GO28753 (POPLAR) and GO28915 (OAK).

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

1.5.2.5 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 regarding immune-mediated adverse events observed in patients treated with atezolizumab.

1.5.3 Clinical Activity

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

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

1.5.3.1 Single-Agent Clinical Activity in Patients with Non–Small Cell Lung Cancer in Study PCD4989g

As of the clinical data cutoff date of 2 December 2014, the safety and efficacy evaluable population included 88 patients with locally advanced or metastatic NSCLC. The median age was 60.5 years (range from 24 to 84 years) and represented a heavily pretreated patient population in that 97.7% of the patients had received ≥ 2 prior systemic therapies and 77.3% of the patients had received ≥ 4 prior systemic therapies.

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

Table 6 displays the confirmed ORR, duration of 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 cells (TCs) and tumor-infiltrating immune cells (ICs) for PD-L1 expression on baseline tumor tissue from NSCLC patients have been performed. Higher ORRs were associated with higher PD-L1 expression.

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

Table 6 Patients with Non–Small Cell Lung Cancer 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 v1.1)

PD-L1 IHC Expression Category	ORR by RECIST, v1.1 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; IHC = immunohistochemistry; NSCLC = non–small cell lung cancer; ORR = objective response rate; PFS = progression-free survival; 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 2 Dec 2014 of NSCLC patients. ORR includes confirmed responses. "+" denotes a censored value.

1.5.3.2 Single-Agent Clinical Activity in Patients with Non–Small Cell Lung Cancer 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 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 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) (see Table 7). Objective responses with atezolizumab were durable, with a median duration of 14.3 months (95% CI: 11.6 months, not estimable) compared with 7.2 months (95% CI: 5.6, 12.5 months) for docetaxel (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%

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 NCSLC.

1.5.3.3 Single-Agent Clinical Activity in Patients with Non–Small Cell Lung Cancer in Study GO28915 (OAK)

The co-primary endpoints of 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).

1.5.3.4 Single-Agent Clinical Activity in Patients with Non–Small Cell Lung Cancer in Study GO28754 (BIRCH)

Primary Efficacy Analysis

The primary analysis of Study GO28754 (BIRCH) was performed approximately 6 months after the last patient was enrolled (clinical cutoff 28 May 2015; Besse et al. 2015). Independent Review Facility (IRF)-assessed ORR by line of therapy is shown in Table 9.

Table 9 Study GO28754 (BIRCH) Independent Review Facility-Assessed Objective Response Rate: Treated Population

Primary Efficacy Endpoint IRF-ORR per RECIST v1.1	Cohort 1 (1L) N = 139	Cohort 2 (2L) N = 267	Cohort 3 (3L+) N = 253
All treated patients (TC2/3 or IC2/3)	n = 139	n = 267	n = 253
Responders (%)	27 (19.4%)	46 (17.2%)	44 (17.4%)
95% CI	13.2, 27.0	12.9, 22.3	12.9, 22.6
TC3 or IC3 patients	n = 65	n = 122	n = 115
Responders (%)	17 (26.2%)	29 (23.8%)	31 (27.0%)
95% CI	16.0, 38.5	16.5, 32.3	19.1, 36.0

1L = first line; 2L = second line; 3L = third line; IC = tumor–infiltrating immune cell; IRF = independent review facility; ORR = objective response rate; RECIST = Response Evaluation Criteria in Solid Tumors; TC = tumor cell.

Source: Besse et al. 2015.

The study met its primary objective of demonstrating a statistically significant and clinically meaningful ORR assessed by IRF per RECIST v1.1 compared with historical control groups (ORR range, 5%–15%) in the seven pre-specified subpopulations (p = 0.0001). At the clinical cutoff, more than 58% of responders assessed by IRF per

RECIST v1.1 had an ongoing response in each line of therapy and each PD-L1 expression level. The estimated median DOR was 8.4 months in the TC2/3 or IC2/3 patients although follow-up is limited. At the time of the primary analysis, OS data were not yet mature.

Updated Efficacy Analysis for Patients Receiving First-Line Treatment (Cohort 1)

An updated efficacy analysis (1 August 2016 data cutoff date) conducted for 138 patients receiving first-line treatment (Cohort 1) with a minimum follow-up of 22.5 months, provided evidence of a clinically meaningful benefit of atezolizumab as first-line treatment for patients with NSCLC, as demonstrated by a median OS of 23.5 months for all patients (TC2/3 or IC2/3). As shown in Table 10, ORR was 25% (95% CI: 18%, 33%) and median PFS was 7.3 months (95% CI: 5.7, 9.7 months) for all patients (TC2/3 or IC2/3) (Garassino et al. 2016).

Table 10 Study GO28754 (BIRCH) Efficacy Results for First-Line Treatment of PD-L1–Selected Patients with NSCLC

	No. of Patients	ORR, % (95% CI)	Median DOR, months (95% CI)	Median PFS, months (95% CI)	Median OS, months (95% CI)
All treated patients (TC2/3 or IC2/3)	138	25 (18, 33)	16.5 (9.9, NE)	7.3 (5.7, 9.7)	23.5 (18.1, NE)
TC3 or IC3 patients	65	34 (23, 47)	NE (8.5, NE)	7.3 (4.9, 12,0)	26.9 (12.0, NE)

CI = confidence interval; DOR = duration of response; IC = tumor-infiltrating immune cell; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TC = tumor cell.

Notes: The data cutoff date is 1 August 2016.

ORR, DOR, and PFS data are based on investigator assessment.

1.5.4 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 and the mean volume of distribution at steady state had a range of 3.11–4.14 mL/kg and 48.1–67.0 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

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

between the detection of ATAs and adverse events or infusion reactions has been observed.

1.5.5 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 mg/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 q21d 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 q21d regimen (or fixed-dose equivalent). From inspection of available observed C_{trough} data, moving further to the 20-mg/kg atezolizumab q21d regimen does not appear to be warranted to maintain targeted C_{trough} levels relative to the proposed 15-mg/kg atezolizumab q21d 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.

1.6 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

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

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

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

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. In Study PCD4989g, a Phase Ia dose-escalation and expansion study, objective responses with atezolizumab monotherapy were observed in a broad range of malignancies. 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. Additionally, there was a clinically meaningful benefit observed with atezolizumab given as first-line treatment for PD-L1–selected patients (TC2/3 or IC2/3) with NSCLC in Study GO28754 (BIRCH).

On the basis of these observations, Study GO29431 (IMpower110) is designed to evaluate whether the anti-tumor effect seen in atezolizumab-treated patients would translate into prolonged OS and PFS compared with platinum-based chemotherapy in patients with NSCLC who are selected on the basis of a minimum level of PD-L1 tumor expression on TCs and/or ICs (TC1/2/3 or IC1/2/3; corresponding to $\geq$1% PD-L1 expressing TCs and $\geq$1% of tumor area occupied by PD-L1 expressing ICs). A PD-L1 immunohistochemistry (IHC) assay will be used to identify patients by their tumor PD-L1 expression (see Appendix 6).

Study GO29431 will enroll patients with Stage IV NSCLC who are naive to chemotherapy treatment and for whom the experimental arm can represent a valuable treatment option and can offer a reasonable benefit-risk balance.

In order to account for the possibility of pseudoprogression/tumor-immune infiltration (i.e., radiographic increase in tumor volume caused by 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 3.3.4 and Section 4.6) with use of modified RECIST criteria (in addition to RECIST v1.1) to evaluate clinical benefit. As 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. Investigators should make a careful assessment of the potential benefit of continuing treatment with atezolizumab, considering radiographic data and the clinical status of the patient. If, after an integrated assessment of radiographic data and clinical status, the decision is made to continue treatment with atezolizumab following apparent radiographic progression, patients must provide written consent at that time to acknowledge deferring other treatment options in favor of continuing study treatment.

Atezolizumab has been generally well tolerated (see Section 1.5.2). Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, hypothyroidism, hepatitis/transaminitis, colitis, and myasthenia gravis have been observed. 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 particular among those having tumor tissue with PD-L1 expression. Because most atezolizumab-related toxicities observed to date have been mild and transient in nature and do not overlap with the adverse effects of chemotherapy, patients who do not respond to study treatment with atezolizumab are considered likely to be able to subsequently receive standard therapies for which they would otherwise have been eligible. Patients will be fully informed of the risk of continuing study treatment with atezolizumab 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 [if available], and the clinical status of the patient.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

For the primary and secondary efficacy objectives, a comparison of the treatment arms will be performed in randomized patients who are selected on the basis of a minimum level of PD-L1 expression on TCs and/or ICs (TC1/2/3 or IC1/2/3; corresponding to $\geq$1% PD-L1 expressing TCs and $\geq$1% of tumor area occupied by PD-L1 expressing ICs) using a centrally performed IHC test (see Appendix 6), with populations excluding patients with a sensitizing EGFR mutation or ALK translocation.

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy consisting of a platinum agent (cisplatin or carboplatin) in combination with either pemetrexed (non-squamous disease) or gemcitabine (squamous disease) in chemotherapy-naive patients with Stage IV NSCLC, as measured by OS.

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy as measured by investigator-assessed PFS according to RECIST v1.1 (see Appendix 4)
- To evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy as measured by ORR according to RECIST v1.1 assessed by investigator
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed DOR according to RECIST v1.1
- To evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy as measured by OS and investigator-assessed PFS according to RECIST v1.1 in patients with PD-L1 expression defined by the SP263 IHC assay
- To evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy as measured by OS and investigator-assessed PFS according to RECIST v1.1 in patients with blood tumor mutational burden (bTMB)
- To evaluate the OS rate at 1- and 2- year landmark timepoints in each treatment arm
- To determine the impact of atezolizumab compared with platinum-based chemotherapy as measured by time to deterioration (TTD) and change from baseline (i.e., improvement or deterioration based on presenting symptomatology) in each of the patient-reported lung cancer symptom (cough, dyspnea, chest pain) score as assessed by the Symptoms in Lung Cancer (SILC) scale (Appendix 9)
- To determine the impact of atezolizumab compared with platinum-based chemotherapy as measured by TTD in patient-reported lung cancer symptoms of cough, dyspnea (multi-item subscale), and chest pain as measured by the European Organisation for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core (QLQ-C30; see Appendix 7) and supplementary Quality-of-Life Questionnaire Lung Cancer Module (QLQ-LC13; see Appendix 8)

2.2 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab compared with platinum-based chemotherapy

- To evaluate the incidence and titers of ATAs against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, pharmacodynamics, safety, and efficacy

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the pharmacokinetics of atezolizumab in chemotherapy-naive patients with Stage IV NSCLC.

2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy as measured by OS and investigator-assessed PFS according to RECIST v1.1 in patients with PD-L1 expression measured using the 22c3 PD-L1 IHC assay, but excluding patients with a sensitizing EGFR mutation or ALK translocation
- To evaluate the efficacy of atezolizumab as measured by PFS rates at 6-month and 1-year landmark timepoints
- To evaluate the efficacy of atezolizumab as measured by OS rate at 3-year landmark timepoint in each treatment arm
- To evaluate the efficacy of atezolizumab as measured by OS and investigator-assessed PFS according to RECIST v1.1 in subgroups based on demographic and baseline characteristics
- 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 atezolizumab
- 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 Dimension, 3 Level (EQ-5D-3L) questionnaire to generate utility scores for use in economic models for reimbursement
- To determine the impact of atezolizumab compared with platinum-based chemotherapy as measured by change from baseline in patient-reported outcomes (PROs) of health-related quality of life, lung cancer related symptoms, and functioning as assessed by the EORTC QLQ-C30 and QLQ-LC13

3. STUDY DESIGN

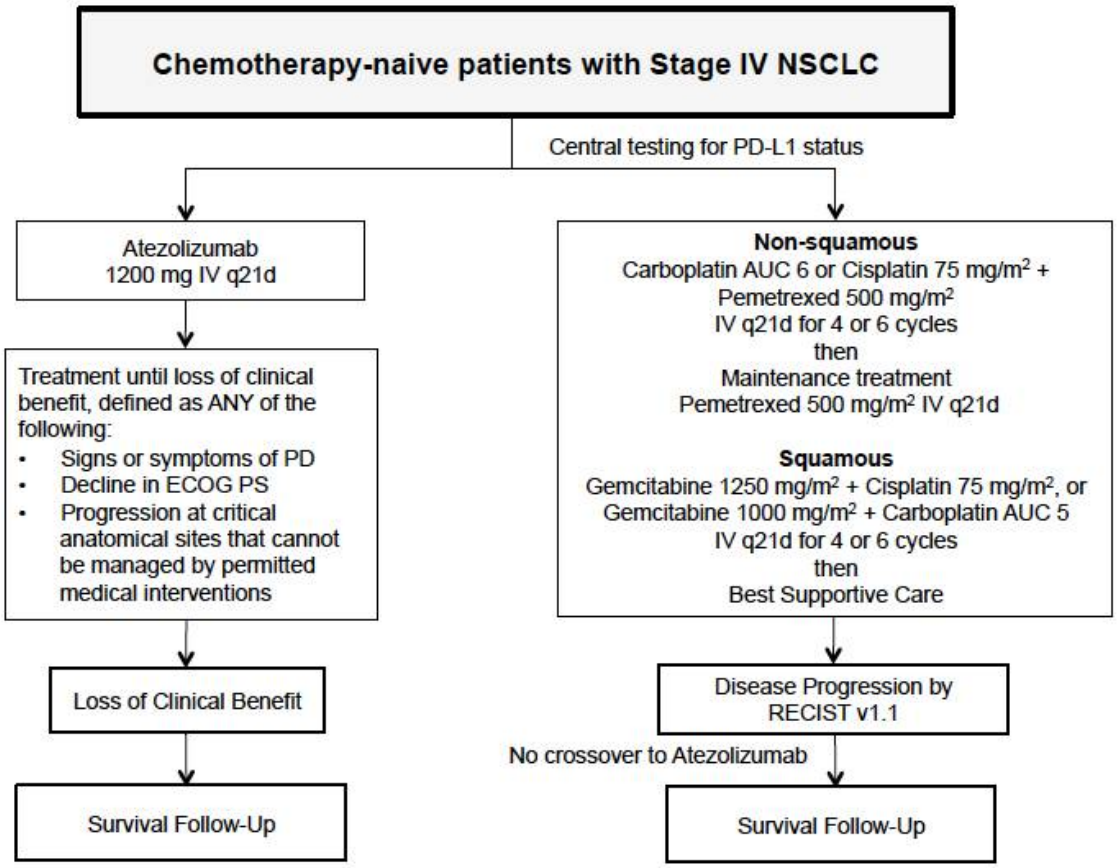
3.1 DESCRIPTION OF STUDY

This is a randomized, Phase III, global, multicenter, open-label study designed to evaluate the safety and efficacy of atezolizumab compared with chemotherapy consisting of a platinum agent (cisplatin or carboplatin per investigator discretion)

combined with either pemetrexed (non-squamous disease) or gemcitabine (squamous disease) in PD-L1–selected, chemotherapy-naive patients with Stage IV NSCLC.

Figure 1 illustrates the study design. A schedule of assessments is provided in Appendix 1.

Figure 1 Study Schema



AUC = area under the concentration–time curve; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IV = intravenous; NSCLC = non–small cell lung cancer; PD-L1 = programmed death–ligand 1; q21d = every 21 days; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Gemcitabine is given on Days 1 and 8.

At screening, tumor specimens from each potentially eligible patient will be tested for PD-L1 expression by a central laboratory using an IHC assay (see Appendix 6). Only patients who are PD-L1 selected (TC1/2/3 or IC1/2/3; corresponding to ≥ 1% PD-L1 expressing TCs and ≥ 1% of tumor area occupied by PD-L1 expressing ICs) will be enrolled. Patients with non-squamous disease will be randomized 1:1 to receive either atezolizumab alone or pemetrexed in combination with cisplatin or carboplatin. Patients

with squamous disease will be randomized 1:1 to receive either atezolizumab alone or gemcitabine in combination with cisplatin or carboplatin. Randomization will be stratified by sex (male vs. female), ECOG Performance Status (0 vs. 1), histology (non-squamous vs. squamous), and PD-L1 tumor expression by IHC (TC1/2/3 and any IC vs. TC0 and IC1/2/3).

Given the toxicities associated with platinum-based chemotherapies (e.g., neutropenia, anemia) and the requirement for pre-medications, this will be an open-label study. No crossover will be allowed from the control arm (platinum-based chemotherapy) to the experimental arm (atezolizumab).

Atezolizumab (fixed dose of 1200 mg) will be administered intravenously on Day 1 of each 21-day cycle. Atezolizumab treatment may continue as long as patients 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) or until unacceptable toxicity or death.

During treatment, patients who are treated with atezolizumab and who show evidence of clinical benefit will be permitted to continue atezolizumab treatment after RECIST v1.1 criteria 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 study treatment at the time of initial radiographic progression per RECIST v1.1

All patients will undergo a mandatory tumor biopsy sample collection, unless not clinically feasible as assessed and documented by investigators, at the first evidence of radiographic disease progression (within 40 days of radiographic progression or prior to the start of the next anti-cancer treatment, whichever is sooner). These data will be used to explore if the radiographic findings are consistent with the presence of tumor or if the appearance of progression was caused by pseudoprogression. In addition, these data will be analyzed for the association between changes in tumor tissue and clinical outcome and to understand further the potential mechanisms of resistance and progression to atezolizumab when compared to such mechanisms after treatment with chemotherapy. This exploratory biomarker evaluation will not be used for any

treatment-related decisions. Patients who are unable to undergo biopsy sample collection but otherwise meet criteria listed above may continue to receive atezolizumab.

Patients randomized to receive pemetrexed in combination with either cisplatin or carboplatin (non-squamous disease) will receive chemotherapy intravenously on Day 1 of each 21-day cycle for four or six cycles, followed by maintenance therapy with pemetrexed. Patients randomized to receive gemcitabine in combination with either cisplatin or carboplatin (squamous disease) will receive cisplatin or carboplatin intravenously on Day 1 and gemcitabine intravenously on Days 1 and 8 of each 21-day cycle for four or six cycles, followed by best supportive care. The intended number of cycles planned for the platinum-based induction chemotherapy (i.e., four or six cycles) will be specified by the investigator prior to study randomization. Treatment will continue until disease progression, unacceptable toxicity, or death. Refer to Sections 4.3.2.2–4.3.2.4 for treatment administration details.

All patients will undergo tumor assessment at baseline and every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1 regardless of treatment delays. After the completion of the Week 48 tumor assessment, tumor assessment will be required every 9 weeks (± 7 days) 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 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 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 after disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by Sponsor, whichever occurs first. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments should continue regardless of whether patients start a new anti-cancer therapy.

3.1.1 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will be used to evaluate safety data when approximately 50 and 150 patients have received at least two 21-day cycles of study therapy, and then every 6 months thereafter until the study data are unblinded or the study is terminated by the Sponsor. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.

All summaries and analyses by treatment arm for the iDMC review will be prepared by an independent Data Coordinating Center (iDCC). The safety data will include demographic data, adverse event data (including serious adverse events and adverse events of special interest), study conduct data, and relevant laboratory data. Efficacy data (excluding data on deaths) will not be included in the iDMC safety data reviews.

Following the safety data reviews, the iDMC will provide a recommendation to the Sponsor as to whether the study may continue, whether amendments to the protocol should be implemented, or whether the study should be stopped. The final decision will rest with the Sponsor.

The iDMC will also be responsible for evaluating efficacy data at the pre-specified OS interim analysis. The interim analysis of efficacy data will be conducted in accordance with the methods that are specified in the Statistical Analysis Plan (SAP). The iDMC recommendations to stop the study because of substantial evidence of efficacy of the study drug or to continue to the final analysis must be based on the specified interim analysis stopping guidelines as specified in the iDMC charter.

Any outcomes of these safety and 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 the study will occur when all of the following criteria have been met:

- The required number of deaths for the final analysis of OS has been observed (see Section 6.10.1).
- The last patient, last visit has occurred.

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

3.3 RATIONALE FOR STUDY DESIGN

This Phase III study design is based on the assumption that in patients with Stage IV NSCLC who are chemotherapy-naive and whose tumors are selected for PD-L1 expression, treatment with atezolizumab may prolong OS compared with treatment with platinum-based chemotherapy.

3.3.1 Rationale for Testing Atezolizumab in PD-L1–Selected Patients with Non–Small Cell Lung Cancer

Despite recent improvements in treatment, the prognosis for patients with advanced NSCLC remains dismal, with a median OS of approximately 12.5 months (Sandler et al. 2006). Patients who receive second-line treatment for their disease have an even more limited prognosis, with 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).

Data from the Phase Ia Study PCD4989g suggest that tumor PD-L1 status as determined by IHC in patients with NSCLC correlates with response to atezolizumab (see Section 1.5.3). In Study GO28753 (POPLAR) and Study GO28915 (OAK), improvement in OS was observed with atezolizumab compared with docetaxel in previously treatment patients with NSCLC, including patients in the TC1/2/3 or IC1/2/3 subgroup (Fehrenbacher et al. 2016; Rittmeyer et al. 2017). In addition, data from Study GO28754 (BIRCH) demonstrated a clinically meaningful benefit of atezolizumab as first-line treatment for PD-L1–selected patients (TC2/3 or IC2/3) with NSCLC, as demonstrated by a median OS of 23.5 months (Garassino et al. 2016). These data provide a rationale for evaluating the efficacy of atezolizumab in patients with Stage IV NSCLC selected on the basis of tumor PD-L1 expression.

3.3.2 Rationale for Control Arm

3.3.2.1 Rationale for Pemetrexed Combined with Either Cisplatin or Carboplatin for Non-Squamous Non–Small Cell Lung Cancer

In the first-line treatment setting for non-squamous NSCLC that does not harbor a driver mutation, standard of care is a platinum doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. Furthermore, in the Phase III clinical study evaluating pemetrexed maintenance therapy following four cycles of platinum-based doublet chemotherapy, pemetrexed significantly improved PFS (4.3 vs. 2.6 months) (HR = 0.50; 95% CI: 0.42, 0.61; $p < 0.0001$) and OS (13.4 vs. 10.6 months) (HR = 0.79; 95% CI: 0.65, 0.95; $p = 0.012$) when compared with placebo (Ciuleanu et al. 2009). This Phase III trial resulted in regulatory approval for pemetrexed in non-squamous NSCLC as maintenance therapy of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

On the basis of these results, patients with non-squamous NSCLC in the control group will receive the combination of a platinum-based chemotherapy (cisplatin or carboplatin) and pemetrexed, which is a standard-of-care regimen for patients with non-squamous NSCLC. This control group will be instrumental in assessing the relative benefit and safety of atezolizumab compared with chemotherapy in the front-line treatment setting.

3.3.2.2 Rationale for Gemcitabine Combined with Either Cisplatin or Carboplatin for Squamous Non–Small Cell Lung Cancer

In the first-line treatment setting for non-squamous NSCLC that does not harbor a driver mutation, standard of care is a platinum doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. However, well-designed clinical studies conducted over the last decade have clearly demonstrated that

bevacizumab and pemetrexed are not appropriate agents for the treatment of patients with squamous-cell carcinoma of the lung (Johnson et al. 2004; Scagliotti et al. 2008; Sandler et al. 2009). The combination of gemcitabine and a platinum agent (either cisplatin or carboplatin) has demonstrated efficacy as first-line treatment for squamous NSCLC and, as a result, is often a reference arm in clinical trials evaluating new therapeutics (see Table 1 in Section 1.2; Schiller et al. 2002; Scagliotti et al. 2008; Treat et al. 2010). Patients with squamous NSCLC in the control group will receive gemcitabine combined with either cisplatin or carboplatin, which is a standard-of-care regimen for patients with squamous NSCLC.

3.3.3 Rationale for Overall Survival as Primary Endpoint

Recent data suggest that OS may be a more sensitive endpoint for cancer immunotherapy than PFS. For example, in Studies GO28753 (POPLAR) and GO28915 (OAK), an OS benefit was observed in the atezolizumab arm compared with the docetaxel arm in the TC1/2/3 or IC1/2/3 subgroup, whereas PFS was similar in the two treatment arms (Barlesi et al. 2016; Smith et al. 2016). In Study GO28754 (BIRCH) study, the median OS observed in PD-L1–selected patients (TC2/3 or IC2/3) with advanced NSCLC who received first-line treatment with atezolizumab (Cohort 1) was favorable compared with data from platinum-based chemotherapy regimens, whereas PFS was consistent with data from platinum-based chemotherapy regimens (Garassino et al. 2016). In addition, improvement in OS is generally accepted as the most objective and best measure of clinical benefit for patients with advanced lung cancer. Therefore, OS has been selected as the primary endpoint for this study.

3.3.4 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 disease progression (by initial radiographic evaluation) does not necessarily reflect therapeutic failure (see Section 1.6). Because of the potential for pseudoprogression/tumor immune infiltration, this study will allow patients randomized to receive atezolizumab to continue to receive study treatment after apparent radiographic progression per RECIST v1.1, 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, biopsy results [if available], and clinical status (see Section 3.1).

Although tumor response will be evaluated according to RECIST v1.1 for the efficacy endpoints (i.e., PFS, objective response, and DOR), tumor response will also be evaluated according to modified RECIST, which allows the incorporation of new lesions into the calculation of total tumor burden after baseline and takes into account the potential for pseudoprogression/tumor immune infiltration (see Appendix 5). Tumor assessments will be performed according to RECIST v1.1 and modified RECIST for

patients in the atezolizumab arm, and only according to RECIST v1.1 for patients in the chemotherapy arm.

3.3.5 Rationale for Patient-Reported Outcome Assessments

In the treatment of lung cancer, it is important to both increase survival and palliate symptoms because disease symptoms have negative impacts on health-related quality of life (HRQoL) (Hyde and Hyde 1974; Hopwood and Stephens 1995; Sarna et al. 2004).

Chest pain, dyspnea, and cough have been regarded as the most frequent and clinically relevant disease-related symptoms experienced by patients with NSCLC. In this study, the SILC scale will be used to assess the effect of atezolizumab and platinum-based chemotherapy on TTD and change from baseline of specific lung cancer symptoms (cough, dyspnea, and chest pain) in patients with Stage IV NSCLC in the first-line setting.

In addition, the BR.21 study (erlotinib vs. BSC in second- or third-line NSCLC) demonstrated that longer TTD in the pain, dyspnea, and cough scales of the EORTC QLQ-C30 and 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). In addition, patients in the afatinib LUX-Lung first-line study reported significant delay of TTD in lung cancer symptoms (cough, pain, dyspnea) as measured by the EORTC QLQ-C30 and QLQ-LC13 (Yang et al. 2013). In order to assess the HRQoL and symptom severity of patients in this study, PRO data will be collected from patients enrolled in this study using the validated questionnaires EORTC QLQ-C30 and QLQ-LC13.

Patients will also complete the EQ-5D-3L PRO instrument (see Appendix 10) to generate utility scores for use in economic models for reimbursement.

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

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), GO28754 (BIRCH) (Besse et al. 2015), GO28753 (POPLAR) (Fehrenbacher et al. 2016), GO28625 (FIR) (Spigel et al. 2015), and GO28915 (OAK) (Rittmeyer et al. 2017).

In this study, archival and/or fresh tumor specimens from patients will be prospectively tested for PD-L1 expression by a central laboratory during the prescreening/screening period. Only patients with PD-L1–selected tumors (defined by expression of PD-L1 on TCs or ICs, corresponding to ≥1% PD-L1 expressing TCs and ≥1% of tumor area occupied by PD-L1 expressing ICs) will be enrolled.

In addition to the assessment of PD-L1 status, this study will assess a correlation between other tumor-based biomarkers and atezolizumab efficacy. This evaluation of

biomarkers may provide evidence for biologic activity of atezolizumab in patients with NSCLC, help to identify which patients may benefit most from atezolizumab and help future development of alternative diagnostic options.

Other exploratory biomarkers, such as potential predictive and prognostic biomarkers 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 NGS and to evaluate expression of genes to assess their association with efficacy and to identify somatic mutations to increase understanding of disease pathobiology. Methods for the biomarkers analysis may also include, but are not limited to, digital polymerase chain reaction (PCR), qRT−PCR, and proteomics-based approaches.

3.3.7 Rationale for Blood Biomarker Assessments

Exploratory analyses of the POPLAR and OAK studies demonstrated that TMB measured by a novel blood-based assay (bTMB) is associated with improved efficacy of atezolizumab in 2L+ NSCLC (Gandara et al. 2018). Importantly, bTMB did not correlate with the PD-L1 status by IHC, suggesting that bTMB may represent an additional biomarker to identify patients who may derive clinical benefit from single-agent atezolizumab. Based on these findings, OS and PFS will be analyzed in patients with defined levels on bTMB (including bTMB $\geq$10, bTMB $\geq$16, and bTMB $\geq$20) as part of the secondary analysis.

Other blood-based biomarkers (including, but not limited to circulating tumor DNA [ctDNA]) may be also evaluated and correlated with atezolizumab efficacy, including evaluation of various predictive cutoffs for novel blood-based assays. This evaluation of blood-based markers may provide evidence for biologic activity of atezolizumab in patients with NSCLC, help to identify patients who may benefit most from atezolizumab, and help future development of tissue-free diagnostic options for patients who have inadequate quality or insufficient quantity of tumor tissue for biomarker testing.

Blood samples will be collected at screening and/or baseline, during therapy, and at first evidence of radiographic disease progression or loss of clinical benefit in order to better understand the changes in blood-based biomarker profiles and potential mechanisms of resistance upon progression. Blood samples may also be evaluated for additional exploratory biomarkers that may be associated with the therapeutic effects of atezolizumab or the pathogenesis of NSCLC. Methods for exploratory analysis include, but are not limited to, digital PCR, qRT−PCR, NGS, immunoassays, and proteomics-based approaches.

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

3.3.8 Rationale for the Collection of 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 radiographic 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).

A mandatory tumor biopsy will be performed in all patients, if clinically feasible, at the time of first radiographic progression, to evaluate the utility of the tissue biopsy in distinguishing pseudoprogression/tumor-immune infiltration from true progression. In addition, mechanisms relating to progression, resistance, predictive, prognostic, and pharmacodynamic relationships in tumor biomarkers (including, but not limited to, PD-L1, CD8, mutation status, and others) and efficacy will be evaluated. DNA and/or RNA extraction may be performed to enable NGS to identify somatic mutations that are associated with disease progression or acquired resistance to atezolizumab and to increase understanding of disease pathobiology.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

3.4.1.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure for this study is OS, defined as the time from randomization to death from any cause.

3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator with use of RECIST v1.1, or death from any cause, whichever occurs first
- Objective response (PR plus CR) as determined by the investigator according to RECIST v1.1
- DOR, defined as the time from the first occurrence of a documented objective response to the time of disease progression, as determined by the investigator with use of RECIST v1.1, or death from any cause, whichever occurs first
- OS at 1- and 2-year landmark timepoints
- TTD and change from baseline (i.e., improvement or deterioration based on presenting symptomatology) in each of the patient-reported lung cancer symptoms (cough, dyspnea, or chest pain) with use of the SILC scale

- TTD in patient-reported lung cancer symptoms, defined as time from randomization to deterioration (10-point change) in any of the following symptom subscales (cough, dyspnea [multi-item scale], and chest pain), whichever occurs first, as measured by the EORTC QLQ-LC13
- OS and investigator-assessed PFS according to RECIST v1.1 in the PD-L1 (defined with SP263 IHC assay) and bTMB subpopulations

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events graded according to the NCI CTCAE v4.0
- Changes in vital signs, physical findings, and clinical laboratory test 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 as follows:

- Maximum serum atezolizumab concentration observed (C_{max}) after infusion on Day 1 of Cycle 1
- Minimum serum atezolizumab concentration observed (C_{min}) prior to infusion on Day 1 of Cycles 2, 3, 4, 8, 16, and every eighth cycle thereafter, at treatment discontinuation, and at 120 ($\pm$30) days after the last dose of atezolizumab

3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- OS and investigator-assessed PFS according to RECIST v1.1 in the PD-L1 (defined with 22c3 assay) subpopulation
- PFS at 6-month and at 1-year landmark timepoints
- OS at 3-year landmark timepoint
- OS and investigator-assessed PFS according to RECIST v1.1 in subgroups based on demographic and baseline characteristics
- Status of immune cell infiltrate and other exploratory biomarkers in mandatory biopsy specimens collected at progression
- 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
- Utility scores of the EQ-5D-3L questionnaire
- Change from baseline in PROs of health-related quality of life, lung cancer-related symptoms, and functioning as assessed by the EORTC QLQ-C30 and QLQ-LC13

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 150 sites globally will participate in the study, and approximately 555 PD-L1–selected chemotherapy-naive patients with Stage IV NSCLC will be enrolled.

4.1.1 Inclusion Criteria

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

- Signed Informed Consent Form
- Age ≥ 18 years
- ECOG Performance Status of 0 or 1 (see Appendix 11)
- Histologically or cytologically confirmed, Stage IV non-squamous or 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 must be classified as non-squamous or squamous based on the major histological component.
- No prior treatment for Stage IV non-squamous or squamous NSCLC

  Patients known to have a sensitizing mutation in the EGFR gene or an ALK fusion oncogene are excluded from the study.

  Patients with non-squamous NSCLC who have an unknown EGFR or ALK status will be required to be tested at prescreening/screening. Patients with squamous NSCLC who have an unknown EGFR or ALK status will not be required to be tested at prescreening/screening.

  EGFR and/or ALK may be assessed locally or at a central lab. Additional tissue will be required for central testing of EGFR and/or ALK.
- 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 cycle.
- 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.

- Tumor PD-L1 expression (TC1/2/3 or IC1/2/3; corresponding to ≥1% PD-L1 expressing TCs and ≥1% of tumor area occupied by PD-L1 expressing ICs), 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. This specimen must be accompanied by the associated pathology report.

  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.

  For freshly collected specimens, resections, core needle biopsies, excisional, incisional, punch, or forceps biopsies are acceptable.

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

  Tumor tissue from bone metastases that have been decalcified is not acceptable.

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

  For patients whose initial archival tumor tissue sample is PD-L1 negative, a biopsy can be performed at screening to submit fresh tissue for the purposes of testing PD-L1 status. A positive test result in any tumor tissue sample will satisfy this eligibility criterion.

- Measurable disease, as defined by RECIST v1.1

  Previously irradiated lesions can only be considered 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 measureable disease

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

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

  Lymphocyte count ≥500 cells/μL

  Platelet count ≥100,000 cells/μL without transfusion

Hemoglobin ≥ 9.0 g/dL

Patients may be transfused to meet this criterion.

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

This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation must have an INR or aPTT within therapeutic limits for at least 1 week prior to randomization.

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 $\leq 1.5 \times$ ULN

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

Calculated creatinine clearance (CrCl) ≥ 45 mL/min, or if using cisplatin, calculated CrCl ≥ 60 mL/min

- For female patients of childbearing potential and male patients with partners of childbearing potential, agreement to use a highly effective form(s) of contraception during study treatment that results in a low failure rate of <1% per year when used consistently and correctly. Female patients should continue contraception use for 5 months after the last dose of atezolizumab and for 6 months after the last dose of cisplatin. Women must refrain from donating eggs during this same period.
  Male patients treated with chemotherapy (cisplatin or carboplatin plus pemetrexed or gemcitabine) should continue contraception use for 6 months after the last dose of chemotherapy. Men must refrain from donating sperm during this same period.
  Such 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 or vasectomized partner (on the understanding that this is the only one partner during the entire study duration), and sexual abstinence.

  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 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 in the following sections will be excluded from study entry.

4.1.2.1 Cancer-Specific Exclusions

- Known sensitizing mutation in the EGFR gene or ALK fusion oncogene
- 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 $\geq$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 loco-regional therapy if appropriate prior to enrollment.
- 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 calcium $>$12 mg/dL or corrected serum calcium $>$ULN)

  Patients who are receiving denosumab prior to randomization must be willing and eligible to discontinue its use and replace it with 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)

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 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 13 for a more comprehensive list of autoimmune diseases)

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

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

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (i.e., 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
  - Disease is well controlled at baseline and only requiring low potency topical steroids
  - No acute exacerbations of underlying condition within the last 12 months requiring treatment with either PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or 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 HIV test

  All patients must be tested for HIV; patients who test positive for HIV will be excluded.

- Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test 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 [HBc Ab] and absence of HBsAg) are eligible. HBV DNA test must be performed in these patients prior to randomization.

  Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction 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

- 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 transplantation
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk 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
- Treatment with any other investigational agent with therapeutic intent within 28 days prior to randomization
- 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.
- 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
- 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–cytotoxic T lymphocyte–associated antigen 4 (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-related adverse effects from anti–CTLA-4 (CTCAE Grade 3 or 4)

- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons or 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 corticosteroids or other 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 are allowed.

4.1.2.4 Exclusion Criteria Related to Chemotherapy

- History of allergic reactions to cisplatin, carboplatin, or other platinum-containing compounds
- Patients with hearing impairment (cisplatin)
- Grade ≥2 peripheral neuropathy as defined by NCI CTCAE v4.0 criteria (cisplatin)
- CrCl <60 mL/min (cisplatin)
- Known hypersensitivity to gemcitabine
- History of radiation therapy within 7 days prior to initiating gemcitabine

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 (including determination of tumor PD-L1 status by central testing), personnel at the study site will enter demographic and baseline characteristics in the interactive voice or Web-based response system (IxRS). For patients who are eligible for enrollment, the study site will obtain the patient's randomization number and treatment assignment from the IxRS. Randomization to one of two treatment arms will occur in a 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)
- ECOG Performance Status (0 vs. 1)
- Histology (non-squamous vs. squamous)
- Tumor tissue PD-L1 expression by IHC TC1/2/3 and any IC vs. TC0 and IC1/2/3)

Patients should receive their first dose of study treatment 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

Patients with non-squamous disease will receive either atezolizumab alone or pemetrexed in combination with cisplatin or carboplatin. Patients with squamous disease will receive either atezolizumab alone or gemcitabine in combination with cisplatin or carboplatin.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab (MPDL3280A)

The atezolizumab (MPDL3280A) drug product is provided by the Sponsor 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 Investigator's Brochure.

4.3.1.2 Cisplatin, Carboplatin, Pemetrexed, and Gemcitabine

Cisplatin, carboplatin, pemetrexed, and gemcitabine will be used in commercially available formulations. For information on the formulation, packaging, and handling of cisplatin, carboplatin, pemetrexed, and gemcitabine, see the local prescribing information for each drug.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for atezolizumab treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.6 and Appendix 14.

4.3.2.1 Atezolizumab

Patients who are randomized to be treated with atezolizumab will receive 1200 mg atezolizumab administered by IV infusion q21d 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 11.

Table 11 Administration of First and Subsequent Infusions of Atezolizumab

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

NaCl = sodium chloride.

Dose modifications to atezolizumab are not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events are provided in Section 5.1.6 and Section 5.1.7, and Appendix 14.

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

4.3.2.2 Pemetrexed in Combination with Cisplatin or Carboplatin (Patients with Non-Squamous Non–Small Cell Lung Cancer Only)

Each study site will administer pemetrexed (non-squamous NSCLC) in combination with platinum-based chemotherapy (cisplatin or carboplatin) for four or six cycles. The intended number of chemotherapy induction cycles (four or six cycles) will be specified by the investigator prior to randomization. The selected platinum chemotherapy agent should remain the same for all cycles (e.g., patients who start on pemetrexed plus cisplatin should remain on this combination and not switch to pemetrexed plus carboplatin or vice versa). However, for patients who experience unacceptable toxicity with the selected platinum chemotherapy, a switch may be considered after discussion with and approval by the Medical Monitor.

Patients should receive steroid, folic acid, and vitamin B12 premedication for pemetrexed. The choice of steroid and timing of premedication can be administered according to the local standard of care and prescribing information (see Table 12 and Section 5.1.8). Folic acid supplementation may be started before randomization in all patients at the discretion of the investigator to meet the local standard of care in anticipation for pemetrexed-based treatment and then discontinued in patients assigned to the atezolizumab arm after randomization. In addition, patients should receive anti-emetic and IV hydration for platinum-based treatments according to the local standard of care and prescribing information.

Table 12 lists the suggested premedication for pemetrexed plus platinum-based chemotherapy and Table 13 lists the doses that will be used and the suggested infusion times for pemetrexed plus platinum-based chemotherapy. Chemotherapy infusion times may be adapted in accordance with local standard of care.

Table 12 Premedication for Pemetrexed plus Platinum-Based Chemotherapy

Premedication	Dose/Route	Timing
Folic acid	350–1000 μg PO	Once daily beginning 5–7 days before Cycle 1, Day 1, and continuing until 3 weeks after discontinuation of pemetrexed or as per local standard of care.
Vitamin B_{12}	1000 μg IM	q9w beginning Cycle 1, Day 1, and continuing until 3 weeks after discontinuation of pemetrexed or as per local standard of care.
Dexamethasone (suggested)	4 mg PO	Twice daily the day prior to, the day of, and the day after each infusion of pemetrexed or as per local standard of care.

IM = intramuscular; PO = oral; q9w = every 9 weeks.
Note: Prophylactic anti-emetics per local practice.

Table 13 Treatment Regimen for Pemetrexed plus Platinum-Based Chemotherapy

Study Drug	Dose/Route	Induction Period (Four or Six Cycles)	Maintenance Period (Until PD)
Pemetrexed	500 mg/m² IV	Over ~10 minutes on Day 1 q21d	Over approximately 10 minutes on Day 1 q21d
Carboplatin	AUC 6 [a] IV	Over ~30–60 minutes on Day 1 q21d	Not applicable
		OR	
Cisplatin	75 mg/m²	Over 1–2 hours on Day 1 q21d	Not applicable

AUC = area under the concentration-time curve; IV = intravenous; PD = progressive disease; q21d = every 21 days.

[a] See Section 4.3.2.4 for details on dose calculation of carboplatin.

Pemetrexed will be administered by IV infusion at a dose of 500 mg/m^2 on Day 1 of each 21-day cycle, followed by carboplatin or cisplatin at approximately 30 minutes after the completion of pemetrexed. Patients who do not experience disease progression per RECIST v1.1 after completing (four or six cycles of) induction treatment, will continue maintenance treatment with pemetrexed, given on Day 1 of each 21-day cycle until disease progression per RECIST v1.1. All patients eligible for pemetrexed therapy should avoid taking non-steroidal anti-inflammatory drugs (NSAIDs) for at least 2 days prior to pemetrexed administration if the NSAID has a short elimination half-life, for at least 5 days prior to pemetrexed administration if the NSAID has a long elimination half-life, on the day of pemetrexed administration, and at least 2 days following pemetrexed administration.

Guidelines for dose modification and treatment interruption or discontinuation are provided in Section 5.1.8 for pemetrexed, Section 5.1.10 for cisplatin, and Section 5.1.11 for carboplatin.

4.3.2.3 Gemcitabine in Combination with Cisplatin or Carboplatin (Patients with Squamous Non–Small Cell Lung Cancer Only)

Each study site will administer gemcitabine (squamous NSCLC) in combination with platinum-based chemotherapy (cisplatin or carboplatin) for four or six cycles. The intended number of chemotherapy induction cycles (four or six cycles) will be specified by the investigator prior to randomization. The selected platinum chemotherapy agent should remain the same for all cycles (e.g., patients who start on gemcitabine plus cisplatin should remain on this combination and not switch to gemcitabine plus carboplatin or vice versa). However, for patients who experience unacceptable toxicity with the selected platinum chemotherapy, a switch may be considered after discussion with and approval by the Medical Monitor.

Patients should receive anti-emetic therapy and IV hydration for platinum-based treatments according to the local standard of care and prescribing information. Table 14 lists the doses that will be used and the suggested infusion times for gemcitabine plus platinum-based treatments. Chemotherapy infusion times may be adapted in accordance with local standard of care.

Table 14 Treatment Regimens for Gemcitabine plus Platinum-Based Chemotherapy

Chemotherapy	Dose/Route	Treatment (Four or Six Cycles)
Gemcitabine	1250 mg/m^2 IV	Over 30 minutes on Days 1 and 8 q21d
Cisplatin	75 mg/m^2 IV	Over 1–2 hours on Day 1 q21d
Gemcitabine	1000 mg/m^2 IV	Over 30 minutes on Days 1 and 8 q21d
Carboplatin	AUC 5 IV	Over approximately 30–60 minutes on Day 1 q21d

AUC = area under the concentration curve; IV = intravenous; q21d = every 21 days.

Gemcitabine will be administered by IV infusion at a dose of 1250 mg/m^2 (in combination with cisplatin) or 1000 mg/m^2 (in combination with carboplatin) over 30 minutes on Days 1 and 8 of each 21-day cycle followed by cisplatin or carboplatin at approximately 30 minutes after the completion of gemcitabine infusion on Day 1 only.

Gemcitabine injection must be diluted prior to infusion. The recommended diluent for reconstitution of gemcitabine is 0.9% sodium chloride injection without preservatives.

The administration of gemcitabine should be done in accordance with local practice and the prescribing information; sites should follow their institutional standard of care for determining the gemcitabine dose for obese patients and for dose adjustment in the event of patient weight changes.

Guidelines for dose modification and treatment interruption or discontinuation are provided in Section 5.1.9 for gemcitabine, Section 5.1.10 for cisplatin, and Section 5.1.11 for carboplatin.

4.3.2.4 Cisplatin or Carboplatin Administration

Each site will choose to treat a given patient with either cisplatin or carboplatin according to local practice.

Cisplatin

Cisplatin should be administered by IV infusion approximately 30 minutes after completion of the pemetrexed or gemcitabine infusion at a dose of 75 mg/m² over 1–2 hours as per Table 13 or Table 14, respectively. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin.

Refer to local clinical practice guidelines for further details.

Carboplatin

Carboplatin should be administered by IV infusion at a dose of AUC 6 when given in combination with pemetrexed (see Table 13) or at a dose of AUC 5 when given in combination with gemcitabine (see Table 14), after completion of the pemetrexed or gemcitabine infusion, with standard anti-emetics per local practice guidelines.

The carboplatin dose 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 CrCl. The CrCl is calculated by institutional guidelines or by the method of Cockcroft and Gault (1976) using the following formula:

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

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

NOTE: For patients with an abnormally low serum creatinine level, estimate 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 U.S. Food and Drug Administration (FDA) recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity caused by 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 125 mL/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 for more details at http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm228974.htm.

4.3.3 Investigational Medicinal Product Accountability

The IMPs for this study are atezolizumab, pemetrexed, gemcitabine, carboplatin, and cisplatin. IMPs required for completion of this study will be provided by the Sponsor or appointed designee if required by local health authority regulations. The study site will acknowledge receipt of atezolizumab with use of the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Study Access to Atezolizumab

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 in addition to protocol–specified study treatment 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 or symptomatic relief of pain) provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be 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
- Megestrol 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, as per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist as 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 12).

All concomitant medications must be recorded on the appropriate Concomitant Medications electronic Case Report Form (eCRF). Protocol-specified study treatments, including maintenance treatment with pemetrexed, should not be recorded as concomitant medications.

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 Section 4.4.3).

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

Refer to Appendix 14 for additional information on the management of adverse events associated with atezolizumab.

4.4.3 Prohibited Therapy

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

The following medications are prohibited during 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 following 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

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

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

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

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly.

4.5.1 Informed Consent Forms and Prescreening/Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations and may be obtained more than 28 days before initiation of study treatment.

Prior to signing the main consent form for the study, patients may specifically allow for the collection and testing of archival or fresh tumor tissue by signing the prescreening consent form. Patients may also allow for central evaluation of their tissue for *EGFR* and/or *ALK* status.

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 prescreening/screening log to record details of all patients prescreened/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 v1.1 at a tumor response evaluation and are eligible and willing to continue treatment with atezolizumab must sign consent at that time to acknowledge deferring other treatment options in favor of continuing treatment with atezolizumab.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, non-NSCLC cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, 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 with non-squamous disease who were 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 prescreening or screening period. If *EGFR* mutations or *ALK* status testing is 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, according to local practice, should be performed at screening. Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions eCRF.

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

4.5.4 Vital Signs

Vital signs will include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressures, and temperature. Vital signs will be measured and recorded at screening and as described in Table 15.

Table 15 Vital Sign Measurements at Cycle 1 and All Subsequent Cycles

	Cycle 1
Treatment Arm	Timepoints
Atezolizumab	Within 60 minutes prior to atezolizumab infusion During the infusion (every 15 [±5] minutes) and within 30 (±10) minutes after atezolizumab infusion, if clinically indicated
Chemotherapy	Within 60 minutes prior to pemetrexed or gemcitabine infusion As clinically indicated prior to, during, or after cisplatin or carboplatin infusion
	Subsequent Cycles
Treatment Arm	Timepoints
Atezolizumab or chemotherapy	Within 60 minutes prior to infusion During the infusion if clinically indicated or if symptoms occurred during the prior infusion Within 30 (±10) minutes after infusion if clinically indicated or if symptoms occurred during the prior infusion

For patients in the atezolizumab arm, refer to Table 11.

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) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. Patients with active or untreated CNS metastases are not eligible for this study (see Section 4.1.2.1 for CNS-related exclusions).

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 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 through use of RECIST v1.1 (see Appendix 4) and modified RECIST (see Appendix 5). Tumor assessments will be performed according to RECIST v1.1 and modified RECIST for patients in the atezolizumab arm, and only according to RECIST v1.1 for patients in the chemotherapy arm. 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 will be performed 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 with atezolizumab after radiographic disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. At the investigator's discretion, CT scans should be repeated at any time if progressive disease is suspected.

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. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments will continue regardless of whether patients start a new anti-cancer therapy.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistries (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total CO_2 (if considered standard of care for the region), calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin)
- Coagulation (INR or aPTT)
- 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. A serum pregnancy test must be performed if the urine pregnancy test result is positive.

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

  Total T3 will be tested only at sites where free T3 is not performed.
- HBV serology: HBsAg, antibodies against HBsAg, total 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.
- HCV serology: hepatitis C virus antibody (anti-HCV)

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

  All patients will be tested for HIV prior to the inclusion into the study and patients who are HIV-positive 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 at the Sponsor. Instruction manuals and supply kits will be provided for all central laboratory assessments. Samples for the following laboratory tests will be sent to one or several central laboratories or to the Sponsor for analysis:

- ATA assays (patients assigned to atezolizumab only)

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

- PK assay (patients assigned to atezolizumab only)

  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.

- Biomarker assays

  Blood samples will be obtained for biomarker evaluation (including, but not limited to PD-L1, PD-1, mutational load, and other 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 may be evaluated for immune-related, tumor type–related, and other exploratory biomarkers (e.g., alterations in gene expression or single nucleotide polymorphisms).

- For patients who consent to the optional collection of samples for the Roche Clinical Repository (RCR), any leftover material from the above sample collection will be stored and used for exploratory analyses as indicated in Section 4.5.12. 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 4.5.12.

Refer to the laboratory manual for additional details on laboratory assessments and sample handling.

4.5.7 Tumor Tissue Samples

A central laboratory will coordinate the sample collection of tissue samples for research-related testing at central laboratories or at the Sponsor. Instruction manuals and supply kits will be provided for all central laboratory assessments.

Refer to the laboratory manual for additional details on tissue sample handling.

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 (on slides) with an associated pathology report must be submitted for determination of PD-L1 status to ensure patient meets eligibility criteria prior to 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 defined by the SP263 IHC assay will be evaluated. Exploratory biomarkers (including, but not limited to PD-L1, PD-1, mutational load, and other biomarkers related to immune or NSCLC biology, such as T-cell biomarkers or non-inherited biomarkers identified through NGS on extracted DNA and/or RNA) may also be evaluated. For patients with non-squamous NSCLC, *EGFR* and/or *ALK* status if unknown may be assessed locally or at a central lab. Additional tissue will be required for central testing of *EGFR* and/or *ALK*.

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

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

Tumor tissue from bone metastases that have been decalcified 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.

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 those outlined below:

- Core needle biopsy sample collection for deep tumor tissue; at least three cores, embedded into a single paraffin block, should be submitted for evaluation
- Excisional, incisional, punch, or forceps biopsy
- Tumor tissue resection

The status of immune-related, tumor type–related and other exploratory biomarkers (including, but not limited to, T-cell biomarkers 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 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 RCR optional consent will be requested (but not required) to also submit these optional fresh biopsy 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 from individual patients will greatly contribute to an improved understanding of the dynamics of PD-L1 expression and relationship with intervening anti-cancer therapy.

4.5.8 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 4.5.12), 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.

4.5.9 Anti-Therapeutic Antibody Testing

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

4.5.10 Electrocardiograms

A twelve-lead ECG is required at screening and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must 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.

4.5.11 Patient-Reported Outcomes

PRO data will be collected via the SILC, EORTC QLQ-C30, QLQ-LC13, and EQ-5D-3L questionnaires 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 pre-specified 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 SILC scale (see Appendix 9) will be used to assess patient-reported severity of lung cancer symptoms (cough, dyspnea, and chest pain). The SILC scale is a nine-item content valid self-report measure of lung cancer symptoms. It measures severity of cough, dyspnea, and chest pain with a total symptom severity score. This questionnaire will be completed using an ePRO device at the patient's home on a weekly basis, then monthly during survival follow-up for 6 months following 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).

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 10 minutes to complete. This questionnaire will be completed on the ePRO tablet at the site according to the tumor assessment schedule during the study treatment period (i.e., every 6 weeks (± 7 days) for 48 weeks following Cycle 1, Day 1, and every 9 weeks (±7 days) thereafter after the completion of the Week 48 tumor assessment 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). During survival follow-up, the questionnaire will be completed at 3 and 6 months following 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) if the patient returns to the clinic.

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 QLQ-LC13 module takes approximately 5 minutes to complete. This questionnaire will be completed on the ePRO tablet at the site according to the tumor assessment schedule during the study treatment period (i.e., every 6 weeks (± 7 days) for 48 weeks following Cycle 1, Day 1, and every 9 weeks (± 7 days) thereafter after the completion of the Week 48 tumor assessment 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). During survival follow-up the questionnaire will be completed at 3 and 6 months following 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) if the patient returns to the clinic.

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 10). The EQ-5D-3L will be utilized in this study for economic modeling. This questionnaire will be completed on the ePRO tablet at the site according to the tumor assessment schedule during the study treatment period (i.e., every 6 weeks (± 7 days) for 48 weeks following Cycle 1, Day 1, and every 9 weeks (± 7 days) thereafter after the completion of the Week 48 tumor assessment 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). During survival follow-up, the questionnaire will be completed at 3 and 6 months following 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) if the patient returns to the clinic.

Patients who discontinue study treatment for any reason other than 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) will complete the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-3L at each tumor assessment visit and will complete the SILC at home on a weekly basis, until 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), unless the patient withdraws consent or the Sponsor terminates the study, whichever occurs first.

Adverse event reports will not be derived from PRO data by the Sponsor. 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 exempted from completing all ePRO assessments.

4.5.12 Samples for Roche Clinical Repository

4.5.12.1 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

4.5.12.2 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 4.5.12) will not be applicable at that site.

4.5.12.3 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 and specimen collection 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 will undergo additional processes to ensure confidentiality, as described below.

4.5.12.4 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.

4.5.12.5 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 or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

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

4.5.12.6 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 trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. 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

A patient's withdrawal from Study GO29431 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 GO29431.

4.5.12.7 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.

4.5.13 Timing of Assessments

4.5.13.1 Screening/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.

4.5.13.2 Assessments during Treatment

All treatment visits must occur within ±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 and visits 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 four or six cycles of pemetrexed or gemcitabine combined with a platinum agent (for patients in the control arm) or after five cycles (for patients in the atezolizumab arm), 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-day cycles are not permitted.

If a dose modification is required due to toxicity, refer to Section 5.1.

Tumor assessments will occur every 6 weeks (± 7 days) for 48 weeks following Cycle 1, Day 1, and every 9 weeks (± 7 days) thereafter after the completion of the Week 48 tumor assessment, regardless of treatment delays 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 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. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments will continue regardless of whether patients start a new anti-cancer therapy.

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

- ECOG Performance Status
- Limited physical examination
- Local laboratory tests

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

Local hematology tests must also be performed prior to gemcitabine infusions on Day 8.

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

4.5.13.3 Assessments at Treatment Discontinuation Visit

Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit within 30 days after the last dose of study treatment. The visit at which a response assessment shows radiographic disease progression according to 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) may be used as the treatment discontinuation visit.

See Appendix 1 and Appendix 2 for assessments to be performed at the treatment discontinuation visit.

Patients who discontinue study treatment must be followed according to the follow-up visit schedule for progression and/or survival until death, loss to follow-up, or withdrawal of consent, which will be defined as study discontinuation.

4.5.13.4 Follow-Up Assessments

After the Treatment 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 will continue at the same frequency as would have been followed if the patient had continued 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 will continue tumor assessments according to the protocol schedule of response 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 the Sponsor, whichever occurs first.

Follow-up data collection will also include ePROs (only for the first 6 months after 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); SILC will be completed monthly for 6 months using an ePRO device at the patient's home and EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-3L will be completed at the site on the ePRO tablet at 3 and 6 months after 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) if the patient returns to the clinic. Patients who discontinue study treatment for any reason other than disease progression per RECIST v1.1 will complete the EORTC QLQ-C30, EORTC QLQ-LC13, 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 as determined by the investigator, unless the patient withdraws consent or the Sponsor terminates the study.

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

See Appendix 1 and Appendix 2 for assessments to be performed during Follow-Up visits.

4.5.13.5 Assessments at Unscheduled Visits

Assessments for unscheduled visits related to a patient's underlying NSCLC, study treatment, or adverse events 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 [if available], 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 study treatments
- Any medical condition that may jeopardize the patient's safety if he or she continues 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-treated patients only: patients will be permitted to continue atezolizumab treatment after RECIST v1.1 criteria for disease progression are met if they meet all of the following criteria (see Figure 2 below for 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 that can be attributed to disease progression

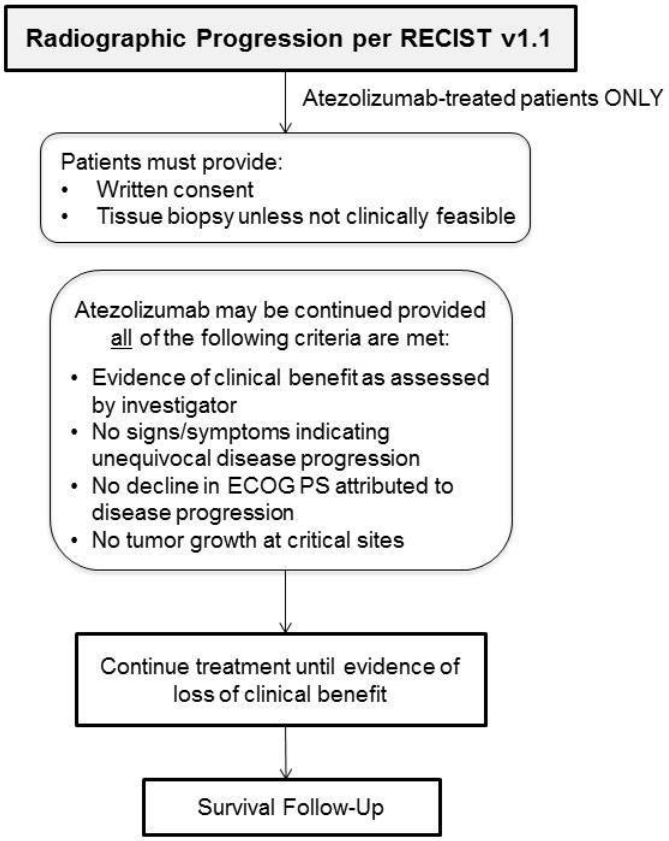
Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing

Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing atezolizumab treatment at the time of initial progression

Availability of 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 drug discontinuation should be documented on the appropriate eCRF.

Figure 2 Criteria for Continuing Atezolizumab in the Presence of Increased Radiographic Tumor Size (Atezolizumab Arm Only)



ECOG PS = Eastern Cooperative Oncology Group Performance Status; RECIST = Response Evaluation Criteria in Solid Tumors.

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 for atezolizumab 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 4.5).
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 monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. All serious adverse events and adverse events of special interest will be recorded during the study and for up to 90 days after the last dose of study treatment or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. All other adverse events will be recorded during the study and for up to 30 days after the last dose of study treatment or until the initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first.

After the adverse event reporting period, all deaths should continue to be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any

serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment (see Section 5.6). 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

Atezolizumab has been associated with risks such as the following: IRRs and *immune-mediated* hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis*, and myositis. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab).* Refer to Appendix 14 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with Pemetrexed

The most common side effects of pemetrexed include gastrointestinal symptoms (nausea, vomiting, diarrhea, or constipation), myelosuppression, infection, fatigue, stomatitis, loss of appetite, and rash.

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

5.1.3 Risks Associated with Gemcitabine

Gemcitabine infusion times that are longer than 60 minutes or gemcitabine administration that occurs more frequently than once a week have been shown to increase toxicity. Pulmonary toxicity has been reported with the use of gemcitabine. Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia has been reported with gemcitabine as a single agent or in combination with other cytotoxic drugs. Hemolytic-uremic syndrome and/or renal failure have been reported following one or more doses of gemcitabine. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs.

Patients will be monitored for gemcitabine-related adverse events. For more details regarding the safety profile of gemcitabine, refer to the gemcitabine prescribing information.

5.1.4 Risks Associated with Platinum-Based Chemotherapy

5.1.4.1 Risks Associated with Cisplatin Chemotherapy

Cisplatin is known to cause myelosuppression, ototoxicity, and nephrotoxicity. Cisplatin-based chemotherapy is considered to be moderately emetogenic. Patients will be monitored for cisplatin-related adverse events.

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

5.1.4.2 Risks Associated with Carboplatin Chemotherapy

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

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

5.1.5 General Plan to Manage Safety Concerns

5.1.5.1 Monitoring

Safety will be evaluated in this study through the monitoring of all 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 and Appendix 2 for the list and timing of study assessments).

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

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

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

5.1.6 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 considers it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during study 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 chemotherapy, the dose of the other chemotherapy component does not require modification and the other chemotherapy component(s) may be administered if there is no contraindication.
- 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 Modifications, Treatment Delays, or Treatment Discontinuation and Management of Specific Adverse Events

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 >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 >105 days from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤ 10 mg/day.
The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

5.1.7 Management of Atezolizumab-Specific Adverse Events

Refer to Appendix 14 for details on management of atezolizumab-specific adverse events. Refer to Appendix 12 for precautions for anaphylaxis.

5.1.8 Pemetrexed Dose Modifications, Treatment Delays, or Treatment Discontinuation and Management of Specific Adverse Events

The dose modification guidelines are applicable for pemetrexed used as a single agent or in combination with cisplatin or carboplatin.

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

Hematologic Toxicity

At the start of each cycle, the ANC must be $\geq$1500/μL and the platelet count must be $\geq$100,000/μL. Treatment should be delayed for up to 63 days to allow sufficient time for recovery. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines (Smith et al. 2006; LitRef_National_Comprehensive_Cancer_Ne2NCCN 2014). Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest (nadir) platelet and neutrophil values from the previous cycle (see Table 16).

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

Table 16 Pemetrexed Dose Modifications for Hematologic Toxicities

Toxicity [a]	Pemetrexed Dose
ANC $<$500/μL and platelets $\geq$50,000/μL	75% of previous dose
Platelets $<$50,000/μL, regardless of ANC	75% of previous dose
Platelets $<$50,000/μL with Grade $\geq$2 bleeding, regardless of ANC	50% of previous dose

[a] Nadir of prior cycle.

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

If chemotherapy 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 can then be resumed.

No dose reductions are recommended for anemia. Patients should be supported per institutional guidelines.

Non-Hematologic Toxicity

At the start of each cycle, the CrCl must be ≥45 mL/min. For enrollment and dosing decisions, CrCl will be estimated using the original, weight-based Cockcroft and Gault formula (1976) or measured using the appropriate radiolabeled method (51-CrEDTA or Tc99m-DTPA) to determine the GFR. The method of CrCl assessment used at baseline should be used throughout the study.

If a patient develops a non-hematologic toxicity (Table 17), pemetrexed should be withheld for up to 63 days until resolution to equal or less than the patient's baseline (or Grade ≤1 if patient did not have that toxicity at baseline). Treatment should be resumed according to the guidelines in Table 17. For Grade 3 or 4 neurotoxicity, pemetrexed should be resumed at 50% of the previous dose upon improvement, or discontinued immediately (based on investigator's clinical judgment).

Table 17 Pemetrexed Dose Modifications for Non-Hematologic Toxicities

Toxicity	Pemetrexed Dose
Any diarrhea requiring hospitalization (irrespective of grade) or Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication.	75% of previous dose
Neurotoxicity Grade 2	75% of previous dose
Grade 3 or 4	50% of previous dose or permanent discontinuation
Any other Grade 3 or 4 toxicities	75% of previous dose

Treatment Delays Caused by Insufficient Folic Acid or Vitamin B12 Supplementation

Cycle 1 should not be started until both of the following requirements are met:

- The patient has taken folic acid for 5 to 7 days preceding the first dose of pemetrexed or as per local standard of care, but not later than Cycle 1, Day 1.
- The patient has received a Vitamin B12 injection (which can be given on Cycle 1, Day 1).

Delay subsequent cycles until the patient has taken folic acid for at least 14 of the 21 days before Day 1 of the subsequent cycle.

For more details regarding pemetrexed dose modification, refer to the pemetrexed prescribing information.

5.1.9 Gemcitabine Dose Modifications, Treatment Delays, or Treatment Discontinuation and Management of Specific Adverse Events

The dose modification guidelines for gemcitabine are provided below.

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

5.1.9.1 Hematologic Toxicities

Gemcitabine dose modifications for hematologic toxicity should be based on the granulocyte and platelet counts taken on Days 1 and 8 of treatment (Table 18 and Table 19). Patients receiving gemcitabine should be monitored prior to each dose with a full blood count, including differential and platelet counts. Treatment should be delayed for up to 63 days to allow sufficient time for recovery. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines (Smith et al. 2006; LitRef_National_Comprehensive_Cancer_Ne2NCCN 2014). Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest (nadir) platelet and neutrophil values from the previous cycle (see Table 16).

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

Table 18 Gemcitabine Dose Modifications or Treatment Delays for Hematologic Toxicities on Day 1

Absolute Granulocyte Count ($\times 10^6$/L)		Platelet Count ($\times 10^6$/L)	Gemcitabine % of Full Dose
$\geq$1500	and	$\geq$100,000	100%
$<$1500	or	$<$100,000	Withhold

Table 19 Gemcitabine Dose Modifications or Treatment Delays for Hematologic Toxicities on Day 8

Absolute Granulocyte Count		Platelet Count	Gemcitabine % of Full Dose
≥1000/μL	and	≥100,000/μL	100%
500–999/μL	or	50,000–99,999/μL	75%
<500/μL	or	<50,000/μL	Withhold

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 can then be resumed.

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

5.1.9.2 Non-Hematologic Toxicities

In general, for Grade 3 or 4 non-hematologic toxicities, gemcitabine should be withheld or dose reduced by 50%, according to investigator's clinical judgment.

Permanent discontinuation should be considered for any of the following events:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary-leak syndrome
- Posterior reversible encephalopathy syndrome

Table 20 provides dose modification guidelines for non-hematologic toxicities.

Table 20 Gemcitabine Dose Modifications, Treatment Delays, or Treatment Discontinuation and Patient Management for Grade 2, 3, or 4 Non-Hematologic Toxicities

	Grade 2	Grade 3	Grade 4
First appearance	Interrupt treatment until resolved to Grade 1 or better, then continue at same dose with prophylaxis where possible.	Interrupt treatment until resolved to Grade 1 or better, then continue at 75% of original dose with prophylaxis where possible.	Discontinue treatment unless considered it to be in the best interest of the patient to continue at 50% of original dose, once toxicity has resolved to Grade 1 or better.
Second appearance of same toxicity	Interrupt treatment until resolved to Grade 1 or better, then continue at 75% of original dose.	Interrupt treatment until resolved to Grade 1 or better, then continue at 50% of original dose.	
Third appearance of same toxicity	Interrupt treatment until resolved to Grade 1 or better, then continue at 50% of original dose.	Discontinue treatment permanently.	
Fourth appearance of same toxicity	Discontinue treatment permanently.		

5.1.10 Cisplatin Dose Modifications, Treatment Delays, or Treatment Discontinuation and Management of Specific Adverse Events

The dose modification guidelines for cisplatin are provided below.

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

5.1.10.1 Hematologic Toxicities

At the start of each cycle, the ANC must be $\geq$1500/μL and the platelet count must be $\geq$100,000/μL. Treatment should be delayed for up to 63 days to allow sufficient time for recovery. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines (Smith et al. 2006; NCCN 2014). Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest platelet and neutrophil values from the previous cycle (see Table 21).

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

Table 21 Cisplatin Dose Modifications for Hematologic Toxicities

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

[a] Nadir of prior cycle.

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

If chemotherapy 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 can then be resumed.

No dose reductions are recommended for anemia. Patients should be supported per institutional guidelines.

5.1.10.2 Non-Hematologic Toxicities

If a patient develops a non-hematologic toxicity (see Table 22), cisplatin should be withheld for up to 63 days until resolution to less than or equal to the patient's baseline (or Grade $\leq$ 1 if patient did not have that toxicity at baseline). Treatment should be resumed according to the guidelines in Table 22.

Diarrhea should be controlled with adequate anti-diarrhea medication. Nausea and/or vomiting should be controlled with adequate anti-emetics.

Table 22 Cisplatin Dose Modifications for Non-Hematologic Toxicities (Excluding Neurotoxicity)

Toxicity	Cisplatin Dose
Any diarrhea requiring hospitalization (irrespective of grade) or Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication	75% of previous dose
Grade 3 or 4 nausea/vomiting [a]	75% of previous dose
Any other Grade 3 or 4 toxicity	75% of previous dose

[a] Despite the use of antiemetics.

Nephrotoxicity

CrCl must be ≥60 mL/min prior to the start of any cycle of cisplatin. If there is a decrease in CrCl between cycles, but the CrCl is still ≥60 mL/min at the time of the next cycle, the investigator should use clinical judgment regarding continuing cisplatin, dose reduction, or delaying the cycle. If a patient's CrCl value has not returned to ≥60 mL/min within 63 days following last cisplatin administration, the patient should be discontinued from cisplatin.

Neurotoxicity

In the event of neurotoxicity, the recommended dose adjustment for cisplatin is documented in Table 23. For Grade 3 or 4 neurotoxicity, cisplatin should be resumed at 50% of the previous dose upon improvement, or discontinued immediately (based on investigator's clinical judgment).

Table 23 Cisplatin Dose Modifications or Treatment Discontinuation for Associated Neurotoxicity

Toxicity	Cisplatin Dose
Grade 1 neurotoxicity	100% of previous dose
Grade 2 neurotoxicity	75% of previous dose
Grade 3 or 4 neurotoxicity	50% of previous dose or permanent discontinuation

If the patient develops ototoxicity, subsequent doses of cisplatin should not be given until an audiometric analysis indicates that auditory acuity is within normal limits (http://www.drugs.com/pro/platinol.html). See Table 23 for dose modifications.

5.1.11 Carboplatin Dose Modifications, Treatment Delays, or Treatment Discontinuation and Management of Specific Adverse Events

The dose modification guidelines for carboplatin are provided below.

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

5.1.11.1 Hematologic Toxicities

At the start of each cycle, the ANC must be ≥1500/μL and the platelet count must be ≥100,000/μL. Treatment should be delayed for up to 63 days to allow sufficient time for recovery. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO) and NCCN guidelines (Smith et al. 2006; NCCN 2012). Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest platelet and neutrophil values from the previous cycle (see Table 24).

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

Table 24 Carboplatin Dose Modifications for Hematologic Toxicities

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

[a] Nadir of prior cycle.

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

If chemotherapy 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 can then be resumed.

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

5.1.11.2 Non-Hematologic Toxicities

For a non-hematologic toxicity (see Table 25), treatment should be delayed for up to 63 days until resolution to less than or equal to the patient's baseline value (or Grade $\leq$ 1 if patient did not have that toxicity at baseline). Dose reductions at the start of the subsequent cycle will be made on the basis of non-hematologic toxicities from the dose administered in the preceding cycle. Table 25 provides the dose modifications for non-hematologic toxicities.

Table 25 Carboplatin Dose Modifications or Treatment Discontinuation for Non-Hematologic Toxicities

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

AUC = area under the concentration curve.

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

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

[c] Despite the use of antiemetics.

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

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, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting 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 Sections 5.3.5.9 and 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE

criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

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

Adverse events of special interest are required to be reported immediately by the investigator to the Sponsor (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- The following confirmed treatment-emergent autoimmune conditions:

  Pneumonitis

  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 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, 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 26 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 26 Adverse Event Severity Grading Scale for Events Not Specifically Listed in the 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 or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

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

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; colloquialisms and abbreviations should be avoided.

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events that are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If 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.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme intensity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it 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

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

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 (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it 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 (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of NSCLC should be recorded only on the Study Discontinuation 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 on the Study Discontinuation eCRF.

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Worsening of Non–Small Cell Lung Cancer

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 v1.1 criteria. In rare cases, the determination of clinical progression will be on the basis of 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 caused by disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or to perform an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event
- Hospitalization caused solely by progression of the underlying cancer

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

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

5.3.5.12 Cases of Accidental Overdose or Medication Error

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

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

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

Special situations are not in themselves adverse events, but may result in adverse events. All special situations associated with study treatment, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

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

For the study drugs (atezolizumab, cisplatin, carboplatin, pemetrexed, gemcitabine), each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, 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). Adverse events associated with special situations should be recorded as described below for each situation:

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

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.3.5.13 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 trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

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

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

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality on the basis of 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 (Roche Medical Responsible) Contact Information

Medical Monitor: [redacted], M.D., Ph.D. (Primary)

E-Mail: [redacted]

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Medical Monitor: [redacted], M.D. (Secondary)

Email: [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 and Medical Monitor contact information will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

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

Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the 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 with use of 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 or within 6 months after the last dose of cisplatin. 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 the 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 study treatment with chemotherapy or within 6 months after the last dose of chemotherapy. 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 related to study drug or trial-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 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
- E.U. Summary of Product Characteristics for each chemotherapy agent

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, open-label study designed to evaluate the safety and efficacy of atezolizumab compared with treatment with chemotherapy consisting of a platinum agent (cisplatin or carboplatin per investigator discretion) combined with either pemetrexed (non-squamous NSCLC) or gemcitabine (squamous NSCLC).

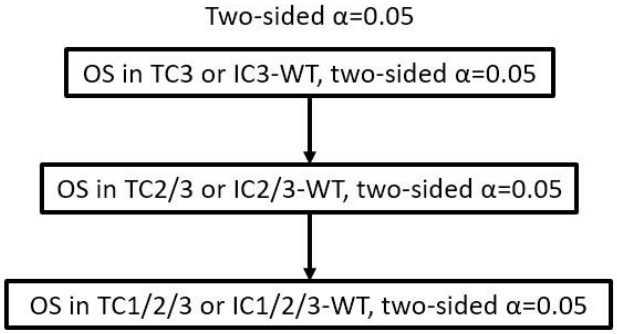
For the efficacy analyses, patients will be grouped according to the treatment assigned at randomization. For the safety analyses, patients will be grouped according to whether any amount of atezolizumab was received, including the case when atezolizumab was received in error.

6.1 DETERMINATION OF SAMPLE SIZE

A total enrollment of approximately 555 patients was planned for this study such that approximately 64% of those enrolled would be PD-L1 TC2/3 or IC2/3 patients. A recent prevalence report shows an increase in the prevalence of TC3 or IC3, which could lead to a fully powered study of OS evaluation in the TC3 or IC3 subpopulation. Data from the atezolizumab first-line NSCLC Phase III Studies GO29436 (IMpower150; Socinski 2018) and GO29437 (IMpower131; Jotte 2018) as well as the atezolizumab second-line NSCLC Phase III Study GO28915 (OAK; Rittmeyer et al. 2017) have shown the greatest treatment benefit of OS in the TC3 or IC3 subpopulation. The OS analysis of this study will therefore first be conducted in the TC3 or IC3 subpopulation excluding patients with a sensitizing EGFR mutation or ALK translocation (i.e., TC3 or IC3-wild type [WT]).

The overall type I error rate will be controlled at a two-sided alpha-level of 0.05. Comparisons with respect to the primary endpoint of OS between treatment arms will be tested in a hierarchical fashion for the following populations: TC3 or IC3-WT, TC2/3 or IC2/3-WT, and TC1/2/3 or IC1/2/3-WT. The updated type I error control plan is shown in Figure 3.

Figure 3 Type I Error Control Plan



IC = tumor-infiltrating immune cells; OS = overall survival; TC = tumor cell; WT=wild type.

Estimates of the number of events required to demonstrate efficacy in terms of OS are based on the following assumptions:

- 1:1 randomization ratio
- One interim analysis of OS in the TC3 or IC3-WT, TC2/3 or IC2/3-WT, and TC1/2/3 or IC1/2/3-WT populations, with stopping boundaries determined by the Lan-DeMets approximation to the Pocock boundaries
- Two-sided significance level of 0.05 (see Figure 3)
- 99% power to detect a HR of 0.45 for OS in the TC3 or IC3-WT subpopulation, 85% power to detect a HR of 0.65 for OS in the TC2/3 or IC2/3-WT subpopulation, and 77% power to detect a HR of 0.75 for OS in the TC1/2/3 or IC1/2/3-WT population
- Median survival of 14 months in the control arm (platinum-based chemotherapy)
- Event times exponentially distributed
- Dropout rate assumed for all treatment arms of 5% per 24 months
- [redacted]

With these assumptions, the final OS analysis will be conducted when approximately 135 deaths have occurred in the TC3 or IC3-WT subpopulation. Details on the timing of the interim analysis and stopping boundaries are provided in Section 6.10.1.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study drug administration, and discontinuation from the study will be summarized by treatment arm. The incidence of study drug discontinuation will similarly be tabulated. Protocol deviations, including major deviations of inclusion/exclusion criteria, will be summarized in a similar manner by treatment arm.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics, such as age, sex, race/ethnicity, and baseline disease characteristics, such as ECOG Performance Status and histology, will be summarized by treatment arm. Baseline measurements are the last available data obtained prior to patients receiving the first dose of study drug, unless otherwise noted.

Descriptive statistics (mean, median, SD, and range) will be presented for continuous data and frequencies and percentages will be presented for categorical data.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy analysis is the comparison of OS between the two treatment arms (atezolizumab arm and chemotherapy control arm).

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

The primary efficacy analysis will be performed for the TC3 or IC3 subpopulation, the TC2/3 or IC2/3 subpopulation, and the TC1/2/3 or IC1/2/3 population, with all populations excluding patients with a sensitizing EGFR mutation or ALK translocation.

The null and alternative hypotheses for the OS analysis can be phrased in terms of the survival functions $S_A(t)$ and $S_B(t)$ in the atezolizumab arm (Arm A) and the control arm (Arm B), respectively:

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

The stratification factors will be: sex (male vs. female), ECOG Performance Status (0 vs. 1), histology (non-squamous vs. squamous), and PD-L1 tumor expression status (TC1/2/3 and any IC vs. TC0 and IC1/2/3). Both stratified and unstratified analysis will be performed. Due to the potential risk of over-stratification (Akazawa et al. 1997), if at least 1 stratum (i.e., for the TC1/2/3 or IC1/2/3 population, a combination of stratification factor levels across sex, ECOG performance status, histology, and PD-L1 tumor expression status per IxRS; for the TC3 or IC3 population and the TC2/3 or IC2/3 population, a combination of stratification factor levels across sex, ECOG performance status, and histology per IxRS) has less than 10 OS events, the stratification factor (1 of 4 stratification factors for the TC1/2/3 or IC1/2/3 population: sex, ECOG performance status, histology, and PD-L1 tumor expression by IHC per IxRS; 1 of 3 stratification factors for the TC3 or IC3 population and the TC2/3 or IC2/3 population: sex, ECOG performance status, and histology per IxRS) which contains the level with the smallest number of patients will be removed from the stratified analyses.
The removal of the stratification factor will continue until there is no stratum with less than 10 OS events in the analysis population. The final set of stratification factors used in the stratified analyses of OS for a specific analysis population (e.g., TC2/3 or IC2/3) will be applied to all other efficacy endpoints where stratified analyses are planned for the same analysis population.

The HR will be estimated using a stratified Cox regression model at the time of both the interim and final analyses.

The unstratified HR will also be presented. Kaplan-Meier methodology will be used to estimate the median OS for each treatment arm and to construct survival curves for the visual description of the difference between the treatment arms. The Brookmeyer-Crowley methodology will be used to construct a 95% CI for the median OS for each treatment arm (Brookmeyer and Crowley 1982).

A group sequential design will be used for testing OS to account for the conduct of the interim analysis, which is expected to occur approximately 40 months after the first patient is enrolled in the study. The type I error control plan is presented in Section 6.1, and details on the timing of the interim analysis and stopping boundaries are provided in Section 6.10.1. Details on the hypothesis testing will be provided in the SAP. On the basis of emerging external data, the testing strategy may be modified to improve the efficiency of the design. Should this occur, modifications to the testing strategy will be documented in the SAP prior to any unblinding of the data.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints, except for OS and PFS in the SP263 PD-L1 and bTMB subpopulations (Section 6.4.2.6), will be analyzed in the TC3 or IC3 subpopulation, the TC2/3 or IC2/3 subpopulation, and/or the TC1/2/3 or IC1/2/3 population (depending on the results of the primary endpoint analyses), with all populations excluding patients with a sensitizing EGFR mutation or ALK translocation (referred to as the "secondary efficacy analysis populations" throughout Section 6.4.2).

6.4.2.1 Progression-Free Survival

PFS is defined as the time (in months) from randomization to the first occurrence of disease progression, as determined by the investigator with use of RECIST v1.1, or death, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day. Final PFS analyses will occur at the time of OS interim analyses (as defined in Section 6.10.1). If the primary OS analyses are significant for the TC3 or IC3 subpopulation, the TC2/3 or IC2/3 subpopulation, and the TC1/2/3 or IC1/2/3 population, with all populations excluding patients with a sensitizing EGFR mutation or ALK translocation, the final PFS analyses will be performed in a fixed order to control the overall type I error rate at 0.05. Specifically, PFS for the TC3 or IC3 subpopulation, the TC2/3 or IC2/3 subpopulation, and TC1/2/3 or IC1/2/3 population will be tested in this fixed order at a significance level of 0.05 respectively, with populations excluding patients with a sensitizing EGFR mutation or ALK translocation. PFS will be analyzed through use of the same methods described for the OS analysis (see Section 6.4.1). Further details regarding the PFS analyses will be described in the SAP.

6.4.2.2 Objective Response Rate

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

ORR is defined as the proportion of patients who had an objective response. ORR will be analyzed in the secondary efficacy analysis populations. Patients must have measurable disease at baseline to be included in the analysis. The confirmation of response in accordance with RECIST v.1.1 is not required, but ORR with confirmation may be evaluated as an exploratory endpoint.

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 arms will be determined using the normal approximation to the binomial distribution. The ORR will be compared between the two arms using the stratified Cochran-Mantel-Haenszel test, stratified by the same factors used in the primary OS analysis (see Section 6.4.1).

6.4.2.3 Overall-Survival Analysis at 1- and 2-Year Landmark Timepoints

The 1-year and 2-year survival rate is defined as the probability that a patient will be alive at 1 year or 2 years, respectively, after randomization. The analysis population for the 1-year and 2-year survival rate will be the secondary efficacy analysis populations. The Kaplan-Meier method will be used to estimate the 1-year and 2-year survival rate for each treatment arm. The 95% CI for the difference in OS rates between the two treatment arms will be estimated through use of the normal approximation method, and standard errors will be computed through use of the Greenwood method.

6.4.2.4 Duration of Response

DOR is defined as the period measured from the date of the first occurrence of a CR or PR (whichever status is recorded first) until the first date that progressive disease or death is documented, whichever occurs first. Disease progression will be determined on the basis of investigator assessment with use of RECIST v1.1. DOR will be assessed in patients who had an objective response during the study as determined by the investigator with use of RECIST v1.1. Patients who have not progressed and who have not died by the date of data cutoff for analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR plus 1 day.

DOR analysis will be performed on the basis of a non-randomized subset of patients who achieve an objective response in the secondary efficacy analysis populations; therefore, formal hypothesis testing will not be performed for this endpoint. DOR will be

estimated using Kaplan-Meier methodology. Comparisons between treatment arms will be made for descriptive purposes only.

6.4.2.5 Patient-Reported Outcome Analyses

TTD with use of the SILC scale is defined as the time from randomization to the first documented deterioration of disease symptom in each of the SILC symptom scores (cough, dyspnea, or chest pain). Data for patients who have not deteriorated will be censored at the last time when they completed an assessment for cough, dyspnea, or chest pain. If no baseline or post-baseline assessment is performed, data for patients will be censored at the date of randomization plus 1 day. TTD with use of the SILC scale will be analyzed in the secondary efficacy analysis populations through use of the same methods described for the OS analysis (see Section 6.4.1).

Change from baseline per SILC scale will also be analyzed. The analysis will be performed for patients in the secondary efficacy analysis populations with a baseline and a post-baseline PRO assessment. The SILC scale comprises three individual symptoms (dyspnea cough, chest pain) and will be scored at the individual symptom level, thus will have a dyspnea score, cough score, and chest pain score. Each symptom score will be calculated as the average of responses for the symptom items. An increase in score is suggestive of a worsening in symptomatology (i.e., frequency or severity). A score change of 0.3 points for the dyspnea and cough symptom scores is considered to be clinically significant; whereas a score change of 0.5 points for the chest pain score is considered to be clinically significant.

Further details regarding all SILC analyses will be described in the SAP.

TTD will be documented for a 3-symptom composite endpoint using the following EORTC QLQ-LC13 symptom scores (cough, chest pain, and dyspnea [multi-item scale]). TTD is defined as the time from baseline to the time the patient's score shows a $\geq$10-point increase above baseline in any of the listed symptom scores, whichever occurs first. A $\geq$10-point change in the score is perceived by patients as clinically significant (Osoba et al. 1998). If no baseline or post-baseline assessment is performed, data for patients will be censored at the date of randomization plus 1 day. TTD with use of the EORTC will be analyzed in the secondary efficacy analysis populations through use of the same methods described for the OS analysis (see Section 6.4.1). Further details regarding the TTD analysis for the EORTC measures will be described in the SAP.

6.4.2.6 Overall Survival and Investigator-Assessed Progression-Free Survival for SP263 PD-L1 and bTMB Subpopulation

OS and investigator-assessed PFS in patients with PD-L1 expression defined by the SP263 IHC assay (including populations of patients with PD-L1 expression on $\geq$1%, $\geq$25%, and $\geq$50% of tumor cells) and in patients with bTMB (including bTMB$\geq$10, bTMB

≥ 16, and bTMB ≥ 20) will be analyzed (pending data availability). This will be analyzed through use of the same methods described for the OS analysis (see Section 6.4.1).

6.5 SAFETY ANALYSES

Safety analyses will include all treated patients, defined as randomized patients who received any amount of study treatment. For the safety analyses, patients will be grouped according to whether any amount of atezolizumab was received, including when atezolizumab was received in error.

Study drug exposure, including treatment duration, number of doses, and dose intensity, will be summarized for each treatment arm using descriptive statistics.

Verbatim description of adverse events will be mapped to thesaurus terms and graded according to NCI CTCAE v4.0. All adverse events occurring during or after the first study drug dose will be summarized by treatment arm and NCI CTCAE grade.
In addition, serious adverse events, severe adverse events (Grade 3, 4, or 5), 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. The proportion of patients experiencing at least one adverse event will be reported by toxicity term and 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.

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

Serum levels and incidence of ATA against atezolizumab will be summarized to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy.

6.6 PHARMACOKINETIC ANALYSES

PK and pharmacodynamic samples will be collected in this study as outlined in Appendix 2.

Atezolizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, and SDs, as appropriate.

Additional PK and pharmacodynamic analysis will be conducted based on the availability of data.

6.7 EXPLORATORY ANALYSES

Unless otherwise indicated, the exploratory efficacy endpoints will be analyzed in the TC3 or IC3 subpopulation, the TC2/3 or IC2/3 subpopulation, and/or the TC1/2/3 or IC1/2/3 population (depending on the results of the primary endpoint analyses), excluding patients with a sensitizing EGFR mutation or ALK translocation (referred to as the "exploratory efficacy analysis populations" throughout Section 6.7).

6.7.1 Analyses of Overall Survival and Progression-Free Survival in the 22c3 PD-L1 IHC Assay Subpopulation

OS and investigator-assessed PFS according to RECIST v1.1 will be analyzed for the subpopulation of patients with PD-L1 expression using the 22c3 PD-L1 IHC assay, excluding patients with a sensitizing EGFR mutation or ALK translocation. Details regarding these analyses will be described in the SAP or the Biomarker Analysis Plan. Results from these analyses may not be included in the Clinical Study Report but may instead be presented in a separate biomarker report.

6.7.2 PFS Analysis at 6-Month and 1-Year Landmark Timepoints

The 6-month and 1-year PFS rate, defined as the probability that a patient will be alive without disease progression at 6 months or 1 year, respectively, after randomization, will be analyzed in the exploratory efficacy analysis populations. The Kaplan-Meier method will be used to estimate the 6-month and 1-year PFS rate for each treatment arm. The 95% CI for the difference in 6-month and 1-year PFS rates between the two treatment arms will be estimated through use of the normal approximation method, and standard errors will be computed through use of the Greenwood method.

6.7.3 Overall Survival Analysis at 3-Year Landmark Timepoint

The 3-year survival rate is defined as the probability that a patient will be alive at 3 years after randomization. The analysis population for the 3-year survival rate will be the exploratory efficacy analysis populations. The methodologies for OS analysis at landmark timepoint outlined in Section 6.4.2.3 will be used.

6.7.4 Impact of Demographic and Baseline Characteristics on Overall Survival and Progression-Free Survival

To assess the consistency of the study results in subgroups defined by demographic (e.g., age, sex, and race/ethnicity) and baseline characteristics (e.g., PD-L1 tumor expression status, histology, ECOG Performance Status, smoking history, number of metastatic sites, location of metastases, size of primary tumor, etc.), OS and investigator-assessed PFS according to RECIST v1.1 will be examined in these subgroups within the exploratory efficacy analysis populations. Summaries of OS and PFS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median OS and PFS, will be produced separately for each level of the categorical variables.

6.7.5 Exploratory Biomarker Analysis

Exploratory biomarker analyses will be performed in all randomized patients in an effort to understand the association of these biomarkers 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. Results from these exploratory analyses will not be included in the Clinical Study Report.

6.7.6 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.

6.7.7 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 SENSITIVITY ANALYSES

6.8.1 Impact of Non–Protocol-Specified Anti-Cancer Therapy

The impact of non–protocol-specified anti-cancer therapy on OS may be assessed, depending on the number of patients who receive non–protocol-specified anti-cancer therapy (i.e., >10% of patients). For example, the duration from initiation of non–protocol-specified anti-cancer therapy to death or censoring date could be discounted in accordance with a range of possible effects on OS of subsequent non–protocol-specified anti-cancer therapy (e.g., 10%, 20%, 30%).

This sensitivity analysis will be conducted in the TC3 or IC3 subpopulation, the TC2/3 or IC2/3 subpopulation, and/or the TC1/2/3 or IC1/2/3 population (depending on the results of the primary endpoint analyses), with all populations excluding patients with a sensitizing EGFR mutation or ALK translocation. Further details regarding these sensitivity analyses will be described in the SAP.

6.8.2 Impact of Proportional Hazards Assumption

If the proportional hazards assumption is equivocal, restricted mean survival time may be assessed and the difference between treatment arms will be evaluated for several timepoints. The weighted log-rank test (Fleming and Harrington 1991) of OS may also be performed for treatment comparison for exploratory purposes. No multiplicity adjustment will be performed for these sensitivity analyses. These sensitivity analyses

will be conducted in the TC3 or IC3 subpopulation, the TC2/3 or IC2/3 subpopulation, and/or the TC1/2/3 or IC1/2/3 population (depending on the results of the primary endpoint analyses), with all populations excluding patients with a sensitizing EGFR mutation or ALK translocation. Further details regarding these sensitivity analyses will be described in the SAP.

6.9 HANDLING OF MISSING DATA

For OS, data for patients who are not reported as having died will be analyzed as censored observations on the date when 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 PFS, patients without a date of disease progression and death will be analyzed as censored observations on the date of the last tumor assessment. If no post-baseline tumor assessment is available, PFS will be censored at the date of randomization plus 1 day.

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

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

For TTD with use of SILC scale analysis, data for patients who have not deteriorated will be censored at the last time when they were known to have not deteriorated (i.e., the last assessment). If no baseline or post-baseline assessment is performed, data for patients will be censored at the date of randomization plus 1 day.

6.10 INTERIM ANALYSES

An iDMC will be used to evaluate interim safety data on a regular basis and interim efficacy data at a pre-specified timepoint. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an external iDCC. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.

6.10.1 Planned Interim Analysis

Because of a lack of the final PD-L1 prevalence, an interim analysis of OS in the TC3 or IC3-WT population will be conducted when both of the following criteria have been met:

- An approximately 45% event–patient ratio has been observed in the TC3 or IC3 subpopulation, excluding patients with a sensitizing EGFR mutation or ALK translocation
- Approximately 96 deaths have occurred in the TC3 or IC3 subpopulation, excluding patients with a sensitizing EGFR mutation or ALK translocation

At this timepoint, it is expected that approximately 154 OS events will have occurred in the TC2/3 or IC2/3-WT population. If the OS interim analysis in the TC3 or IC3-WT population is claimed as statistically significant, the OS analysis in the TC2/3 or IC2/3-WT population will be conducted with the stopping boundaries for the interim and final analyses calculated using the Lan-DeMets approximation to the Pocock boundaries. If there are significantly fewer than 154 OS events (i.e., <135 events) at the TC3 or IC3-WT interim analysis, a nominal two-sided alpha of 0.0001 (negligible impact on overall type I error rate) will be spent on the OS analysis in the TC2/3 or IC2/3-WT population at the time of the TC3 or IC3-WT interim analysis. The next interim and final OS analysis in the TC2/3 or IC2/3-WT population will be conducted when approximately 154 and 216 events are observed, respectively, with the stopping boundaries calculated in the same manner as above. The interim and final analyses of OS in the TC1/2/3 or IC1/2/3-WT population would be conducted at the same time as those for the TC2/3 or IC2/3-WT population.

If the OS interim analysis in the TC3 or IC3-WT population is not claimed as statistically significant, the final analysis will be conducted when approximately 135 OS events have occurred in this population, and the OS in the TC2/3 or TC2/3-WT and TC1/2/3 or IC1/2/3-WT populations will be tested at the planned interim and final analyses accordingly.

The interim and final analyses are expected to occur approximately 40 and 55 months, respectively, after the first patient is enrolled in the study, but the exact timing of these analyses will depend on the occurrence of OS events. The stopping boundaries for the interim and final analyses are shown in Table 27.

Table 27 Analysis Timing and Stopping Boundaries for Interim and Final Analysis for Overall Survival

Interim and Final Analysis for OS			
Analysis Population		Analysis Timing Approximate Time from First Patient in (months)	
		40	55
TC3 or IC3-WT	Information Fraction (No. of events)	71% (96)	100% (135)
	Stopping Boundary HR (p-value [a])	HR ≤ 0.657 (p ≤ 0.0399)	HR ≤ 0.678 (p ≤ 0.0242)
TC2/3 or IC2/3-WT	Information Fraction (No. of events)	71% (154)	100% (216)
	Stopping Boundary HR (p-value [a])	HR ≤ 0.718 (p ≤ 0.0400)	HR ≤ 0.736 (p ≤ 0.0242)
TC1/2/3 or IC1/2/3-WT	Information Fraction (No. of events)	72% (281)	100% (390)
	Stopping Boundary HR (p-value [a])	HR ≤ 0.783 (p ≤ 0.0403)	HR ≤ 0.796 (p ≤ 0.0241)

HR = hazard ratio; IC = tumor-infiltrating immune cell; OS = overall survival; TC = tumor cell; WT=wild type.

[a] Two-sided p-value.

6.10.2 Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one additional interim efficacy analysis for the primary endpoint of OS beyond what is specified in Section 6.10.1. 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 efficacy and safety analysis will be conducted by an iDCC and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter.

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

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 with 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 with use of electronic devices provided by an ePRO vendor. The electronic device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with the FDA regulations for electronic records (21 Code of Federal Regulations, Part 11). The data will be transmitted to a centralized database at the ePRO vendor. 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 trial 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 is 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, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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 trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational 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, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site.
If applicable, it will be provided in a certified translation of the local language.
The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent 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, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason. A separate, specific signature will be required to document a patient's agreement to allow the collection of optional samples and 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 investigator, 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 of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval,

and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

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

8.4 CONFIDENTIALITY

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

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

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

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient last visit).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann-La Roche Ltd. Approximately 150 sites globally will participate in the study, and approximately 555 patients will be randomized.

Randomization will occur through an IxRS. Central facilities will be used for certain 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 trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. 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 investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials 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 Days –28 to –1	All Treatment Cycles [a] Every 21 days (± 3 Days) [c]	Treatment Discontinuation Visit ≤ 30 Days after Last Dose	Survival Follow-Up [b] Every 3 Months after Disease Progression or Loss of Clinical Benefit
Informed consent Prescreening for PD-L1 testing [d] Main ICF for study participation	x			
Tumor tissue specimen for PD-L1 testing (15 FFPE slides required; blocks preferred) [e, f] Fresh or archival tissue can be used.	x			
EGFR and/or *ALK* assessment if status unknown (required for patients with non-squamous disease) [g]	x			
Demographic data	x			
Medical history and baseline conditions	x			
NSCLC cancer history	x			
Vital signs [h]	x	x [i]	x [i]	
Weight	x	x	x	
Height	x			
Complete physical examination	x			
Limited physical examination [j]		x	x	
ECOG Performance Status	x	x	x	
12-lead ECG	x	x [k]	x [k]	

Appendix 1
Schedule of Assessments (cont.)

Procedure	Screening Days –28 to –1	All Treatment Cycles [a] Every 21 days (± 3 Days) [c]	Treatment Discontinuation Visit ≤ 30 Days after Last Dose	Survival Follow-Up [b] Every 3 Months after Disease Progression or Loss of Clinical Benefit
Hematology [l]	x [m]	x	x	
Serum chemistry [n]	x [m]	x	x	
Coagulation test (INR or aPTT)	x [m]		x	
Pregnancy test (women of childbearing potential ONLY)	x [o]	x [p]	x [p]	
TSH, free T3, free T4 [q]	x	x [r]	x [r]	
HIV, HBV, HCV serology [s]	x			
Urinalysis [t]	x			
Study treatment administration		x [u]		
Tumor response assessment	x [v]	x [w]		x [x]
Serum sample for ATA assessment (atezolizumab-treated patients only) [y]		x	x	120 (±30) days after last dose
Serum sample for PK sampling (atezolizumab-treated patients only) [y]		x	x	120 (±30) days after last dose
Blood samples for PD biomarkers [y]	x	x	x	120 (±30) days after last dose
Informed consent to continue treatment beyond radiographic progression (atezolizumab-treated patients only)		At time of radiographic progression		

Appendix 1
Schedule of Assessments (cont.)

Procedure	Screening Days –28 to –1	All Treatment Cycles [a] Every 21 days (± 3 Days) [c]	Treatment Discontinuation Visit ≤ 30 Days after Last Dose	Survival Follow-Up [b] Every 3 Months after Disease Progression or Loss of Clinical Benefit
Tumor biopsy		At time of radiographic progression [z]		
Adverse events	x [aa]	x	x [bb]	
Concomitant medications	From 7 days before screening	x	x	
Patient-reported outcomes [cc]		x		x [dd]
Survival and anti-cancer therapy follow-up [b]				x

anti-HBc = antibody against hepatitis B core antigen; ATA = anti-therapeutic antibody; CT = computerized tomography; ECOG=Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; ePRO = electronic patient-reported outcome; EQ-5D-3L = EuroQoL5 Dimension, 3 Level; FFPE = formalin-fixed paraffin-embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; ICF = Informed Consent Form; IV = intravenous; QLQ-LC13 = Lung Cancer module; MRI = magnetic resonance imaging; NSCLC = non–small cell lung cancer; PD = pharmacodynamic; PD-L1 = programmed death–ligand 1; PK = pharmacokinetic; QLQ-C30 = Quality-of-Life Questionnaire Core 30; SILC = Symptoms in Lung Cancer; TSH = thyroid-stimulating hormone.

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

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

Appendix 1
Schedule of Assessments (cont.)

[c] Cycle 1 must be performed within 5 days after the patient is randomized. Screening assessments performed ≤ 96 hours before Cycle 1 Day 1 are not required to be repeated for Cycle 1 Day 1. In addition, ECOG Performance Status, limited physical examination, and local laboratory tests may be performed ≤ 96 hours before Day 1 of each cycle as specified in Section 4.5.13.2.

[d] Patients have the option to sign the Prescreening ICF to consent to PD-L1 tissue testing during prescreening, prior to signing the main ICF for study participation. Consent may be obtained more than 28 days before initiation of study treatment. For patients with non-squamous NSCLC, *EGFR* and/or *ALK* status if unknown may be assessed locally or at a central lab. Additional tissue will be required for central testing of *EGFR* and/or *ALK*.

[e] If a representative FFPE tumor specimen in paraffin block (preferred) or 15 (or more), freshly cut, unstained serial sections (on slides) from an FFPE tumor specimen are 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 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 more than 28 days prior to randomization. See Section 4.5.7.1 and Section 4.1.1 for details.

[f] For patients whose initial archival tumor tissue sample is PD-L1 negative, a biopsy can be performed at screening to submit fresh tissue for the purposes of testing PD-L1 status. A positive result in any tumor tissue sample will satisfy this eligibility criterion.

[g] Patients with non-squamous NSCLC who have an unknown *EGFR* and/or *ALK* status will be required to be tested at prescreening/screening. Patients with squamous NSCLC who have an unknown status will not be required to be tested at prescreening/screening. *EGFR* and/or *ALK* may be assessed locally or at a central lab. Additional tissue will be required for central testing of *EGFR* and/or *ALK*. See Section 4.1.1 Inclusion criteria for details.

[h] Vital signs include pulse rate, respiratory rate, blood pressures, and temperature.

[i] For both study treatment arms, the patient's vital signs should be recorded within 60 minutes before infusion, and during and after the infusion if clinically indicated. For the atezolizumab arm, vital signs should also be collected during the first infusion every 15 (± 5) minutes and within 30 (± 10) minutes after the first infusion if clinically indicated. For subsequent infusions in both arms, vital signs will be collected within 60 minutes prior to the infusion and should be collected during the infusion and within 30 (± 10) minutes after the infusion, if clinically indicated or if symptoms occurred in the prior infusion. See Section 4.5.4 for details.

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

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

Appendix 1
Schedule of Assessments (cont.)

[l] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. Hematology tests must be performed prior to Day 1 infusions, and for gemcitabine administration, also prior to Day 8 infusions.

[m] At screening, the patient must have adequate hematologic and end-organ function defined by laboratory results obtained within 14 days prior to randomization, as described in Section 4.1.1.

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

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

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

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

[r] Thyroid function testing (TSH, free T3, free T4) collected at Cycle 1, Day 1, and every fourth cycle thereafter.

[s] 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; HBV DNA must be performed prior to randomization in these patients. 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.

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

[u] For atezolizumab, the initial dose will be delivered over 60 (±10) 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 chemotherapy, study drug will be administered according to the doses and suggested infusion times, including premedication, as described in Section 4.3.2.2–4.3.2.4.

[v] 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.

Appendix 1
Schedule of Assessments (cont.)

[w] 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 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. CT scans may be repeated at any time if progressive disease is suspected. Tumor assessments will be performed according to RECIST v1.1 (see Appendix 4) and modified RECIST (see Appendix 5) for patients in the atezolizumab arm, and only according to RECIST v1.1 for patients in the chemotherapy arm. See Section 4.5.5 for details.

[x] 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 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, even if patient starts another anti-cancer therapy after study treatment discontinuation.

[y] See Appendix 2 for detailed schedule.

[z] Mandatory tumor biopsy at radiographic disease progression, 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).

[aa] Only serious adverse events caused by protocol-mandated intervention should be reported.

[bb] All serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new systemic anti-cancer therapy after last dose of study treatment. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new systemic anti-cancer therapy after last dose of study treatment. After this period, all deaths should continue to be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment (see Section 5.6).

Appendix 1
Schedule of Assessments (cont.)

[cc] EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-3L questionnaires will be completed by the patients on the ePRO tablet according to the tumor assessment schedule (i.e., every 6 weeks (± 7 days) for 48 weeks following Cycle 1, Day 1, and every 9 weeks (±7 days) thereafter after the completion of the Week 48 tumor assessment 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)prior to administration of study drug and prior to any other study assessments. The SILC scale will be completed using an electronic device at the patient's home on a weekly basis. Patients who discontinue study treatment for any reason other than 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) will complete the EORTC QLQ-C30, EORTC QLQ-LC13, 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, 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 in the ePRO device or who are deemed by the investigator incapable of inputting their ePRO assessment after undergoing appropriate training are exempt from all ePRO assessments.

[dd] 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 who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1) if the patient returns to the clinic. The SILC scale 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).

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

Study Visit	Time	Patients Randomized to Chemotherapy	Patients Randomized to Atezolizumab
Screening	—	Biomarkers [a]	Biomarkers [a]
Cycle 1, Day 1	Prior to dosing (same day as treatment administration)	Biomarkers [b]	ATA Atezolizumab pharmacokinetics Biomarkers [b]
	30 (±10) minutes after end of atezolizumab infusion	—	Atezolizumab pharmacokinetics
Cycles 2, 3, 4, 8 and 16, Day 1	Prior to dosing (same day as treatment administration)	Biomarkers [b]	ATA Atezolizumab pharmacokinetics Biomarkers [b]
After Cycle 16, every eighth cycle, Day 1	Prior to dosing (same day as treatment administration)	Biomarkers [b]	ATA Atezolizumab pharmacokinetics Biomarkers [b]
At time of fresh biopsy (on-treatment, or at progression, including during follow-up)	At visit	Biomarkers [b]	Biomarkers [b]
Treatment discontinuation visit	At visit	Biomarkers [b]	ATA Atezolizumab pharmacokinetics Biomarkers [b]
120±30 days after last dose of atezolizumab	At visit	—	ATA Atezolizumab pharmacokinetics Biomarkers [b]
Any timepoint during the study (RCR consent required)		Optional RCR blood (DNA extraction) [b]	Optional RCR blood (DNA extraction) [b]

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

[a] Whole blood for biomarkers.

[b] Plasma and serum for biomarkers.

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 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)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with $\geq$ 10 to $<$ 15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

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

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

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

c. Special Considerations Regarding Lesion Measurability

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

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

a. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

b. Method of Assessment

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

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

Clinical Lesions. Clinical lesions will be considered measurable only when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

Chest X-Ray. Chest CT 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, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

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

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

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

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-target lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs but, additionally, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

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

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

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum during the 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 during the 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 during the study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While in the 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.

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

- 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

  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 trials 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.

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

e. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

EVALUATION OF RESPONSE

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

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

Table 1 Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; 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.

[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 ≥ 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 ≥ 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.

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

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 ≥ 15 mm by CT scan. Only the short

axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 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 $\geq$ 10mm; see note for new lymph node lesions below). Up to a maximum of five new lesions total (and a maximum of two lesions per organ), all with measurements at all timepoints, can be included in the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the tumor response evaluation.

New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint will be measured from that point on and contribute to the sum

of longest diameters (SLD), if the maximum number of 5 measurable new lesions being followed has not been reached.

B.2 CALCULATION OF SUM OF THE DIAMETERS

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as a measure of tumor burden.

The sum of the diameters is calculated at baseline and at each tumor assessment for the purpose of classification of tumor responses.

Sum of the Diameters at Baseline: The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

Sum of the Diameters at Tumor Assessment: For every on-study tumor assessment collected per protocol or as clinically indicated the sum of the diameters at tumor assessment will be calculated using tumor imaging scans. All target lesions selected at baseline and up to five new measurable lesions (with a maximum of two new lesions per organ) that have emerged after baseline will contribute to the sum of the diameters at tumor assessment. Hence, each net percentage change in tumor burden per assessment with use of modified RECIST accounts for the size and growth kinetics of both old and new lesions as they appear.

Note: In the case of new lymph nodes, RECIST v1.1 criteria for measurability (equivalent to baseline target lesion selection) will be followed. That is, if at first appearance the short axis of a new lymph node lesion ≥ 15 mm, it will be considered a measureable new lesion and will be tracked and included in the SLD. Thereafter, the lymph node lesion will be measured at subsequent timepoints and measurements will be included in the SLD, even if the short axis diameter decreases to < 15 mm (or even < 10 mm). However, if it subsequently decreases to < 10 mm, and all other lesions are no longer detectable (or have also decreased to a short axis diameter of < 10 mm if lymph nodes), then a response assessment of CR may be assigned.

If at first appearance the short axis of a new lymph node is ≥ 10 mm and < 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion. It will not be included in the SLD unless it subsequently becomes measurable (short axis diameter ≥ 15 mm).

The appearance of new lymph nodes with diameter < 10 mm should not be considered pathological and not considered a new lesion.

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

B.3 RESPONSE CRITERIA

Timepoint Response

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

Complete Response (CR): Disappearance of all target and non-target lesions. Lymph nodes that shrink to <10 mm short axis are considered normal.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.

Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the sum of the diameters increases by $\geq 20\%$ when compared with the sum of the diameters at nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the diameters while in the 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 during the study (nadir SLD; this includes the baseline sum if that is the smallest during the 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, since a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm in order to meet the definition of CR.

Appendix 6
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 GO29431, the anti–PD-L1 (SP142) IHC assay will be used for investigational purposes only.

The Ventana PD-L1 (SP142) rabbit monoclonal primary antibody is intended for the qualitative immunohistochemical assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded non–small cell lung carcinoma (NSCLC) tissue stained with a BenchMark ULTRA automated staining instrument. It is indicated as an aid in identifying patients who are eligible for treatment with atezolizumab.

The clinical interpretation of any staining, or the absence of staining, must be complemented by histological studies and evaluation of proper controls. Evaluation must be made by a qualified pathologist within the context of the patient's clinical history and other diagnostic tests.

CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use.

DEVICE DESCRIPTION

The Ventana 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.

SCORING SYSTEM

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

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
Symptoms in Lung Cancer Scale

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 9
Symptoms in Lung Cancer Scale (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 9
Symptoms in Lung Cancer Scale (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 10
EuroQoL 5 Dimension, 3 Level Questionnaire

Health Questionnaire

(English version for the US)

Appendix 10
EuroQoL 5 Dimension, 3 Level Questionnaire (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

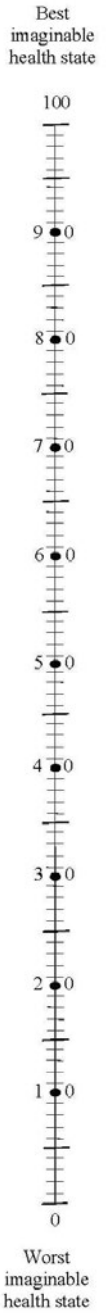
I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

Appendix 10
EuroQoL 5 Dimension, 3 Level Questionnaire (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 11
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about $>$50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair $>$50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 12
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study drug infusion, the following procedures should be performed:

1. Stop the study drug infusion.
2. Maintain an adequate airway.
3. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
4. Continue to observe the patient and document observations

Appendix 13
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 subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone will 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	Epidermolysis bullosa acquista	Ord's thyroiditis
Addison's disease	Gestational pemphigoid	Pemphigus
Ankylosing spondylitis	Giant cell arteritis	Pernicious anemia
Antiphospholipid antibody syndrome	Goodpasture's syndrome	Polyarteritis nodosa
Aplastic anemia	Graves' disease	Polyarthritis
Autoimmune hemolytic anemia	Guillain-Barré syndrome	Polyglandular autoimmune syndrome
Autoimmune hepatitis	Hashimoto's disease	Primary biliary cirrhosis
Autoimmune hypoparathyroidism	IgA nephropathy	Psoriasis
Autoimmune hypophysitis	Inflammatory bowel disease	Reiter syndrome
Autoimmune myocarditis	Interstitial cystitis	Rheumatoid arthritis
Autoimmune oophoritis	Kawasaki's disease	Sarcoidosis
Autoimmune orchitis	Lambert-Eaton myasthenia syndrome	Scleroderma
Autoimmune thrombocytopenic purpura	Lupus erythematosus	Sjögren's syndrome
Behcet's disease	Lyme disease - chronic	Stiff-Person syndrome
Bullous pemphigold	Meniere's syndrome	Takayasu's arteritis
Chronic fatigue syndrome	Mooren's ulcer	Ulcerative colitis
Chronic inflammatory demyelinating polyneuropathy	Morphea	Vitiligo
Chung-Strauss syndrome	Multiple sclerosis	Vogt-Kovanagi-Harada disease
Crohn's disease	Myasthenia gravis	Wegener's granulomatosis
Dermatomyositis	Neuromyotonia	
Diabetes mellitus type 1	Opsoclonus myoclonus syndrome	
Dysautonomia	Optic neuritis	

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most *immune-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. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, *immune-mediated* toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over $\geq$1 month to $\leq$ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for $>$ 105 days after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for $>$ 105 days to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for $>$ 105 days if the Medical Monitor agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for

pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

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

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

Table 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 3.

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

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist $>$ 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 4.

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

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening *immune-mediated* hyperthyroidism. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab. *Immune-mediated* myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, *laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities,* dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. *Immune-mediated* myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 6 Management Guidelines for *Immune-Mediated* Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 1	• Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated myocarditis, Grade 3–4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

INFUSION-RELATED REACTIONS *AND CYTOKINE-RELEASE SYNDROME*

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) *or cytokine-release syndrome (CRS)* with atezolizumab may receive premedication with antihistamines*,* anti-pyretics*, and/or* analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

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

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs *and CRS* are provided in Table 7.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 7 Management Guidelines for Infusion-Related Reactions *and Cytokine-Release Syndrome*

Event	Management
Grade 1 [a] *Fever [b] with or without constitutional symptoms*	• *Immediately interrupt infusion.* • *Upon symptom resolution, wait for 30 minutes and then restart infusion at* half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • *If symptoms recur, discontinue infusion of this dose.* • *Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration.* • *In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2.* • *For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.*

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

Grade 2 [a] *Fever [b] with hypotension not requiring vasopressors* ***and/or*** *Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by*	• *Immediately interrupt* infusion. • *Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.* • *If symptoms recur, discontinue infusion of this dose.* • *Administer symptomatic treatment.* [c] • *For hypotension, administer IV fluid bolus as needed.* • *Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.* • *Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix.* • *Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).* • *Consider anti-cytokine therapy.* [e] • *Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor.* • *If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered.* For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs *and/or CRS*. • *If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.*

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

Grade 3 [a] *Fever [b] with hypotension requiring a vasopressor (with or without vasopressin)* ***and/or*** *Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask*	• Permanently discontinue atezolizumab and contact Medical Monitor. [f] • *Administer symptomatic treatment. [c]* • *For hypotension, administer IV fluid bolus and vasopressor as needed.* • *Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.* • *Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix.* • *Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).* • *Consider anti-cytokine therapy. [e]* • *Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.*
Grade 4 [a] *Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin)* ***and/or*** *Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)*	• *Permanently discontinue atezolizumab and contact Medical Monitor. [f]* • *Administer symptomatic treatment. [c]* • *Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice.* • *Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix.* • *Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).* • *Consider anti-cytokine therapy. [e] For patients who are refractory to anti-cytokine therapy, experimental treatments [g] may be considered at the discretion of the investigator and in consultation with the Medical Monitor.* • *Hospitalize patient until complete resolution of symptoms.*

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

ASTCT =American Society for Transplantation and Cellular Therapy; BiPAP =bi-level positive airway pressure; CAR =chimeric antigen receptor; CPAP =continuous positive airway pressure; CRS =cytokine-release syndrome; CTCAE =Common Terminology Criteria for Adverse Events; eCRF =electronic Case Report Form; HLH =hemophagocytic lymphohistiocytosis; ICU =intensive care unit; IRR=infusion-related reaction*; MAS =macrophage activation syndrome; NCCN =National Cancer Comprehensive Network; NCI =National Cancer Institute.*

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] *Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.*

[b] *Fever is defined as temperature ≥38 ℃ not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.*

[c] *Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.*

[d] *Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.*

[e] *There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.*

[f] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. *For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after consulting the Medical Monitor and considering the benefit–risk ratio.*

[g] *Refer to Riegler et al. (2019) for information on experimental treatments for CRS.*

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	• Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-MEDIATED MENINGOENCEPHALITIS

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

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for *Immune-Mediated* Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Refer patient to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

RENAL EVENTS

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. *R*enal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal

renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13 Management Guidelines for *Immune-Mediated* Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 13 Management Guidelines for *Immune-Mediated* Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- *Fever ≥38.5°C*
- *Splenomegaly*
- *Peripheral blood cytopenia consisting of at least two of the following:*
  - *Hemoglobin <90 g/L (9 g/dL) (<100 g/L [10 g/dL] for infants <4 weeks old)*
  - *Platelet count <100 ×10^9/L (100,000/μL)*
  - *ANC <1.0 ×10^9/L (1000/μL)*
- *Fasting triglycerides >2.992 mmol/L (265 mg/dL) and/or fibrinogen <1.5 g/L (150 mg/dL)*
- *Hemophagocytosis in bone marrow, spleen, lymph node, or liver*
- *Low or absent natural killer cell activity*
- *Ferritin >500 mg/L (500 ng/mL)*
- *Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥2 standard deviations above age-adjusted laboratory-specific norms*

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

- *Ferritin >684 mg/L (684 ng/mL)*
- *At least two of the following:*
  - *Platelet count ≤181 ×10^9/L (181,000/μL)*
  - *AST ≥48 U/L*
  - *Triglycerides >1.761 mmol/L (156 mg/dL)*
  - *Fibrinogen ≤3.6 g/L (360 mg/dL)*

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	*Management*
Suspected HLH or MAS	• *Permanently discontinue atezolizumab and contact Medical Monitor.* • *Consider patient referral to hematologist.* • *Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines.* • *Consider initiation of IV corticosteroids and/or an immunosuppressive agent.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

HLH =hemophagocytic lymphohistiocytosis; MAS =macrophage activation syndrome.

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