Official Title: A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY EVALUATING THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (MPDL3280A, ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH CARBOPLATIN + NAB-PACLITAXEL FOR CHEMOTHERAPY-NAIVE PATIENTS WITH STAGE IV NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

NCT Number: NCT02367781

Document Dates: Protocol Amendment Version 7: 24 October 2018

SAP Version 4: 4 May 2018

PROTOCOL

TITLE: **A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY EVALUATING THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (MPDL3280A, ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH CARBOPLATIN + NAB-PACLITAXEL FOR CHEMOTHERAPY-NAIVE PATIENTS WITH STAGE IV NON-SQUAMOUS NON–SMALL CELL LUNG CANCER**

PROTOCOL NUMBER: GO29537/NCT02367781

VERSION NUMBER: 7

EUDRACT NUMBER: 2014-003206-32

IND NUMBER: 117296

TEST PRODUCT: Atezolizumab (MPDL3280A, RO5541267)

MEDICAL MONITOR: [redacted], M.D.

SPONSOR: F. Hoffmann-La Roche Ltd

DATE FINAL: 21 November 2014

DATES AMENDED: Version 2: 29 March *2015*
Version 3: *24* August 2015
Version 4: 11 November 2015
Version 5: 15 June 2016
Version 6: 1 March 2017
Version 7: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	24-Oct-2018 09:26:56

PROTOCOL AMENDMENT, VERSION 7:
RATIONALE

Protocol GO29537 has been amended to reflect a change in the definition for the end of study. Changes to the protocol, along with a rationale for each change, are summarized below:

- The end of study definition has been corrected. This correction ensures that the study continues until last patient, last visit or until the Sponsor terminates the study (Section 3.2).
- The inclusion criterion that addresses female contraception has been modified to specify when women must refrain from donating eggs (Section 4.1.1).
- Instructions about patient withdrawal from the Roche Clinical Repository after site closure have been modified to indicate that the investigator must inform the Sponsor of patient withdrawal by emailing the study number and patient number to global_rcr-withdrawal@roche.com (Section 4.5.11.6).
- The Medical Monitor has been changed, and the contact information has been revised accordingly (Section 5.4.1).
- Language has been revised to account for the fact that some sites may not allow follow-up on partner pregnancies (Section 5.4.3.2).
- Language has been updated to indicate that therapeutic or elective abortions are not considered adverse events unless performed because of an underlying maternal or embryofetal toxicity. In such cases, the underlying toxicity should be reported as a serious adverse event. Language has also been added to clarify that all abortions are to be reported on the paper Clinical Trial Pregnancy Reporting Form (Section 5.4.3.3).
- Language has been added for consistency with Roche's current data retention policy and to accommodate more stringent local requirements (if applicable) (Section 7.6).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY EVALUATING THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (MPDL3280A, ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH CARBOPLATIN + NAB-PACLITAXEL FOR CHEMOTHERAPY-NAIVE PATIENTS WITH STAGE IV NON-SQUAMOUS NON–SMALL CELL LUNG CANCER**
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TEST PRODUCT:	Atezolizumab (MPD3280A, RO5541267)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy to the Sponsor or their designee.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY EVALUATING THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (MPDL3280A, ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH CARBOPLATIN + NAB-PACLITAXEL FOR CHEMOTHERAPY-NAIVE PATIENTS WITH STAGE IV NON-SQUAMOUS NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO29537
VERSION NUMBER:	7
EUDRACT NUMBER:	2014-003206-32
IND NUMBER:	117296
TEST PRODUCT:	Atezolizumab (MPDL3280A, RO5541267)
PHASE:	III
INDICATION:	Non-squamous non–small cell lung cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

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

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

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

Efficacy Objectives

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

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

The secondary efficacy objectives for this study are the following:

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

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed duration of response according to RECIST v1.1 for both the tGE-WT population and the ITT-WT population
- To evaluate the OS rate at 1 and 2 years in each treatment arm in the tGE-WT population and the ITT-WT population
- To determine the impact of atezolizumab as measured by time to deterioration (TTD) in patient-reported lung cancer symptoms of cough, dyspnea (single-item and multi-item subscales), chest pain, or arm/shoulder pain, using the European Organisation for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire–Core 30 (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13) in the tGE-WT population and the ITT-WT population
- To determine the impact of atezolizumab as measured by change from baseline (i.e., improvement or deterioration based upon presenting symptomatology) in patient-reported lung cancer symptom (chest pain, dyspnea, and cough) score using the Symptoms in Lung Cancer (SILC) scale symptom severity score in the tGE-WT population and the ITT-WT population

Safety Objectives

The safety objectives for this study are the following:

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

Pharmacokinetic Objectives

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

- To characterize the pharmacokinetics of atezolizumab when given in combination with carboplatin and nab-paclitaxel
- To characterize the pharmacokinetics of carboplatin when given in combination with nab-paclitaxel with and without atezolizumab
- To characterize the pharmacokinetics of nab-paclitaxel when given in combination with carboplatin with and without atezolizumab

Exploratory Objectives

The exploratory objectives for this study are the following:

- To evaluate PFS at 6 months and at 1 year in each treatment arm
- To evaluate the OS rate at 3 years in each treatment arm
- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status, mechanisms of resistance, and/or response to study treatment
- To evaluate the utility of biopsy at the time of apparent disease progression to distinguish apparent increases in tumor volume related to the immunomodulatory activity of atezolizumab (i.e., pseudoprogression/tumor immune infiltration) from true disease progression
- To evaluate and compare patient's health status as assessed by the EuroQoL 5 Dimensions 3-Level (EQ-5D-3L) questionnaire to generate utility scores for use in economic models for reimbursement
- To determine the impact of atezolizumab as measured by change from baseline in patient-reported outcomes of health-related quality of life, lung cancer–related symptoms, and functioning as assessed by the EORTC QLQ-C30 and QLQ-LC13

Study Design

Description of Study

This is a randomized, Phase III, multicenter, open-label study (IMpower130) designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin + nab-paclitaxel compared with treatment with carboplatin + nab-paclitaxel in approximately 715 chemotherapy-naive patients with Stage IV non-squamous non–small cell lung cancer (NSCLC).

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

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

Treatment Arm B: Carboplatin + nab-paclitaxel (Induction: four or six 21-day cycles); best supportive care or pemetrexed (Maintenance: 21-day cycles)

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

Following the induction phase, patients who are randomized to atezolizumab (Arm A) may continue treatment with atezolizumab beyond radiographic disease progression according to RECIST v1.1, provided they are experiencing clinical benefit as assessed by the investigator (i.e., in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results [if available], and clinical status). Patients randomized to carboplatin + nab-paclitaxel (Arm B) will be offered best supportive care provided they have non-progressive disease. Switch maintenance to pemetrexed is also permitted for patients randomized to Arm B. Switch maintenance must be administered within 6 weeks of Day 1 of the last induction cycle.

Patients who entered Study GO29537 under Protocol Versions 1–4 and are randomized to carboplatin + nab paclitaxel will be given the option to cross over to receive atezolizumab as monotherapy upon progressive disease per RECIST v1.1, provided they continue to meet eligibility criteria. Safety data for patients who crossed over from Arm B to receive atezolizumab as allowed under Protocol Versions 1–4 will be summarized for exploratory purposes.

For Atezolizumab-Treated Patients Only

During treatment (induction or maintenance), patients receiving atezolizumab (including patients in Arm B who entered Study GO29537 under Protocol Versions 1–4 and crossed over to receive atezolizumab after disease progression according to RECIST v1.1) who show evidence of clinical benefit will be permitted to continue atezolizumab after the criteria per RECIST v1.1 for progressive disease are met if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values, e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing atezolizumab at the time of initial progression

Treatment with induction chemotherapy (Arms A and B) and pemetrexed (Arm B) as switch maintenance must be discontinued in all patients who exhibit evidence of progressive disease according to RECIST v1.1.

Patients will undergo tumor assessments at baseline and every 6 weeks for the first 48 weeks following Cycle 1, Day 1, regardless of dose delays. After 48 weeks, tumor assessment will be required every 9 weeks. Patients will undergo tumor assessments until radiographic disease progression 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), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. Patients who discontinue treatment for reasons other than radiographic disease progression according to RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments until radiographic disease progression 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), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.

All primary imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints. The independent reviews of the stored scans will be performed when requested.

Patients in all treatment arms will undergo a mandatory tumor biopsy sample collection, unless not clinically feasible as assessed and documented by investigators, at the first evidence of radiographic disease progression. These data will be used to explore whether radiographic findings are consistent with the presence of tumor. Additionally, these data will be analyzed to evaluate the association between changes in tumor tissue and clinical outcome and to understand further the potential mechanisms of progression and resistance to atezolizumab as compared with such mechanisms after treatment with chemotherapy alone. This exploratory biomarker evaluation will not be used for any treatment-related decisions. Patients in Arm A and patients in Arm B (who entered Study GO29537 under Protocol Versions 1–4) who are unable to undergo biopsy sample collection but who otherwise meet the criteria listed above may continue/crossover to receive atezolizumab.

Number of Patients

Approximately 105 sites globally will participate in the study, and approximately 715 patients will be randomized.

Target Population

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

Inclusion Criteria

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

- Signed Informed Consent Form
- Male or female, 18 years of age or older
- ECOG performance status of 0 or 1
- Histologically or cytologically confirmed, Stage IV non-squamous NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 7th edition)

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

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

  Patients known to have an *ALK* fusion oncogene must have experienced disease progression (during or after treatment) or intolerance to treatment with one or more ALK

inhibitors (e.g., crizotinib) appropriate for the treatment of NSCLC in patients having an *ALK* fusion oncogene.

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

Patients who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomization since the last chemotherapy, radiotherapy, or chemoradiotherapy cycle.

- Patients with a history of treated asymptomatic central nervous system (CNS) metastases are eligible, provided they meet all of the following criteria:

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

  No ongoing requirement for corticosteroids as therapy for CNS disease

  No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomization

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

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

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

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

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

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

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

- Measurable disease, as defined by RECIST v1.1

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

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

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

  Lymphocyte count $\geq$ 500/μL

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

  Hemoglobin $\geq$ 9.0 g/dL

  Patients may be transfused to meet this criterion.

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

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

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

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

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

  Serum bilirubin $\leq$ 1.25 $\times$ ULN

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

  Serum creatinine $\leq$ 1.5 $\times$ ULN
- For female patients of childbearing potential agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate [< 1% per year] when used consistently and correctly, and to continue its use for 5 months after the last dose of atezolizumab or for 30 days after the last dose of nab-paclitaxel, whichever is later. *Women must refrain from donating eggs during this same period.* For male patients with female partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate [< 1% per year] when used consistently and correctly, and to continue its use for 6 months after the last dose of nab-paclitaxel and/or carboplatin, whichever is later. 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, intrauterine hormone-releasing system, bilateral tubal occlusion or vasectomized partner (on the understanding that this is the only one partner during the whole study duration), and sexual abstinence. Male patients should not donate sperm during this study and for at least 6 months after the last dose of nab-paclitaxel and/or carboplatin, whichever is later.
- Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drug. The same rules are valid for male patients involved in this clinical study if they have a partner of childbirth potential. Male patients must always use a condom.
- Women who are not postmenopausal ($\geq$ 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.

<u>Exclusion Criteria</u>

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

Cancer-Specific Exclusions

- Active or untreated CNS metastases as determined by computed tomography 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 locoregional therapy, if appropriate, prior to randomization.

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

  Patients with indwelling catheters (e.g., PleurX®) are allowed.

- Uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > ULN)

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

- Malignancies other than NSCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
- Known tumor PD-L1 expression status as determined by an IHC assay from other clinical studies (e.g., patients whose PD-L1 expression status was determined during screening for entry into a study with anti–PD-1 or anti–PD-L1 antibodies but were not eligible are excluded)

General Medical Exclusions

- Women who are pregnant, lactating, or intending to become pregnant during the study
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

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

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

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

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

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

No acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high-potency or oral steroids)

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

- Positive test for HIV

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

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

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible only if they are negative for HBV DNA.

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

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

- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within the 3 months prior to randomization, unstable arrhythmias, or unstable angina

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction $<$ 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

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

Exclusion Criteria Related to Medications

- Any approved anti-cancer therapy, including hormonal therapy within 21 days prior to initiation of study treatment; the following exceptions are allowed:

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

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

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

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

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

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

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

Exclusions Related to Chemotherapy

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

Length of Study

The final PFS analysis will be conducted when all of the following criteria have been met: approximately 225 PFS events have occurred in the tGE-WT population, approximately 475 PFS events have occurred in the ITT-WT population, and the last patient has been enrolled in the study. This is expected to occur approximately 32 months after the first patient is enrolled.

The final OS analysis will be conducted when approximately 457 OS events have occurred in the ITT-WT population. This is expected to occur approximately 42 months after the first patient is enrolled.

End of Study

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

Outcome Measures

Efficacy Outcome Measures

The co-primary efficacy outcome measures for this study are as follows:

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

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

- OS in the tGE-WT population
- PFS, as determined by the investigator according to RECIST v1.1, and OS in the TC2/3 or IC2/3 WT population and the TC1/2/3 or IC1/2/3 WT population
- PFS, as determined by the investigator according to RECIST v1.1, and OS in the tGE population and the ITT population
- Objective response, defined as a partial response or a complete response as determined by the investigator according to RECIST v1.1 for the tGE-WT population and the ITT-WT population
- DOR, defined as the time interval from first occurrence of a documented objective response to the time of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first for the tGE-WT population and the ITT-WT population
- OS rates at 1 and 2 years for the tGE-WT population and the ITT-WT population
- TTD in patient-reported lung cancer symptoms, defined as time from randomization to deterioration (10-point change) on each of the EORTC QLQ-C30 and EORTC QLQ-LC13 symptom subscales (cough, dyspnea [single item], dyspnea [multi-item subscale], chest pain, and arm/shoulder pain) in the tGE-WT population and the ITT-WT population
- Change from baseline in patient-reported lung cancer symptoms (chest pain, dyspnea, and cough) on the symptom severity score of the SILC scale in the tGE-WT population and the ITT-WT population

Safety Outcome Measures

The safety outcome measures for this study are the following:

- Incidence, nature, and severity of adverse events graded according to the NCI CTCAE v4.0
- Changes in vital signs, physical findings, and clinical laboratory results during and following atezolizumab administration
- Incidence of ATA response to atezolizumab and potential correlation with PK, pharmacodynamic, safety, and efficacy parameters

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are the following:

- For patients randomized to atezolizumab + carboplatin + nab-paclitaxel:

  Maximum observed serum atezolizumab concentration (C_{max}) after infusion on Cycle 1, Day 1

  Minimum observed serum atezolizumab concentration (C_{min}) prior to infusion at selected cycles, at treatment discontinuation, and at 120 days (±30 days) after the last dose of atezolizumab

  Plasma concentrations for carboplatin (Arms A and B)

  Plasma concentrations for nab-paclitaxel reported as total paclitaxel (Arms A and B)

- For patients randomized to carboplatin + nab-paclitaxel who crossed over to receive open-label atezolizumab as monotherapy (allowed under Study GO29537 Protocol Versions 1–4):

  C_{max} of serum atezolizumab after infusion on Day 1 of the first cycle following crossover to atezolizumab as monotherapy

  C_{min} of serum atezolizumab prior to infusion on Day 1 at selected cycles following crossover to atezolizumab as monotherapy, at treatment discontinuation, and at 120 (±30 days) after the last dose of atezolizumab

Exploratory Outcome Measures

The exploratory outcome measures for this study are the following:

- PFS at 6 months and at 1 year
- OS rate at 3 years
- Status of PD-L1–, immune- , and NSCLC-related and other exploratory biomarkers in archival and/or freshly obtained tumor tissues and blood (or blood derivatives) collected before, during, or after treatment with atezolizumab or at progression and association with disease status and/or response to atezolizumab in combination with chemotherapy
- Status of ICs and other exploratory biomarkers in mandatory biopsy specimens and blood collected at progression
- Utility scores of the EQ-5D-3L
- Change from baseline in patient-reported outcomes of HRQoL, lung cancer-related symptoms, and functioning as assessed by the EORTC QLQ-C30 and QLQ-LC13

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal products (IMPs) for this study are atezolizumab and erlotinib.

Atezolizumab (1200 mg IV) will be administered on Day 1 of each 21–day cycle. Atezolizumab will be administered to patients who are randomized to Arm A and to patients in Arm B who cross over at progression.

Switch maintenance treatment with erlotinib is no longer permitted. However, patients who had already started switch maintenance treatment with erlotinib under Protocol Versions 1–4 may be allowed to continue treatment with erlotinib upon discussion of the risks, potential benefits and alternative treatment options with the investigator. For those patients who receive switch maintenance, institutions should follow the dosage and administration instructions in the prescribing information.

Comparator

Nab-paclitaxel (100 mg/m^2 IV) will be administered on Days 1, 8, and 15 of each 21-day cycle for four or six cycles during the induction phase. Nab-paclitaxel will be considered an IMP for study purposes in countries where nab-paclitaxel is considered an IMP by local regulations.

Non-Investigational Medicinal Products

Comparator

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

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

Statistical Methods

Primary Analysis

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

described below (see "Determination of Sample Size"). At least one interim OS analysis will be performed.

PFS is defined as the time between the date of randomization and the date of first documented disease progression or death, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

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

The following analyses will be performed for both PFS and OS. PFS and OS will be compared between treatment arms with the use of the stratified log-rank test. The HR for PFS and OS for treatment comparisons will be estimated using a stratified Cox regression model, respectively. The 95% CI for the HR will be provided.

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

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

Analyses will be conducted according to an analysis hierarchy and an α-spending algorithm to control for the type I error rate and to account for an interim analysis.

To control the overall type I error rate for the one-sided test at 0.025, a one-sided type I error (α) of 0.003 and 0.022 (ratio of 3:22) will be allocated to PFS and OS, respectively.

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

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

Determination of Sample Size

This study will randomize approximately 715 patients. The ITT-WT population will include approximately 650 patients, assuming a prevalence of approximately 10% for sensitizing EGFR mutations or ALK translocations. The tGE-WT population will include approximately 325 patients, assuming a 50% prevalence with the chosen tGE cutoff.

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

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

- 93% power to detect an HR of 0.55, corresponding to an improvement in median PFS from 6 months to 10.9 months in the tGE-WT population with a one-sided α of 0.003
- 95% power to detect an HR of 0.65, corresponding to an improvement in median PFS from 6 months to 9.2 months in the ITT-WT population with a one-sided α of 0.003
- No interim analyses for PFS
- Dropout rate of 5% per 12 months

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

- 80% power to detect an HR of 0.75, corresponding to an improvement in median OS from 12 months to 16 months in the ITT-WT population with a one-sided α of 0.022
- One interim OS analysis performed at the time of the final PFS analysis, at which time approximately 77% of the total number of OS events required for the final analysis are expected to have occurred as determined through use of the Lan-DeMets approximation to the O'Brien-Fleming boundary
- Dropout rate of 5% per 24 months

With these assumptions, approximately 715 patients in total will be enrolled in this study, with approximately 650 patients in the ITT-WT population. The final PFS analysis will be conducted when all of the following criteria have been met: approximately 225 PFS events have occurred in the tGE-WT population, approximately 475 PFS events have occurred in the ITT-WT population, and the last patient has been enrolled in the study. The final PFS analysis is expected to occur approximately 32 months after the first patient is enrolled. These numbers of events would allow for a minimum detectable difference corresponding to an HR of 0.68 in the tGE-WT population and 0.76 in the ITT-WT population, respectively.

With a sample size of 650 patients, approximately 457 OS events are expected to occur in the ITT-WT population. The final OS analysis is expected to occur approximately 42 months after the first patient is enrolled. This number of events would allow for a minimum detectable difference corresponding to an HR of 0.81 in the ITT-WT population.

Interim Analyses

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

If approximately 352 OS events have occurred in the ITT-WT population at the time of the PFS final analysis, an interim OS analysis will be conducted in the ITT-WT population. If there are significantly fewer than the expected 352 OS events at the final PFS analysis, a nominal α of 0.01% (negligible impact on overall type I error rate) will be spent on the OS analysis at the time of the PFS final analysis and a second interim OS analysis will then be conducted after approximately 352 OS events have occurred.

The final OS analysis will be conducted when approximately 457 OS events have occurred in the ITT-WT population. This is expected to occur approximately 42 months after the first patient is enrolled.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALK	anaplastic lymphoma kinase
anti-HBc	antibody to hepatitis B core antigen
ATA	anti-therapeutic antibody
AUC	area under the concentration–time curve
BSC	best supportive care
CL	clearance
C_{max}	maximum observed serum concentration
C_{min}	minimum observed serum concentration
CR	complete response
CRC	colorectal cancer
CRCL	creatinine clearance
CRF	Case Report Form
ctDNA	circulating-tumor DNA
C_{trough}	trough concentration
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	electronic PRO
EQ-5D-3L	EuroQoL 5 Dimensions 3-Level Version
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FOLFOX	oxaliplatin, leucovorin, and 5-fluorouracil
GFR	glomerular filtration rate
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
HRQoL	health-related quality of life

Abbreviation	Definition
IC	tumor-infiltrating immune cell
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IRF	Independent Review Facility
ITT	intent to treat
IV	intravenous
IxRS	interactive voice or Web-based response system
LFT	liver function test
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PVC	polyvinylchloride
Q3W	every 3 weeks
QLQ-C30	Quality-of-Life Questionnaire Core 30
QLQ-LC13	Quality-of-Life Questionnaire Lung Cancer Module
qRT-PCR	quantitative reverse transcriptase–polymerase chain reaction
RCC	renal cell carcinoma
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RRR	response rate ratio
SAP	Statistical Analysis Plan

Abbreviation	Definition
SILC	Symptoms in Lung Cancer
TC	tumor cell
TE	thromboembolic events
tGE	tumor gene expression
TIR	time in response
TKI	tyrosine kinase inhibitor
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
TTD	time to deterioration
UBC	urothelial bladder cancer
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
V_{ss}	volume of distribution at steady state
WT	wild type

1. BACKGROUND

1.1 BACKGROUND ON LUNG CANCER

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

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

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

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

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

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

1.1.1 First-Line Treatment for Advanced NSCLC with an *EGFR* Mutation or *ALK* Rearrangement

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

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

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

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

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

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

Recently, immune checkpoint inhibitors, including PD-L1 and 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 (TCs). Patients with sensitizing mutation of the EGFR gene or translocation of the ALK gene were excluded from this study. In this study, median PFS was 10.3 months in the pembrolizumab group versus 6.0 months in the chemotherapy group (HR = 0.50; 95% CI: 0.37, 0.68; p<0.001). The estimated rate of overall survival (OS) at 6 months was 80.2% (95% CI: 72.9%, 85.7%) in the pembrolizumab group versus 72.4% (95% CI: 64.5%, 78.9%) in the chemotherapy group; median OS was not reached in either group. OS was significantly longer in the pembrolizumab group than in the chemotherapy group (HR = 0.60; 95% CI: 0.41, 0.89; p = 0.005) (Reck et al. 2016). On the basis of this study, pembrolizumab was approved for the first-line treatment of metastatic NSCLC in patients whose tumors have high PD-L1 expression (tumor proportion score ≥ 50%) with no EGFR or ALK gene aberrations.

1.1.3 nab-Paclitaxel + Carboplatin for First-Line NSCLC

Socinski et al. (2012) conducted a Phase III randomized study evaluating the efficacy and safety of albumin-bound paclitaxel (nab-paclitaxel; ABRAXANE®) + carboplatin compared with solvent-based paclitaxel + carboplatin in 1052 previously untreated patients with NSCLC. The primary efficacy endpoint of this study was ORR with secondary endpoints of PFS and OS. Patients treated with nab-paclitaxel + carboplatin demonstrated a significantly improved ORR compared with patients treated with paclitaxel + carboplatin (33% vs. 25%; response rate ratio [RRR] = 1.31; p = 0.005), with patients with squamous histology experiencing the greatest improvement (41% vs. 24%; RRR = 1.68; p < 0.001). In patients with non-squamous histology, nab-paclitaxel + carboplatin achieved a similar ORR as paclitaxel + carboplatin (26% vs.

25%, respectively). There was a comparable improvement in PFS (6.3 months vs. 5.8 months; HR = 0.902; 95% CI: 0.767, 1.060) and OS (12.1 months vs. 11.2 months; HR = 0.922; 95% CI: 0.797, 1.066) in patients treated with nab-paclitaxel + carboplatin compared with paclitaxel + carboplatin in the intent-to-treat (ITT) population, respectively. No clinically meaningful differences were seen with respect to PFS (6.9 months [nab-paclitaxel + carboplatin] vs. 6.5 months [paclitaxel + carboplatin]; HR = 0.933) or OS (13.1 months [nab-paclitaxel + carboplatin] vs. 13.0 months [paclitaxel + carboplatin]; HR = 0.950) in the non-squamous subgroups. A statistically non-significant improvement in OS was seen in patients with squamous histology (10.7 months [nab-paclitaxel + carboplatin] vs. 9.5 months [paclitaxel + carboplatin]; HR = 0.890; 95% CI: 0.719, 1.101), with no difference in PFS observed in this subgroup. On the basis of these comparable clinical results, the regimen of nab-paclitaxel + carboplatin was approved for the treatment of NSCLC in the first-line setting in all histologies.

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

Table 1 Randomized Phase III Trials in Patients with Previously Untreated NSCLC

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 (0.67, 0.92)
Carboplatin, paclitaxel, and bevacizumab (n = 434)	35	6.2	12.3	
Chemotherapy [c]				
Cisplatin and pemetrexed, overall (n = 839)	31	4.8	10.3	0.94 (0.84, 1.05)
Cisplatin and gemcitabine, overall (n = 830)	28	5.1	10.3	
Cisplatin and pemetrexed, non-squamous	NR	5.3	11.8	0.81 (0.70, 0.94)
Cisplatin and gemcitabine, non-squamous	NR	4.7	10.4	
Cisplatin and pemetrexed, squamous	NR	4.4	9.4	1.23 (1.00, 1.51)
Cisplatin and gemcitabine, squamous	NR	5.5	10.8	

Table 1 Randomized Phase III Studies in Patients with Previously Untreated NSCLC (cont.)

Treatment Group	ORR (%)	Median PFS (Months)	Median OS (Months)	OS HR (95% CI)
Chemotherapy [d]				
Carboplatin and nab-paclitaxel, overall (n = 521)	33	6.3	12.1	0.922 0.797, 1.066
Carboplatin and paclitaxel, overall (n = 531)	25	5.8	11.2	
Carboplatin and nab-paclitaxel, non-squamous (n = 221)	26	6.9	13.1	0.950 NR
Carboplatin and paclitaxel, non-squamous (n = 292)	25	6.5	13.0	
Carboplatin and nab-paclitaxel, squamous (n = 300)	41	5.6	10.7	0.890 0.719, 1.101
Carboplatin and paclitaxel, squamous (n = 229)	24	5.7	9.5	
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 0.41–0.89
Platinum-based chemotherapies, PD-L1 positive (≥ 50%) (n = 151)	28	6.0	Not reached	

HR = hazard ratio; NR = not reported; NSCLC = non–small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

[a] Schiller et al. 2002.

[b] Sandler et al. 2006.

[c] Scagliotti et al. 2008.

[d] Socinski et al. 2012.

[e] Pirker et al. 2009.

[f] Reck et al. 2016.

1.1.4 AVASTIN® and Vascular Endothelial Growth Factor

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

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

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

The first study, conducted by the ECOG (Study E4599) was an open-label, randomized, Phase III study comparing the regimen of 15 mg/kg bevacizumab every 3 weeks (Q3W) in combination with carboplatin and paclitaxel versus carboplatin and paclitaxel alone as first-line treatment of patients with advanced non-squamous NSCLC. The Phase III study was based on a randomized Phase II study in patients with recurrent or advanced NSCLC that evaluated carboplatin and paclitaxel (up to six cycles) with or without bevacizumab (7.5 or 15 mg/kg) and found that the combination of bevacizumab 15 mg/kg with carboplatin and paclitaxel for up to six cycles followed by maintenance bevacizumab until disease progression resulted in increased response rates (31.5% vs. 18.8%) and prolonged time to progression (7.4 vs. 4.2 months; $p = 0.023$) compared with chemotherapy alone (Johnson et al. 2004). There was also a non-significant improvement in OS (17.7 vs. 14.9 months) (Johnson et al. 2004). A higher incidence of bleeding was noted in the bevacizumab-treated patients. Severe pulmonary hemorrhage, which was observed in 6 patients (9.1%) and led to 4 fatalities, was more common in patients with squamous cell histology, tumor necrosis, and cavitation, and central tumors (Johnson et al. 2004). On the basis of the results of this Phase II study, patients with squamous cell histology were excluded from this and other studies utilizing bevacizumab in NSCLC. In Study E4599, patients who received six cycles of bevacizumab plus chemotherapy without disease progression continued on single-agent bevacizumab until progression. A total of 878 patients were enrolled. Median OS was 12.3 months versus 10.3 months ($HR = 0.79$; $p < 0.003$); PFS was 6.2 months versus 4.5 months ($HR = 0.66$; $p < 0.001$), and the response rate was 35% (133 of 381 patients) versus 15% (59 of 392 patients) ($p < 0.001$) for patients treated with bevacizumab versus chemotherapy alone (Sandler et al. 2006).

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

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

1.1.5 Targeted Therapy for NSCLC

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

Despite progress with new targeted treatments and new chemotherapy combinations, survival rates for advanced disease remain low and acquired resistance to targeted agents is a major clinical problem. Therefore, alternative treatment options that yield durable responses and enhance OS remain an important focus of research. Against this background, immunotherapeutic agents, such as cancer vaccines and antibodies that modulate immune cell activity, offer an alternative treatment approach that could potentially improve the prognosis of patients with this disease.

1.1.6 Erlotinib or Pemetrexed Maintenance Therapy for NSCLC

NCCN guidelines (2014) on chemotherapy for Stage IV NSCLC recommend that cytotoxic regimens consisting of two drugs should be given for no more than six cycles. The guidelines also recommend stopping first-line cytotoxic chemotherapy at disease progression. At study initiation, switch maintenance treatment with erlotinib in unselected patients or pemetrexed in those with non-squamous histology could be considered for patients with stable disease or continued response to therapy after four to six cycles of chemotherapy (NCCN 2014). This recommendation was based on two randomized Phase III studies, which had shown a PFS and OS benefit after the initiation of pemetrexed or erlotinib after induction treatment in patients with non-progressive disease. In the sequential Tarceva unresectable NSCLC study (SATURN), the median

PFS in patients receiving maintenance therapy with erlotinib was significantly longer than in patients receiving placebo (12.3 vs. 11.1 weeks; HR = 0.71; 95% CI: 0.62, 0.81; $p < 0.0001$). Maintenance treatment with erlotinib also yielded a statistically significant yet clinically modest improvement in OS (12.0 vs. 11.0 months; HR = 0.81; 95% CI: 0.70, 0.95; p = 0.0088). A statistically significant improvement in PFS and OS was seen in patients with *EGFR* wild-type and *EGFR* mutation–positive tumors (Cappuzzo et al. 2010). In the JMEN 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). These Phase III studies resulted in regulatory approval (U.S. Food and Drug Administration [FDA] and European Medicines Agency) for erlotinib and pemetrexed, respectively, 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. However, recent data from Study BO25460, a Phase III, randomized, double-blind, placebo-controlled study, have demonstrated that patients with advanced or recurrent (Stage IIIB) or metastatic (Stage IV) NSCLC whose tumor did not harbor an *EGFR*-activating mutation did not achieve benefit from first-line maintenance therapy with erlotinib compared with placebo. OS was not superior in patients who were randomized to receive maintenance erlotinib followed by chemotherapy or best supportive care upon disease progression compared with patients who were randomized to receive maintenance placebo followed by erlotinib upon disease progression (HR = 1.02; 95% CI: 0.85, 1.22; p = 0.82). In the maintenance phase, patients who received erlotinib also did not have superior PFS compared with patients who received placebo (HR = 0.94; 95% CI: 0.80, 1.11; p = 0.48). This change in the benefit–risk assessment of erlotinib as switch maintenance therapy in patients whose tumors do not harbor an activating *EGFR* mutation has led to the removal of this treatment option from this protocol.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets 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 carcinoma after prior chemotherapy.

1.2.1 Summary of Nonclinical Studies

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

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

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

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

1.3 CLINICAL EXPERIENCE WITH ATEZOLIZUMAB

1.3.1 Ongoing Clinical Studies

Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as monotherapy and in combination with several anti-cancer therapies (see the Atezolizumab Investigator's Brochure for study descriptions). The single-agent safety and efficacy data 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 Q3W to patients with locally advanced or metastatic solid malignancies or hematologic malignancies
- Study GO28753 (POPLAR): A randomized, Phase II, open-label study assessing the clinical benefit of atezolizumab as a single agent versus docetaxel in patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen

- Study GO28915 (OAK): A randomized, Phase III, open-label study assessing the efficacy and safety of atezolizumab as a single agent versus docetaxel in patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen
- Study GP28328: A Phase Ib study assessing the safety and pharmacology of atezolizumab in combination with bevacizumab and/or chemotherapy in patients with advanced solid tumors

1.3.2 Clinical Safety

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

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

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

The safety profile of atezolizumab as a single agent is observed to be consistent across different indications. The most common cancer types for these patients include NSCLC, urothelial bladder cancer (UBC), melanoma, and renal cell carcinoma (RCC). Safety data for NSCLC are also derived from Studies GO28625 (FIR), GO28915 (OAK), and Study GO28753 (POPLAR).

Adverse Events

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

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

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

Note: "—" refers to missing Common Terminology Criteria grade.

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

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

Immune-Mediated Adverse Events

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

Refer to the Atezolizumab Investigator's Brochure for details on immune-mediated adverse events that were observed in patients treated with atezolizumab. Guidelines for the management of immune-mediated adverse events are described in Section 5.1.8.

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

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

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

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

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

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

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

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

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

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

A total of 141 of 144 patients (97.9%) reported at least one adverse event while receiving study drug. The majority of these events were Grade 2 or 3 in severity. The five most commonly reported adverse events across the study arms (≥ 10% of patients) included fatigue, nausea, diarrhea, decreased appetite, and pyrexia. The adverse events were consistent with the known safety profile of each agent (atezolizumab monotherapy and chemotherapy). No additive effects were observed when atezolizumab was administered with chemotherapy.

Table 5 Study GP28328: All Reported Adverse Events

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

AE = adverse event.

All 39 patients who were enrolled in Arm A reported 1 or more adverse events. The 5 most frequently reported events were consistent with the overall population and included fatigue, nausea, diarrhea, decreased appetite, and pyrexia. There were 36 patients enrolled in Arm B, and 97% of patients reported at least 1 adverse event. The most frequently reported adverse events (> 20% of patients) included fatigue, pyrexia, peripheral neuropathy, neutropenia, anemia, diarrhea, decreased appetite, temperature intolerance, constipation, vomiting, and nausea.

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

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

1.3.3 Clinical Activity

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

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

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

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

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

Table 6 displays the confirmed ORR, duration of response (DOR), and 6-month PFS rates by PD-L1 expression for patients with NSCLC. These results are based on investigator-assessed RECIST v1.1. Analyses of tumor-infiltrating immune cells (ICs) and TCs 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 in patients with NSCLC treated to date.

Table 6 Patients with NSCLC in Study PCD4989g: Investigator-Assessed Confirmed Objective Response Rate by Tumor PD-L1 Expression, Duration of Response, and Six-Month Progression-Free Survival Rates (according to 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 v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TC = tumor cell.

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

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

The primary OS analysis in Study GO28753 (POPLAR) was conducted when 173 deaths had occurred (clinical cutoff, 8 May 2015). Key efficacy results for the 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%
Duration of response		
Median (months) 95% CI	14.3 11.6, NE	7.2 5.6, 12.5

NE = not estimable.

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

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

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

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

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

Notes: The data cutoff date is 1 December 2015.

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

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

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

The co-primary endpoints of 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 according to RECIST v1.1. Objective responses with atezolizumab were durable, with a median duration of 16.3 months (95% CI: 10.0 months, not estimable) in the atezolizumab arm compared with 6.2 months (95% CI: 4.9, 7.6 months) in the docetaxel arm (Rittmeyer et al. 2017).

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

As of the 10 February 2015 data cutoff, 58 patients with NSCLC were enrolled in Arms C, D, or E of the Phase Ib study GP28328. Patients who had received their first dose of atezolizumab by 10 November 2014 were evaluable for efficacy (n = 41). Patients who were enrolled in Arms C, D, and E received 15 mg/kg atezolizumab administered Q3W in combination with carboplatin + paclitaxel, carboplatin + pemetrexed, and carboplatin + nab-paclitaxel, respectively. All patients had histologically or cytologically documented Stage IIIB, Stage IV, or recurrent NSCLC and had not received prior chemotherapy for advanced disease. The median age was 65 years, and 79% of patients had non-squamous histology. The overall confirmed ORR according to RECIST v1.1 in all three arms combined was 63% (26 of 41 patients). The ORR was 50% (95% CI: 16%, 84%) in Arm C (4 partial responses [PRs] among 8 patients), 77% (95% CI: 50%, 93%) in Arm D (13 PRs among 17 patients), and 56% (95% CI: 30%, 80%) in Arm E (5 PRs and 4 complete responses [CRs] among 16 patients). Patients with high levels of PD-L1 expression appeared to have higher response rates, but responses were also seen in patients with lower PD-L1 expression levels (Liu et al. 2015).

1.3.4 Clinical Pharmacokinetics and Immunogenicity

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

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

1.3.5 Rationale for Atezolizumab Dosage

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

The target exposure for atezolizumab was projected on the basis of nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, the observed atezolizumab interim pharmacokinetics in humans, and other factors. The

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

The atezolizumab dose is also informed by available clinical activity, safety, pharmacokinetics, and immunogenicity data. Anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg. The MTD of atezolizumab was not reached, and no DLTs have been observed at any dose in Study PCD4989g. Currently available PK and ATA data suggest that the 15-mg/kg atezolizumab Q3W regimen (or fixed-dose equivalent) for Phase II and Phase III studies would be sufficient to both maintain $C_{trough} \geq 6$ μg/mL and further safeguard against both interpatient variability and the potential effect of ATAs that could lead to subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab Q3W regimen (or fixed-dose equivalent). From inspection of available observed C_{trough} data, moving further to the 20-mg/kg atezolizumab Q3W regimen does not appear to be warranted to maintain targeted C_{trough} relative to the proposed 15-mg/kg atezolizumab Q3W level.

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

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

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

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

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

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

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

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies and who have failed standard of care therapies. At the time of Study GO29537 initiation, Study PCD4989g, a Phase Ia dose-escalation and expansion study of patients treated with atezolizumab as a single agent had the following clinical activity: 345 evaluable patients were dosed by 21 October 2013 (data cutoff date as of 21 April 2014) with a minimum of 6 months of follow-up; 62 patients experienced objective responses according to RECIST v1.1 with an ORR of 18.0% (95% CI: 14.1%, 22.3%). Objective responses were observed across a broad range of malignancies, including NSCLC, RCC, melanoma, and UBC. In Studies GO28753 (POPLAR) and GO28915 (OAK), there was significant improvement in OS with atezolizumab compared with docetaxel in patients with previously treated advanced NSCLC.

1.4.1 Rationale for Testing Atezolizumab in Combination with Carboplatin/nab-Paclitaxel

Platinum-based regimens remain the standard first-line option for patients with locally advanced or metastatic NSCLC not harboring *EGFR* mutations or *ALK* gene rearrangements. However, the survival benefit conferred by cytotoxic chemotherapy has reached a plateau, with overall response rates of approximately 20% and 1-year survival ranging from 31%–36% (Schiller et al. 2002), leaving considerable room for improvement in outcomes. TC killing by cytotoxic chemotherapy can reasonably be expected to expose the immune system to high levels of tumor antigens, and invigorating tumor-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007). Evaluating the safety and efficacy of these treatment combinations in patients with NSCLC will enable future tests of this hypothesis.

Nivolumab, a fully human IgG4 PD-1 antibody, was evaluated in combination with platinum-based doublet therapy in PD-1–unselected, chemotherapy-naive patients with NSCLC, and interim results were presented at the American Society of Clinical Oncology 2014 meeting (Antonia et al. 2014). The ORR for patients treated with gemcitabine + cisplatin, pemetrexed + cisplatin, and paclitaxel + carboplatin, in addition to 10 mg nivolumab, was 33% (n = 12), 47% (n = 15), and 47% (n = 15), respectively. The median DOR ranged from 24 weeks with nivolumab in combination with paclitaxel + carboplatin to 45 weeks with nivolumab in combination with

gemcitabine + cisplatin. The 1-year OS for patients treated with gemcitabine + cisplatin, pemetrexed + cisplatin, and paclitaxel + carboplatin in addition to 10 mg nivolumab was 50%, 87%, and 60%, respectively. Grade 3/4 treatment-related adverse events were reported in 45% of patients across all treatment arms with the most common treatment-related Grade 3/4 adverse events being pneumonitis (7%), fatigue (5%), and acute renal failure (5%) (Antonia et al. 2014).

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

Carboplatin + nab-paclitaxel was approved for the first-line treatment of patients with NSCLC on the basis of results from the randomized Phase III study comparing nab-paclitaxel + carboplatin with solvent-based paclitaxel + carboplatin. In nonclinical models, the combination with of nab-paclitaxel + atezolizumab demonstrated significantly greater anti-tumor activity than either agent alone.

In light of these observations, Study GO29537 is designed to evaluate whether the anti-tumor effect seen in atezolizumab-treated patients would translate into a statistically significant and clinically relevant improvement in prolonged PFS when used in combination with carboplatin + nab-paclitaxel compared with carboplatin + nab-paclitaxel in patients with non-squamous NSCLC. This study will allow for the evaluation of the efficacy of atezolizumab in both the ITT population, as well as in patients with PD-L1–selected tumors (defined by expression of PD-L1 in TCs and/or ICs). A PD-L1 immunohistochemistry (IHC) assay will be used to identify patients by their tumor PD-L1 expression (see Appendix 7).

Study GO29537 will enroll patients with Stage IV non-squamous NSCLC who are naive to chemotherapy treatment and for whom the experimental arm can represent a valuable treatment option and a reasonable benefit–risk balance. Patients whose tumors are known to harbor sensitizing *EGFR* mutations or *ALK* rearrangements must have experienced disease progression during or have proven intolerance during or after treatment with an EGFR tyrosine kinase or at least one ALK inhibitor, respectively (see specific inclusion criteria in Section 4.1.1), before they can enroll in the study.

In order to account for the possibility of pseudoprogression/tumor-immune infiltration (i.e., radiographic increase in tumor volume due to the influx of immune cells) (Hales et al. 2010) and the potential for delayed anti-tumor activity, this study will allow patients treated with atezolizumab to receive treatment beyond the initial apparent radiographic progression (see Section 3.3.5 and Section 4.6) and will use modified RECIST (in addition to RECIST v1.1) to evaluate clinical benefit. Because it is not yet possible to reliably differentiate pseudoprogression/tumor-immune infiltration from true tumor progression, the risk exists that some patients who are not responding to

treatment but yet continuing to receive atezolizumab may experience further progression of NSCLC and delay treatment with subsequent therapies for which they are eligible. Investigators should make every effort to fully inform patients of this risk.

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

In summary, treatment with atezolizumab offers the potential for clinical benefit in patients with NSCLC, in addition to carboplatin + nab-paclitaxel. Patients will be fully informed of the risk of continuing study treatment in spite of apparent radiographic progression and investigators should make a careful assessment of the potential benefit of doing so, considering radiographic data, biopsy results, and the clinical status of the patient.

2. OBJECTIVES

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

2.1 EFFICACY OBJECTIVES

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

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

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

2.1.1 Co-Primary Efficacy Objectives

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

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

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives for this study are the following:

- To evaluate the efficacy of atezolizumab as measured by OS in the tGE-WT population
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed PFS according to RECIST v1.1 and OS in the TC2/3 or IC2/3 WT population and the TC1/2/3 or IC1/2/3 WT population
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed PFS according to RECIST v1.1 and OS in the tGE population and the ITT population
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed ORR according to RECIST v1.1 for the tGE-WT population and the ITT-WT population
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed DOR according to RECIST v1.1 for the tGE-WT population and the ITT-WT population
- To evaluate the OS rate at 1 and 2 years in each treatment arm in the tGE-WT population and the ITT-WT population
- To determine the impact of atezolizumab as measured by time to deterioration (TTD) in patient-reported lung cancer symptoms of cough, dyspnea (single-item and multi-item subscales), chest pain, or arm/shoulder pain, using the European Organisation for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire–Core 30 (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13) in the tGE-WT population and the ITT-WT population
- To determine the impact of atezolizumab as measured by change from baseline (i.e., improvement or deterioration based upon presenting symptomatology) in patient-reported lung cancer symptom (chest pain, dyspnea, and cough) score using the Symptoms in Lung Cancer (SILC) scale symptom severity score in the tGE-WT population and the ITT-WT population

2.2 SAFETY OBJECTIVES

The safety objectives for this study are the following:

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

2.3 PHARMACOKINETIC OBJECTIVES

The PK objectives for this study are the following:

- To characterize the pharmacokinetics of atezolizumab when given in combination with carboplatin and nab-paclitaxel
- To characterize the pharmacokinetics of carboplatin when given in combination with nab-paclitaxel with and without atezolizumab
- To characterize the pharmacokinetics of nab-paclitaxel when given in combination with carboplatin with and without atezolizumab

2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are the following:

- To evaluate PFS at 6 months and at 1 year in each treatment arm
- To evaluate the OS rate at 3 years in each treatment arm
- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status, mechanisms of resistance, and/or response to study treatment
- To evaluate the utility of biopsy at the time of apparent disease progression to distinguish apparent increases in tumor volume related to the immunomodulatory activity of atezolizumab (i.e., pseudoprogression/tumor immune infiltration) from true disease progression.
- To evaluate and compare patient's health status as assessed by the EuroQoL 5 Dimensions 3-Level (EQ-5D-3L) questionnaire to generate utility scores for use in economic models for reimbursement
- To determine the impact of atezolizumab as measured by change from baseline in patient-reported outcomes of health-related quality of life, lung cancer–related symptoms, and functioning as assessed by the EORTC QLQ-C30 and QLQ-LC13

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a randomized, Phase III, multicenter, open-label study (IMpower130) designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin + nab-paclitaxel compared with treatment with carboplatin + nab-paclitaxel in approximately 715 chemotherapy-naive patients with Stage IV non-squamous NSCLC. Figure 1 illustrates the study design. The schedules of assessments are provided in Appendix 1 through Appendix 3.

Tumor specimens will be prospectively tested for PD-L1 expression by a central laboratory. Eligible patients will be stratified by sex (male vs. female), presence of liver metastases at baseline (yes vs. no), and by PD-L1 tumor expression by IHC (TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1). Patients will be randomized in a 2:1 ratio to receive one of the following treatment regimens detailed in Table 9.

Table 9 Study GO29537 Treatment Arms

Treatment Arm	Induction (Four or Six 21-Day Cycles)	Maintenance (21-Day Cycles)
A	Atezolizumab + carboplatin + nab-paclitaxel	Atezolizumab
B	Carboplatin + nab-paclitaxel	Best supportive care or pemetrexed

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

Following the induction phase, patients who are randomized to atezolizumab (Arm A) may continue treatment with atezolizumab beyond radiographic disease progression according to RECIST v1.1, provided they are experiencing clinical benefit as assessed by the investigator (i.e., in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results [if available], and clinical status). Patients randomized to carboplatin + nab-paclitaxel (Arm B) will be offered best supportive care provided they have non-progressive disease. Switch maintenance to pemetrexed is also permitted for patients randomized to Arm B. Switch maintenance must be administered within 6 weeks of Day 1 of the last induction cycle.

Patients who entered Study GO29537 under Protocol Versions 1–4 and are randomized to carboplatin + nab-paclitaxel will be given the option to cross over to receive atezolizumab as monotherapy upon progressive disease according to RECIST v1.1, provided they continue to meet eligibility criteria (see Section 4.1.1). Safety data for patients who crossed over from Arm B to receive atezolizumab as allowed under Protocol Versions 1–4 will be summarized for exploratory purposes.

For Atezolizumab-Treated Patients Only

During treatment (induction or maintenance), patients receiving atezolizumab (including patients in Arm B who entered Study GO29537 under Protocol Versions 1–4 and crossed over to receive atezolizumab after disease progression according to RECIST v1.1) who show evidence of clinical benefit will be permitted to continue atezolizumab after the criteria according to RECIST v1.1 for progressive disease are met if they meet all of the following criteria:

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

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

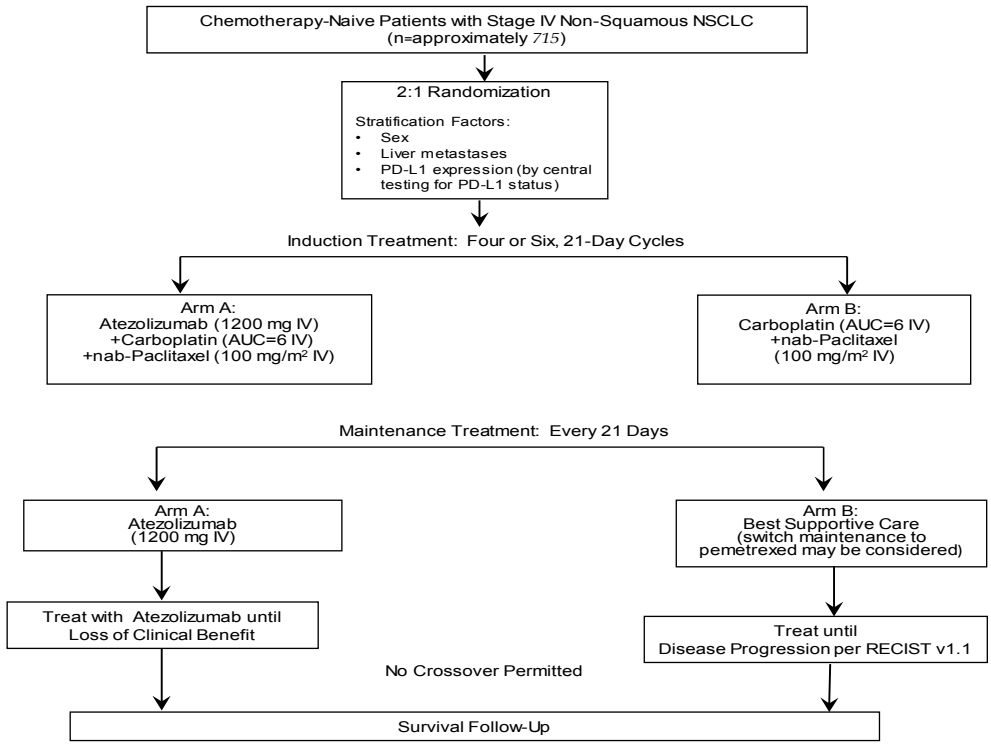
Treatment with induction chemotherapy (Arms A and B) and pemetrexed (Arm B) as switch maintenance must be discontinued in all patients who exhibit evidence of progressive disease according to RECIST v1.1.

Patients will undergo tumor assessments at baseline and every 6 weeks for the first 48 weeks following Cycle 1, Day 1, regardless of dose delays. After 48 weeks, tumor assessment will be required every 9 weeks. Patients will undergo tumor assessments until radiographic disease progression 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), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. Patients who discontinue treatment for reasons other than radiographic disease progression according to RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments until radiographic disease progression 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), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.

All primary imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints. The independent reviews of the stored scans will be performed when requested.

Patients in all treatment arms will undergo a mandatory tumor biopsy sample collection, unless not clinically feasible as assessed and documented by investigators, at the first evidence of radiographic disease progression. These data will be used to explore whether radiographic findings are consistent with the presence of tumor. Additionally, these data will be analyzed to evaluate the association between changes in tumor tissue and clinical outcome and to understand further the potential mechanisms of progression and resistance to atezolizumab as compared with such mechanisms after treatment with chemotherapy alone. This exploratory biomarker evaluation will not be used for any treatment-related decisions. Patients in Arm A and patients in Arm B (who entered Study GO29537 under Protocol Versions 1–4) who are unable to undergo biopsy sample collection but who otherwise meet the criteria listed above may continue/crossover to receive atezolizumab.

Figure 1 Study Schema



AUC = area under the concentration–time curve; IV = intravenous; NSCLC = non–small cell lung cancer; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

3.1.1 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will be used to evaluate safety during the study. Unblinded safety data will be reviewed by the iDMC on a periodic basis, approximately every 6 months from the point of first patient in (FPI). The safety data will include demographic data, adverse events, serious adverse events, and relevant laboratory data.

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

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

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

3.2 END OF STUDY

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

3.3 RATIONALE FOR STUDY DESIGN

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

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

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

Atezolizumab monotherapy has demonstrated clinical efficacy and is generally well-tolerated in patients with squamous or non-squamous NSCLC (Besse et al. 2015; Horn et al. 2015; Spigel et al. 2015; Fehrenbacher et al. 2016). In the second- and third-line setting, the POPLAR study, the first randomized Phase II study of atezolizumab in advanced NSCLC, showed significant improvement in OS with atezolizumab (12.6 vs. 9.7 months; HR = 0.73; 95% CI: 0.53, 0.99; p = 0.04) versus docetaxel (Fehrenbacher et al. 2016). In the Phase III study GO28915 (OAK), which investigated the efficacy and safety of atezolizumab compared with docetaxel in patients with previously treated locally advanced or metastatic NSCLC, OS was significantly prolonged with atezolizumab (median OS 13.8 months vs 9.6 months, HR = 0.73; 95% CI: 0.62, 0.87; p = 0.0003). In patients with squamous and non-squamous disease, OS was 8.9 versus 7.7 months (HR = 0.73; 95% CI: 0.54, 0.98), and 15.6 versus 11.2 months (HR = 0.73; 95% CI: 0.60, 0.89), respectively, in the atezolizumab arm compared with the docetaxel arm (Rittmeyer et al. 2017).

On the basis of promising efficacy of atezolizumab as a single agent (Study GO28753 [POPLAR], Study PCD4989g) and in combination with platinum-doublet therapy (Study GP28328) and the safety findings from Study GP28328 indicating no additive toxicity of atezolizumab in combination with platinum-based chemotherapy, this study will evaluate atezolizumab in combination with platinum-based chemotherapy. TC killing by cytotoxic chemotherapy may expose the immune system to high levels of tumor antigens, and invigorating tumor-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007), and this may reasonably occur in tumors regardless of PD-L1 expression.

3.3.2 Rationale for Control Arm

In this study, the control group will receive the platinum doublet of carboplatin + nab-paclitaxel, an approved regimen in the first-line treatment of advanced stage non-squamous NSCLC. Patients enrolled into the experimental arm will receive this standard chemotherapy regimen in addition to atezolizumab. The emerging safety profile of atezolizumab suggests that there is minimal risk of significant additive toxicity when it is administered with chemotherapy and that patients will be able to receive standard treatment for their disease in the setting of this clinical study. In addition, treatment with this chemotherapy regimen does not require premedication with steroids, which may attenuate potential beneficial immunologic effects of treatment with atezolizumab. This control group will be instrumental in assessing the relative benefit and safety of atezolizumab in combination with carboplatin + nab-paclitaxel compared with chemotherapy alone in the front-line treatment setting.

Based on the results from a randomized Phase III study that has shown a PFS and OS benefit after the initiation of pemetrexed after induction treatment in patients with non-progressive disease, pemetrexed is approved as maintenance treatment for patients with NSCLC in the first-line setting. Therefore, in accordance with the NCCN guidelines, switch maintenance therapy with pemetrexed may be considered for patients who are randomized to the control arm.

3.3.3 Rationale for Open-Label Study

An open-label study design was chosen for this study for the following reasons. A blinded study would require prolonged administration of placebo during the maintenance phase for patients who are randomized to Arm B, which could pose a significant burden to patients. Furthermore, because of the potential for pseudoprogression in patients randomized to atezolizumab-containing arms, a blinded study would require the option that all patients continue treatment until loss of clinical benefit regardless of whether they were receiving atezolizumab. In the absence of pseudoprogression, this could then delay subsequent treatment with approved therapies for NSCLC in patients assigned to any treatment arm, as well as increase the complexity of treatment decisions.

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

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

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

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

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

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

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

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

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Because of the potential for pseudoprogression/tumor-immune infiltration, this study will allow patients randomized to the atezolizumab treatment arm and those patients who crossed over (patients who entered Study GO29537 under Protocol Versions 1–4) to remain on atezolizumab after apparent radiographic progression, provided the benefit–risk ratio is judged to be favorable. Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status (see Section 3.1).

3.3.6 Rationale for Patient-Reported Outcome Assessments

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

Chest pain, dyspnea, and cough have been regarded as the most frequent and clinically relevant disease-related symptoms experienced by patients with NSCLC. The BR.21 study (erlotinib vs. best supportive care in second- or third-line NSCLC) demonstrated that longer TTD in the pain, dyspnea, and cough scales of the EORTC QLQ-C30 and EORTC QLQ-LC13 was consistent with superior PFS, OS, and quality-of-life benefits in the erlotinib arm compared with the placebo arm (Aaronson et al. 1993; Bergman et al. 1994; Bezjak et al. 2006). Patients in the afatinib LUX-Lung 3 first-line study also reported significant delay of TTD in lung cancer symptoms (chest pain, dyspnea, and cough) as measured by the EORTC QLQ-C30 and EORTC QLQ-LC13. (Yang et al. 2013). In this study, the validated EORTC QLQ-C30 and EORTC QLQ-LC13 will be used to assess HRQoL and symptom severity.

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

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

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

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

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

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

3.3.8 Rationale for Blood Sampling for Biomarkers

An exploratory objective of this study is to evaluate surrogate biomarkers (that may include circulating-tumor DNA [ctDNA], gene expression, tumor burden biomarkers, and

others) in blood samples. Evaluation of blood biomarkers may provide evidence for biologic activity of atezolizumab in patients with NSCLC and may allow for the development of blood-based biomarkers to help predict which patients may benefit from atezolizumab.

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

3.3.9 Rationale for the Collection of Mandatory Tumor Specimens at Radiographic Progression

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

If clinically feasible, collection of a mandatory tumor biopsy at the time of radiographic progression is required in order to evaluate the utility of the biopsy in distinguishing pseudoprogression/tumor-immune infiltration from true progression. Additionally, mechanisms relating to progression, resistance, predictive, prognostic, and pharmacodynamic relationships in tumor biomarkers (including, but not limited to, PD-L1, CD8, mutation status, and others) and efficacy will be evaluated. DNA and/or RNA extraction may be performed to enable identification of somatic mutations, by use of NGS, that are associated with disease progression or acquired resistance to atezolizumab and to increase understanding of disease pathobiology.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

3.4.1.1 Co-Primary Efficacy Outcome Measures

The co-primary efficacy outcome measures for this study are as follows:

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

3.4.1.2 Secondary Efficacy Outcome Measures

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

- OS in the tGE-WT population

- PFS, as determined by the investigator according to RECIST v1.1, and OS in the TC2/3 or IC2/3 WT population and the TC1/2/3 or IC1/2/3 WT population
- PFS, as determined by the investigator according to RECIST v1.1, and OS in the tGE population and the ITT population
- Objective response, defined as PR or CR as determined by the investigator according to RECIST v1.1 for the tGE-WT population and the ITT-WT population
- DOR, defined as the time interval from first occurrence of a documented objective response to the time of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first for the tGE-WT population and the ITT-WT population
- OS rates at 1 and 2 years for the tGE-WT population and the ITT-WT population
- TTD in patient-reported lung cancer symptoms, defined as time from randomization to deterioration (10-point change) on each of the EORTC QLQ-C30 and EORTC QLQ-LC13 symptom subscales (cough, dyspnea [single item], dyspnea [multi-item subscale], chest pain, and arm/shoulder pain) in the tGE-WT population and the ITT-WT population
- Change from baseline in patient-reported lung cancer symptoms (chest pain, dyspnea, and cough) on the symptom severity score of the SILC scale in the tGE-WT population and the ITT-WT population

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are the following:

- Incidence, nature, and severity of adverse events graded according to the NCI CTCAE v4.0
- Changes in vital signs, physical findings, and clinical laboratory results during and following atezolizumab administration
- Incidence of ATA response to atezolizumab and potential correlation with PK, pharmacodynamic, safety, and efficacy parameters

3.4.3 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are the following:

- For patients randomized to atezolizumab + carboplatin + nab-paclitaxel:

  Maximum observed serum atezolizumab concentration (C_{max}) after infusion on Cycle 1, Day 1

  Minimum observed serum atezolizumab concentration (C_{min}) prior to infusion at selected cycles, at treatment discontinuation, and at 120 days ($\pm$30 days) after the last dose of atezolizumab
- Plasma concentrations for carboplatin (Arms A and B)
- Plasma concentrations for nab-paclitaxel reported as total paclitaxel (Arms A and B)

- For patients randomized to carboplatin + nab-paclitaxel who crossed over to receive open-label atezolizumab as monotherapy (allowed under Study GO29537 Protocol Versions 1–4):

  C_{max} of serum atezolizumab after infusion on Day 1 of the first cycle following crossover to atezolizumab as monotherapy

  C_{min} of serum atezolizumab prior to infusion on Day 1 at selected cycles following crossover to atezolizumab as monotherapy, at treatment discontinuation, and at 120 (±30 days) after the last dose of atezolizumab

3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are the following:

- PFS at 6 months and at 1 year
- OS rate at 3 years
- Status of PD-L1–, immune- , and NSCLC-related and other exploratory biomarkers in archival and/or freshly obtained tumor tissues and blood (or blood derivatives) collected before, during, or after treatment with atezolizumab or at progression and association with disease status and/or response to atezolizumab in combination with chemotherapy
- Status of ICs and other exploratory biomarkers in mandatory biopsy specimens and blood collected at progression
- Utility scores of the EQ-5D-3L
- Change from baseline in patient-reported outcomes of HRQoL, lung cancer-related symptoms, and functioning as assessed by the EORTC QLQ-C30 and QLQ-LC13

4. MATERIALS AND METHODS

4.1 PATIENTS

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

4.1.1 Inclusion Criteria

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

- Signed Informed Consent Form
- Male or female, 18 years of age or older
- ECOG performance status of 0 or 1 (see Appendix 11)
- Histologically or cytologically confirmed, Stage IV non-squamous NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 7th edition; Detterbeck et al. 2009; see Appendix 4).

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

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

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

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

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

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

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

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

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

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

- Measurable disease, as defined by RECIST v1.1

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

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

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

  Lymphocyte count $\geq$ 500/μL

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

  Hemoglobin $\geq$ 9.0 g/dL

  Patients may be transfused to meet this criterion.

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

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

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

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

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

  Serum bilirubin $\leq$ 1.25 $\times$ ULN

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

  Serum creatinine $\leq$ 1.5 $\times$ ULN

- For female patients of childbearing potential agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate (< 1% per year) when used consistently and correctly, and to continue its use for 5 months after the last dose of atezolizumab or for 30 days after the last dose of nab-paclitaxel, whichever is later. *Women must refrain from donating eggs during this same period.* For male patients with female partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate (< 1% per year) when used consistently and correctly, and to continue its use for 6 months after the last dose of nab-paclitaxel and/or carboplatin, whichever is later. 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 whole study duration), and sexual abstinence. Male patients should not donate sperm during this study and for at least 6 months after the last dose of nab-paclitaxel and/or carboplatin, whichever is later.
- Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drug. The same rules are valid for male patients involved in this clinical study if they have a partner of childbearing potential. Male patients must always use a condom.
- Women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.

4.1.2 Exclusion Criteria

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

4.1.2.1 Cancer-Specific Exclusions

- Active or untreated CNS metastases as determined by CT or MRI evaluation during screening and prior radiographic assessments
- Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for > 2 weeks prior to randomization
- Leptomeningeal disease

- Uncontrolled tumor-related pain

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

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

  Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for locoregional therapy, if appropriate, prior to randomization.

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

  Patients with indwelling catheters (e.g., PleurX®) are allowed.

- Uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > ULN)

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

- Malignancies other than NSCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
- Known tumor PD-L1 expression status as determined by an IHC assay from other clinical studies (e.g., patients whose PD-L1 expression status was determined during screening for entry into a study with anti–PD-1 or anti–PD-L1 antibodies but were not eligible are excluded)

4.1.2.2 General Medical Exclusions

- Women who are pregnant, lactating, or intending to become pregnant during the study
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 13 for a more comprehensive list of autoimmune diseases)

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

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

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

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

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

No acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high-potency or oral steroids).

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

- Positive test for HIV

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

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

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible only if they are negative for HBV DNA.

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

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

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

- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to randomization, unstable arrhythmias, or unstable angina

    Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction $<$ 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
- Major surgical procedure other than for diagnosis within 28 days prior to randomization or anticipation of need for a major surgical procedure during the course of the study
- Prior allogeneic bone marrow transplantation or solid organ transplant
- Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation that such a live attenuated vaccine will be required during the study
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications
- Illness or condition that interferes with the patient's capacity to understand, follow, and/or comply with study procedures

4.1.2.3 Exclusion Criteria Related to Medications

- Any approved anti-cancer therapy, including hormonal therapy within 21 days prior to initiation of study treatment; the following exceptions are allowed:

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

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

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

        No history of severe immune-mediated adverse effects from anti–CTLA-4 (NCI CTCAE Grades 3 and 4)
- Treatment with systemic immunostimulatory agents (including, but not limited to, IFNs, IL-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to randomization

    Prior treatment with cancer vaccines is allowed.

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

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

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

4.1.2.4 Exclusions Related to Chemotherapy

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

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study.

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

Randomization to one of the two treatment arms will occur in a 2:1 ratio. Permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm. Randomization will be stratified by the following criteria:

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

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

Following disease progression, patients consented under Protocol GO29537, Versions 1–4, and randomized to Arm B will be given the option to receive atezolizumab monotherapy provided they continue to meet crossover eligibility criteria (except for no prior treatment for Stage IV non-squamous NSCLC and no prior treatment with immune checkpoint blockade therapy).

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab (MPDL3280A)

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

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

4.3.1.2 Carboplatin and nab-Paclitaxel

Carboplatin will be obtained in commercially available formulations. nab-Paclitaxel will be supplied to the sites by the Sponsor. For countries in which the Sponsor is required to provide all study drugs, including standard-of-care drugs, carboplatin will be provided by Roche or its designee.

For information on the formulation, packaging, and handling of carboplatin and nab-paclitaxel, see the prescribing information for each drug.

4.3.1.3 Erlotinib and Pemetrexed

Switch maintenance to pemetrexed is permitted for patients randomized to Arm B. Switch maintenance to erlotinib is no longer permitted. However, patients randomized to Arm B who had already started switch maintenance treatment with erlotinib under Protocol Versions 1–4 may be allowed to continue treatment with erlotinib upon discussion of the risks, potential benefits, and alternative treatment options with the investigator. Because erlotinib is considered an investigational medicinal product (IMP), erlotinib will be provided by the Sponsor if required by local health authority regulations. Pemetrexed will be obtained from commercial sources at each participating site. For information on the formulation, packaging, and handling of pemetrexed, see the prescribing information.

4.3.2 Dosage, Administration, and Compliance

Study treatment will be assigned by the IxRS. The induction phase of the study will consist of four or six cycles of chemotherapy. Atezolizumab and carboplatin will be administered on Day 1 of each 21-day cycle. nab-Paclitaxel will be administered on Days 1, 8, and 15 of each 21-day cycle. The Day 1 order of administration is as follows:

Arm A: Atezolizumab → nab-paclitaxel → carboplatin

Arm B: nab-Paclitaxel → carboplatin

During the induction phase, a chemotherapy cycle counts toward the prespecified number of induction chemotherapy cycles (four or six) as long as at least one chemotherapy component has been administered at least once during a 21-day cycle. Cycles in which no chemotherapy component is given do not count toward the total number of induction chemotherapy cycles. Additional guidance is provided in Appendix 16.

Patients who experience no further clinical benefit (for patients enrolled in Arm A, see Section 3.1 for definition) or disease progression (for patients enrolled in Arm B) at any time during the induction phase will discontinue all study treatment. In the absence of the above criteria, after the 4- or 6-cycle induction phase, patients randomized to Arm A will begin maintenance therapy with atezolizumab. Patients randomized to Arm B will receive best supportive care until disease progression. Switch maintenance to pemetrexed is also permitted for patients who are randomized to Arm B. Switch maintenance must be administered within 6 weeks of Day 1 of the last induction cycle.

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

Patients should receive anti-emetics and IV hydration for platinum-based treatments according to the local standard of care and manufacturer's instruction. On days of scheduled infusions of atezolizumab (Arm A), carboplatin and nab-paclitaxel (i.e., Day 1 of every cycle) chemotherapy should be administered in the following manner:

1. Arm A only: Atezolizumab administered over 60 (±15) minutes (for the first infusion, shortening to 30 [±10] minutes for subsequent infusions; see Table 10) followed by
2. nab-Paclitaxel (100 mg/m^2) IV administered over 30 minutes followed immediately by
3. Carboplatin IV administered over 15–30 minutes to achieve an initial target area under the concentration–time curve (AUC) of 6 mg/mL/min (Calvert formula dosing)

On Days 8 and 15, nab-paclitaxel (100 mg/m^2) IV will be administered over 30 minutes.

Chemotherapy infusion times may be adapted in accordance with local standard of care in lieu of the suggested infusion times. Chemotherapy dose modifications are allowed only to address toxicities (see Section 5.1.7.1 and Section 5.1.9 for guidelines). The investigator may use discretion in modifying or accelerating the chemotherapy dose modification, depending on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing patient compliance and access to supportive care.

Guidelines for dose modification and treatment interruption or discontinuation for carboplatin and nab-paclitaxel are provided in Section 5.1.7 and Section 5.1.9.

4.3.2.1 Atezolizumab

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

Atezolizumab infusions will be administered per the instructions outlined in Table 10.

Table 10 Administration of First and Subsequent Infusions of Atezolizumab

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

Dose modifications to atezolizumab are not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events are provided in Sections 5.1.7, 5.1.7.2, and 5.1.8.

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

4.3.2.2 Carboplatin and nab-Paclitaxel

nab-Paclitaxel

nab-Paclitaxel injection must be diluted prior to infusion. nab-Paclitaxel should be diluted in 0.9% sodium chloride injection to a final concentration of 5 mg/mL. Sites should follow their institutional standard of care for determining nab-paclitaxel dose adjustments in the event of patient weight changes. The infusion site should be closely monitored for possible infiltration during drug administration. Limiting the infusion of nab-paclitaxel to 30 minutes, as directed, reduces the likelihood of infusion-related reactions. Following administration, the IV line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection to ensure administration of the complete dose, according to local practice.

See the nab-paclitaxel prescribing information for more information.

Carboplatin

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

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

Calvert Formula

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

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

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

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

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 based on serum creatinine measurements by the isotope dilution mass spectroscopy method, the FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. Based on 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 using the following URL for more details:

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

4.3.2.3 Erlotinib and Pemetrexed

Switch maintenance treatment with erlotinib is no longer permitted. However, patients who had already started switch maintenance treatment with erlotinib under Study GO29537 Protocol Versions 1–4 may be allowed to continue treatment with erlotinib upon discussion of the risks, potential benefits, and alternative treatment options with the investigator. For those patients who receive switch maintenance, institutions should follow the dosage and administration instructions in the prescribing information.

For those patients receiving switch maintenance treatment with erlotinib see the prescribing information for erlotinib for more information on erlotinib dosing.

For those patients receiving switch maintenance treatment with pemetrexed, see the prescribing information for pemetrexed for more information on pemetrexed dosing.

4.3.2.4 Additional Required Medication

Prophylactic Measures for Carboplatin

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

4.3.3 Investigational Medicinal Product Accountability

The IMPs for this study are atezolizumab and erlotinib. Depending on local classification, in this study, nab-paclitaxel may either be considered a non-investigational medicinal product (NIMP) or an IMP. IMPs required for completion of this study will be provided by the Sponsor if required by local health authority regulations. The Sponsor or

appointed designee will supply other medicinal products in accordance with local regulations.

The study site will acknowledge receipt of the IMPs using IxRS to confirm shipment condition and content. Any damaged shipments will be replaced.

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

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

4.3.4 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 from 7 days prior to screening until the treatment discontinuation visit. All such medications should be reported to the investigator.

4.4.1 Permitted Therapy

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

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

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin or warfarin at a stable dose level)

- Palliative radiotherapy (e.g., treatment of known bony metastases) provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion being irradiated is not the only site of disease as that would render the patient not evaluable for response by tumor assessments according to RECIST v1.1)

  It is not a requirement to withhold atezolizumab during palliative radiotherapy.
- Inactive influenza vaccinations
- Megastrol administered as an appetite stimulant
- Corticosteroids ($\leq$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

Switch maintenance therapy with pemetrexed is permitted and can be considered for patients randomized to Arm B only. Switch maintenance therapy with erlotinib is no longer permitted. However, patients who had already started treatment with erlotinib under Study GO29537 Protocol Versions 1–4 may be allowed to continue treatment with erlotinib upon discussion of the risks, potential benefits, and alternative treatment options with the investigator.

Switch maintenance must be administered within 6 weeks of Day 1 of the last induction cycle. Investigators should follow the NCCN guidelines and dosage and administration instructions in the prescribing information for pemetrexed.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H_2-receptor antagonist 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). Erlotinib and pemetrexed use will be recorded on separate erlotinib and pemetrexed administration eCRFs.

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations where systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered first by the treating

physician. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the treating physician except in the case of patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance) (see also Section 4.4.3).

Systemic corticosteroids are recommended, with caution at the discretion of the treating physician, for the treatment of specific adverse events when associated with atezolizumab therapy. Guidelines for the management of immune-mediated adverse events are described in Section 5.1.8.

4.4.3 Prohibited Therapy

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

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

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

The concomitant use of herbal therapies is not recommended as 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 that are intended for the treatment of cancer are prohibited.

4.5 STUDY ASSESSMENTS

Flowcharts of scheduled study assessments are provided in Appendix 1, Appendix 2, and Appendix 3.

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

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

4.5.1 Informed Consent Forms and Screening Log

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

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

Patients who are treated with atezolizumab and who show apparent radiographic progression according to 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 have a biopsy of the progressing lesion (if clinically feasible) and to acknowledge deferring other treatment options available to them in favor of continuing treatment with atezolizumab.

Patients who entered Study GO29537 under Protocol Versions 1–4, who were assigned to the control arm, and who show disease progression by RECIST v1.1 must sign a consent to cross over to atezolizumab treatment at the time of progression to acknowledge deferring other treatment options.

4.5.2 Medical History and Demographic Data

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

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

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

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

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

4.5.4 Vital Signs

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

Vital signs will be measured and recorded as described in Table 11.

Table 11 Vital Sign Measurements at Cycle 1 and All Subsequent Cycles

Cycle 1	
Treatment Arm	Timepoints
Arm A	• Within 60 minutes prior to atezolizumab infusion • During the infusion at 15 min, 30 min, 45 min, and 60 min (± 5-min window) and within 30 (± 10) minutes after atezolizumab infusion if clinically indicated • Within 30 (± 10) minutes after carboplatin infusion
Arm B	• Within 60 minutes prior to nab-paclitaxel infusion • Within 30 (± 10) minutes after carboplatin infusion
Subsequent Cycles	
Treatment Arm	Timepoints
Arm A	• Within 60 minutes prior to atezolizumab infusion • During (every 15 [± 5] minutes) and within 30 (± 10) minutes after atezolizumab infusion if clinically indicated or symptoms occurred during prior infusion
Arm B	• Within 60 minutes prior to nab-paclitaxel infusion • During infusion if clinically indicated or if symptoms occurred during the prior infusions • Within 30 (± 10) minutes after carboplatin infusion if clinically indicated or if symptoms occurred during the prior infusion

For patients in the atezolizumab arm, also refer to Table 10.

4.5.5 Tumor and Response Evaluations

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

A CT (with contrast if not contraindicated) or MRI scan of the head must be done at screening to exclude CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. Patients with active or untreated CNS metastases are not eligible for the study (see Section 4.1.2.1).

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

Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as according to 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 using RECIST v1.1 and modified RECIST. Tumor assessments will be performed according to RECIST v1.1 and modified RECIST for patients in the atezolizumab-containing treatment arm (Arm A) and only according to RECIST v1.1 for patients in the carboplatin + nab-paclitaxel treatment arm (Arm B).

Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

Tumor assessments should occur every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1, and then every 9 weeks (±7 days) after completion of the Week 48 tumor assessment, regardless of treatment delays until radiographic disease progression according to RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab beyond 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 according to RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments until 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), 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 according to RECIST v1.1 will continue scheduled tumor assessments until

radiographic disease progression according to RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

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

Scans will be submitted to an IRF.

4.5.6 Laboratory Assessments and Biomarker Samples

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

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

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

  Total T3 to be tested only at sites where free T3 testing is not performed.
- HBV serology: hepatitis B surface antigen (HBsAg), antibodies against HBsAg, and total hepatitis B core antibody (HBcAb)

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

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

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

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

- ATA assays (all atezolizumab-treated patients)

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

- PK assays

  Blood samples for PK assessments will be obtained according to the schedule in Appendix 2 and Appendix 3.

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

  At selected sites, a subset of 20 patients in each arm will undergo the additional PK assessments for carboplatin and nab-paclitaxel.

    Plasma carboplatin and nab-paclitaxel concentrations (reported as total paclitaxel) will be assayed using validated methods.

- Biomarker assays in blood samples

  Blood samples will be obtained for biomarker evaluation (including but not limited to biomarkers that are related to NSCLC or tumor immune biology) from all eligible patients according to the schedule in Appendix 2 and Appendix 3. Samples will be processed to obtain plasma and serum for the determination of changes in blood-based biomarkers (e.g., ctDNA, cytokines). Whole blood samples may be processed to obtain their derivatives (e.g., RNA and DNA) and evaluated for immune-related, tumor type–related, and other exploratory biomarkers (e.g., alterations in gene expression or single nucleotide polymorphisms).

- For patients who consent to the optional collection of samples for the Roche Clinical Repository (RCR), any leftover material from the above sample collection will be stored and used for exploratory analyses as indicated in Section 4.5.11. For patients who consent to RCR optional future research on their whole blood samples collected at screening but are determined to be ineligible for study participation, these samples and their derivatives (e.g., DNA, RNA, protein) may be used for future development of biomarker and/or diagnostic tests as indicated in Section 4.5.11.

4.5.7 Tumor Tissue Samples

4.5.7.1 Archival and Freshly Collected Tumor Tissue Samples for Screening

Representative tumor specimens in paraffin blocks (preferred) or 15 (or more) freshly cut, serial unstained sections on slides, with an associated pathology report, must be submitted at screening for determination of PD-L1 status prior to study randomization. If fewer than 15 slides are available at baseline (but no fewer than 10), the patient may still be eligible, upon discussion with the Medical Monitor. In addition, expression of PD-L1 and T-effector gene signature will be evaluated. Exploratory biomarkers (including, but not limited to, markers related to immune or NSCLC biology, such as T-cell markers or non-inherited biomarkers identified through NGS on extracted DNA and/or RNA) may also be evaluated. The biomarkers will be identified by IHC, quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR), NGS, and/or other methods.

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

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

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

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

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

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

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

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

4.5.7.2 Tumor Samples at the Time of Radiographic Progression

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

Acceptable samples include the following:

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

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

NGS may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator can obtain results from the samples collected at the time of disease progression in the form of an NGS report, which is available upon request directly from Foundation Medicine. The investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by the U.S. FDA; results from these investigational tests should not be used to guide future treatment decisions.

4.5.7.3 Tumor Samples at Other Timepoints

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

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

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

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

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed, or earlier depending on local regulations.

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

4.5.8 Anti-Therapeutic Antibody Testing

Treatment with atezolizumab may elicit an immune response. Patients with signs of any potential immune response to atezolizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect ATAs at multiple timepoints before, during, and after treatment with atezolizumab (see Appendix 1, Appendix 2, and Appendix 3 for the schedule). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Rosenberg and Worobec 2004; Koren et al. 2008) to characterize ATA responses to atezolizumab in support of the clinical development program. This tiered strategy may include an assessment of whether detected ATA responses correlate with relevant clinical endpoints. Implementation of ATA characterization assays will depend on the safety profile and clinical immunogenicity data.

4.5.9 Electrocardiograms

A 12-lead ECG is required at screening and thereafter as clinically indicated. ECGs should be obtained on the same machine whenever possible. Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine position for at least 10 minutes.

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

4.5.10 Patient-Reported Outcomes

PRO data will be collected via the EORTC QLQ-C30, the EORTC QLQ-LC13, SILC, PGIS, and EQ-5D-3L to more fully characterize the clinical profile of atezolizumab.

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

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

The EORTC QLQ-C30 (see Appendix 8) is a validated and reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) that consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scale scores can be obtained for the multi-item scales. The EORTC QLQ-C30 module takes approximately 15 minutes to complete. This questionnaire will be completed on the ePRO tablet at each scheduled cycle visit during the treatment induction phase and then according to the tumor assessment schedule during the treatment maintenance phase. During survival follow-up, the questionnaire will be completed at 3 months and 6 months following disease progression (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment after radiographic disease progression according to RECIST v1.1).

The EORTC QLQ-LC13 (see Appendix 9) module incorporates one multiple-item scale to assess dyspnea and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. The EORTC QLQ-LC13 module takes approximately 15 minutes to complete. This questionnaire will be completed on the ePRO tablet at each scheduled cycle visit during the treatment induction phase and then according to the tumor assessment schedule during the treatment maintenance phase. During survival follow-up, the questionnaire will be completed at 3 months and 6 months following disease progression (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment after radiographic disease progression according to RECIST v1.1).

The SILC scale will be used to assess patient-reported severity of lung cancer symptoms (chest pain, dyspnea, and cough). The SILC scale is a 9-item content valid

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

The EQ-5D-3L is a generic, preference-based health-utility measure with questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that is used to build a composite of the patient's health status (see Appendix 10). The EQ-5D-3L will be utilized in this study for economic modeling. This questionnaire will be completed on the ePRO tablet at each scheduled cycle visit during the treatment induction phase and then according to the tumor assessment schedule during the treatment maintenance phase. During survival follow-up, the questionnaire will be completed at 3 months and 6 months following disease progression (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment after disease progression according to RECIST v1.1).

The PGIS consists of a single question used to assess patient global impression of disease severity. This question will be completed on the ePRO tablet at each scheduled cycle visit during the treatment induction phase and then according to the tumor assessment schedule during the treatment maintenance phase. The PGIS is not required during survival follow-up.

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

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

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

4.5.11 Samples for Roche Clinical Repository

4.5.11.1 Overview of the Roche Clinical Repository

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

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

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

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

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

- Optional fresh biopsy samples
- Leftover tumor tissue samples
- Remaining fluids (serum, plasma, blood cell derivatives) after study-related tests have been performed
- Remaining FFPE tissue (with the exception of archival FFPE blocks, which will be returned to sites) after study-related tests have been performed
- Whole blood samples collected at screening (for screen-fail patients only)

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

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

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

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

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

4.5.11.4 Confidentiality

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

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

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

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

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

4.5.11.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

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

4.5.11.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. A patient's withdrawal from Study GO29537 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 GO29537.

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

global_rcr-withdrawal@roche.com

4.5.11.7 Monitoring and Oversight

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

4.5.12 Timing of Assessments

4.5.12.1 Screening and Baseline Assessments

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

See Appendix 1 for the schedule of screening assessments and Appendix 2 and Appendix 3 for the schedule of PK, ATA, and biomarker sampling.

4.5.12.2 Assessments during Treatment

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

Patients who are randomized to Arm B who had started erlotinib (allowed under Study GO29537 Protocol Versions 1–4) or pemetrexed switch maintenance after the induction phase will continue with cycle visits as outlined in Appendix 1 for the maintenance phase until erlotinib or pemetrexed treatment termination, disease progression, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Patients who are randomized to Arm B who receive BSC after the induction phase are not required to continue with cycle visits. Their treatment discontinuation visit will take place when patients discontinue BSC.

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

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

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

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

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

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

Local hematology tests must also be performed prior to nab-paclitaxel infusions on Day 8 and Day 15.

See Appendix 1 for the schedule of assessments performed during the treatment period and Appendix 2 and Appendix 3 for the schedule of PK, pharmacodynamic, ATA, and biomarker sampling.

4.5.12.3 Assessments for Treatment-Crossover Patients

The same treatment-phase schedule of assessments and procedures will apply to patients in Arm B who crossed over to Arm A (allowed under Study GO29537 Protocol Versions 1–4). That is, patients will begin on Cycle 1 (now to be called Cycle 1A) and will follow the same assessments and procedures as outlined in this protocol for this cycle (with the exception of an alternate schedule for PK and pharmacodynamic assessments [see Appendix 3] and a biopsy upon progression will not be requested for these patients), as well as for all subsequent cycles (i.e., Cycle 2, which will now be called Cycle 2A, etc.).

In addition, patients who crossed over from Arm B to Arm A following disease progression (allowed under Study GO29537 Protocol Versions 1–4) will not follow the treatment-phase schedule for PRO assessments during crossover. These patients will complete PRO assessments according to the post-progression schedule (i.e., SILC monthly for the first 6 months only and EORTC QLQ-C30, QLQ-LC13, and EQ-5D 3L at 3 and 6 months only).

4.5.12.4 Assessments at Study Drug Discontinuation Visit

When a patient discontinues all study treatment (including pemetrexed and erlotinib [allowed under Study GO29537 Protocol Versions 1–4] switch maintenance, and BSC), regardless of the reason for discontinuation, the patient will be asked to return to the clinic within 30 days after the treatment for the study drug discontinuation visit. The visit

at which the decision is made to discontinue treatment (e.g., loss of clinical benefit is confirmed) may be used as the study drug discontinuation visit.

Arm B Crossover Patients Allowed under Study GO29537, Protocol Versions 1–4

For patients who entered Study GO29537 under Protocol Versions 1–4, who were assigned to the control arm, and who are allowed to cross over to receive atezolizumab, the study drug discontinuation visit must be repeated when they discontinue receiving atezolizumab. The same study drug discontinuation visit procedures as listed below and in Appendix 1 must be performed for both study drug discontinuation visits.

See Appendix 1, Appendix 2, and Appendix 3 for the schedule of follow-up assessments.

4.5.12.5 Follow-Up Assessments

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

For patients who discontinue study treatment (including chemotherapy induction, switch maintenance of erlotinib [allowed under Study GO29537 Protocol Versions 1–4] or pemetrexed switch maintenance for patients randomized to Arm B) for any reason other than radiographic progressive disease according to RECIST v1.1, tumor assessments should continue at the same frequency as would have been followed if the patient had remained on study treatment until radiographic disease progression (or loss of clinical benefit for patients treated with atezolizumab [Arm A patients and Arm B patients who cross over] who had continued treatment with atezolizumab after 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 according to RECIST v1.1 should continue tumor assessments according to the protocol schedule of response assessments until 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 (the SILC will be completed monthly only for the first 6 months after disease progression [or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1] using an ePRO device at the patient's home and EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-3L will be completed 3 and 6 months after disease progression [or loss of clinical benefit for atezolizumab-treated patients] at the site using the ePRO tablet), study treatment–related adverse events (including serious adverse events), subsequent anti-cancer therapies, and date and cause of death. Patients who discontinue study

treatment for any reason other than progressive disease or loss of clinical benefit will complete the EORTC QLQ-C30, EORTC QLQ-LC13, PGIS, and EQ-5D-3L at each tumor assessment visit and will complete the SILC at home on a weekly basis, until radiographic disease progression 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) 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 every 3 months or more frequently until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from the study (this request must be documented in the source documents and signed by the investigator). If the patient withdraws from study, the study staff may use a public information source (e.g., county records), when permissible, to obtain information about survival status only.

See Appendix 1, Appendix 2, and Appendix 3 for the schedule of follow-up assessments.

4.5.12.6 Assessments at Unplanned Visits

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

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

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

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

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

- Symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status.
- Intolerable toxicity related to atezolizumab, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Intolerable toxicity related to other components of the study treatment
- If one component of study treatment is discontinued permanently due to tolerability concerns, the patient may continue with other components of study treatment until disease progression or loss of clinical benefit (for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1) if agreed upon by the investigator and patient
- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment
- Use of another non–protocol-specified anti-cancer therapy (see Section 4.4.3)
- Pregnancy
- Radiographic disease progression according to RECIST v1.1
- Exception for atezolizumab treatment: patients randomized to atezolizumab treatment will be permitted to continue atezolizumab after RECIST v1.1 for progressive disease are met if they meet all of the following criteria (see Figure 2 for the schematic representation):

    Evidence of clinical benefit as assessed by the investigator

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

    No decline in ECOG performance status

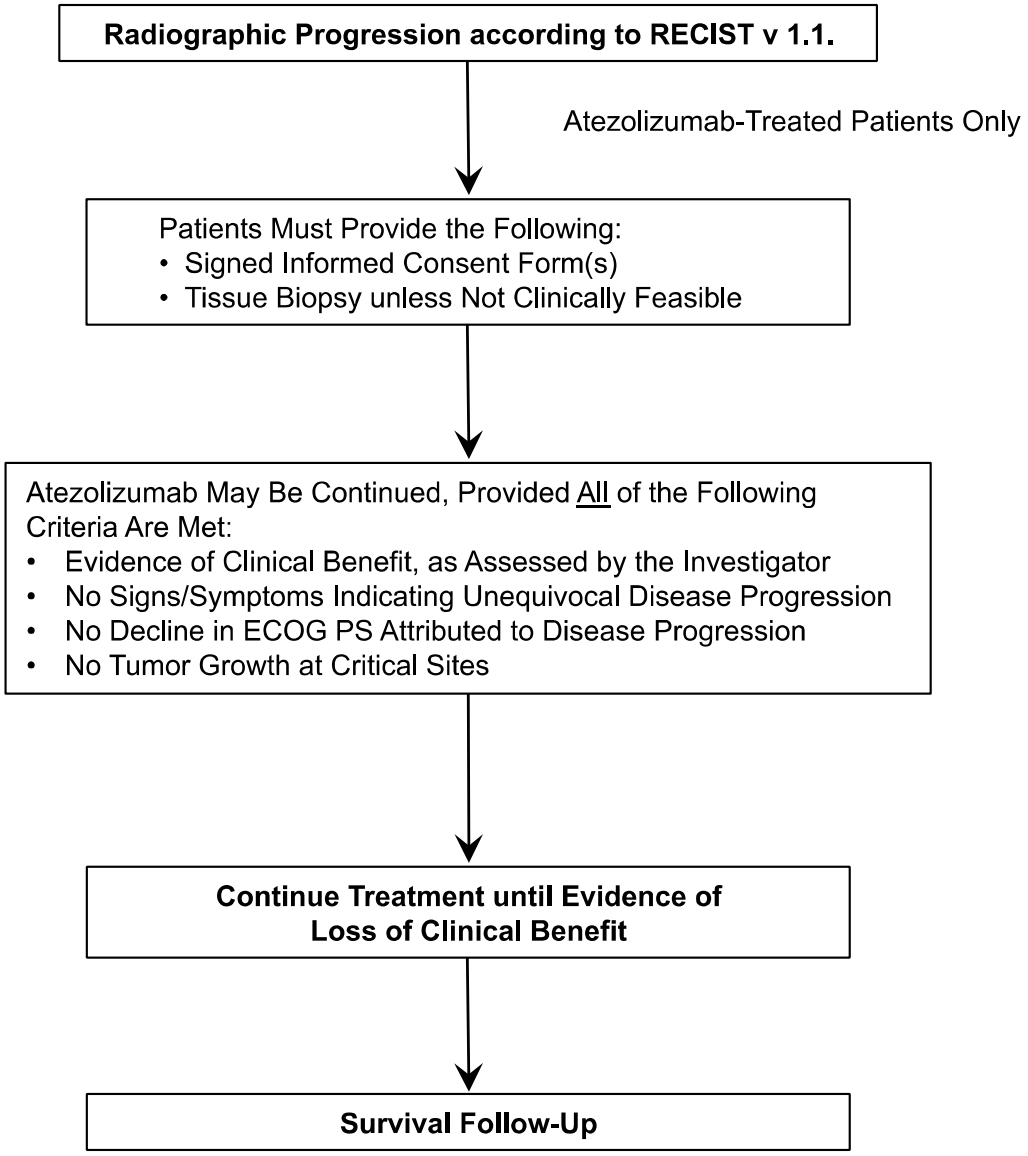
    Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing

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

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

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

Figure 2 Conditions for Continuing Atezolizumab in Presence of Increased Radiographic Tumor Size (Applicable to Arm A and Arm B Crossover Patients Consented under Study GO29537 Protocol Versions 1–4)



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

4.6.3 Study and Site Discontinuation

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

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

- Patient enrollment is unsatisfactory.

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

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

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

5. ASSESSMENT OF SAFETY

The following information is based on results from nonclinical and clinical studies and published data on similar molecules.

5.1 SAFETY PLAN

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2) and close monitoring (as indicated below and in Section 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 setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. All serious adverse events and adverse events of special interest will be recorded during the study and for up to 90 days after the last dose of study treatment (inclusive of erlotinib or pemetrexed switch maintenance for patients randomized to Arm B who receive erlotinib [allowed under Study GO29537 Protocol Versions 1–4] or pemetrexed switch maintenance) or until 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 (inclusive of erlotinib or pemetrexed switch maintenance for patients randomized to Arm B who receive erlotinib [allowed under previous versions of this protocol] or pemetrexed switch maintenance) or until initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first.

After the adverse event reporting period, all deaths should continue to be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that is believed to be related to prior

exposure to study treatment (see Section 5.6). The potential safety issues anticipated in this trial, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

5.1.1 Risks Associated with Atezolizumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events, specifically the induction or enhancement of autoimmune conditions. Adverse events with potentially immune-mediated causes, including rash, hypothyroidism, hepatitis/transaminitis, colitis, pneumonitis, myositis, and myasthenia gravis, have been observed in the Phase Ia Study PCD4989g. For further details regarding clinical safety, including a detailed description of the anticipated safety risks for atezolizumab, see the Atezolizumab Investigator's Brochure.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo et al. 2010). Suggested workup procedures for suspected immune-mediated adverse events are provided in Section 6 (Guidance for the Investigator) of the Atezolizumab Investigator's Brochure.

5.1.2 Risks Associated with Carboplatin

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

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

5.1.3 Risks Associated with nab-Paclitaxel

In clinical studies, nab-paclitaxel has been associated with alopecia, myelosuppression (neutropenia, anemia, thrombocytopenia), peripheral neuropathy, cranial nerve palsies, hypersensitivity reactions, pneumonitis, gastrointestinal events (i.e., nausea, vomiting, diarrhea), myalgia, anthralgia, cardiotoxicity (myocardial disorders, cardiac failure, angina, tachycardia, ventricular arrhythmia), cystoid macular edema, Stevens-Johnson syndrome/toxic epidermal necrolysis, sepsis, drug-induced lupus erythematous, infusion site reactions/extravasation, hepatic toxicity (drug-induced liver injury), acute renal failure, and hemolytic-uremic syndrome.

Patients will be monitored for nab-paclitaxel–related adverse events, including hematologic, gastrointestinal and hepatic toxicities, and peripheral neuropathy.

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

5.1.4 Risks Associated with Erlotinib

This section applies to patients already receiving erlotinib switch maintenance therapy under Study GO29537 Protocol Versions 1–4. The most commonly reported adverse drug reactions with erlotinib were rash and diarrhea. Most were Grade 1 or 2 in severity and were manageable without intervention. In general, rash manifests as a mild or moderate erythematous and papulopustular rash and may occur or worsen in sun-exposed areas. For patients who are exposed to the sun, protective clothing and/or the use of sunscreen (e.g., mineral-containing) may be advisable.

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

5.1.5 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.

5.1.6 General Plan to Manage Safety Concerns

5.1.6.1 Monitoring

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

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

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

All serious adverse events and protocol-defined events of special interest will be reported in an expedited fashion (see Sections 5.2.2 and 5.2.3). 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 Section 5.3.1, 5.3.5.7, 5.5, and 5.6.

5.1.7 Dose Modification

5.1.7.1 General Notes Regarding Dose Modification

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

- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and treated as Grade 1 toxicity for dose-modification purposes.
- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment (i.e., atezolizumab, carboplatin, or nab-paclitaxel) and the dose of that component is delayed or modified in accordance with the guidelines below, other components may be administered if there is no contraindication.
- When treatment is temporarily interrupted because of toxicity caused by, atezolizumab, carboplatin and/or nab-paclitaxel, the treatment cycles will be restarted such that the atezolizumab infusions remain synchronized and aligned with the chemotherapy schedule.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one chemotherapy drug, the dose of the other chemotherapy drug does not require modification. (Exception for nab-paclitaxel and carboplatin: In the case of peripheral neuropathy, hematologic, and gastrointestinal toxicities, nab-paclitaxel and carboplatin require modification. See Section 5.1.9)

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.

5.1.7.2 Atezolizumab Dose Modification

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

safety and efficacy as specified in Section 5.2.1. Exceptions require Medical Monitor approval.

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

5.1.8 Management of Atezolizumab-Specific Adverse Events

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

Refer to Appendix 12 for precautions for anaphylaxis.

Refer to Section 5.1.9.5 and Table 15 for management of pulmonary events and pneumonitis when atezolizumab and nab-paclitaxel are administered together, or when nab-paclitaxel is administered without atezolizumab.

Systemic Immune Activation

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternate etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

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

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

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

Dose reductions, holds, and discontinuations for each study drug may be made as outlined below. The investigator may use discretion in modifying or accelerating the dose modification guidelines described below, depending on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing patient compliance and access to supportive care.

When a treatment cycle is delayed or interrupted because of toxicity resulting from either component of the regimen, all study treatment should generally be withheld and resumed together to remain synchronized. However, if it is anticipated that chemotherapy will be delayed by ≥2 weeks, then atezolizumab should be given without the chemotherapy if there is no contraindication; this should be discussed with the Medical Monitor prior to re-initiating therapy.

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

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

5.1.9.1 Hematologic Toxicity

In general, ANC must be ≥ 1500 cells/μL and platelet count must be ≥ 100,000/μL on Day 1 of each cycle. When nab-paclitaxel is administered on Day 1, it should not be administered on Days 8 or 15 of the cycle unless ANC ≥ 500 cells/μL and platelets ≥ 50,000 cells/μL. In certain situations, a cycle may begin with the administration of atezolizumab alone (without nab-paclitaxel on Day 1). If Day 1 of a cycle begins with only atezolizumab but without the administration of nab-paclitaxel due to low platelet or ANC levels, nab-paclitaxel should not be administered subsequently within that cycle until ANC ≥1500 cells/μL and platelet count ≥100,000/μL. If the delay in re-starting nab-paclitaxel is >7 days (i.e., counts do not recover until Day 15), dosing should be resumed with applicable reductions. If the start of a cycle is delayed (i.e., both atezolizumab and nab-paclitaxel are withheld) for low counts, postpone Day 1 and resume dosing when counts recover. If nab-paclitaxel cannot be administered on Day 15 of the cycle, the next dose of nab-paclitaxel should be administered with carboplatin on Day 1 of the following cycle when ANC and platelets counts have recovered to permissible levels. When dosing resumes, the carboplatin and nab-paclitaxel doses should be permanently reduced as outlined in Table 12.

Table 12 nab-Paclitaxel and Carboplatin Permanent Dose Reductions Based on Nadir ANC and Platelets

Hematologic Toxicity	Occurrence	Weekly nab-Paclitaxel Dose (mg/m^2)	Every-3-Week Carboplatin Dose (AUC mg•min/mL)
Neutropenic fever (ANC < 500 cells/μL with fever > 38°C) OR Delay of next scheduled dose by > 7 days for ANC < 1500 cells/μL OR ANC < 500 cells/μL for > 7 days	First	75	4.5
	Second	50	3
	Third	Discontinue treatment	
Platelet count < 50,000 cells/μL	First	75	4.5
	Second	Discontinue treatment	

AUC = area under the concentration–time curve.

5.1.9.2 Gastrointestinal Toxicity

For Grade 3 or 4 gastrointestinal toxicities, treatment should be delayed until resolution to less than or equal to the patient's baseline value. Dose reductions at the start of the subsequent cycle will be based on gastrointestinal toxicities from the dose administered in the preceding cycle. Table 12 provides the relevant dose adjustments for gastrointestinal toxicities.

Table 13 Carboplatin and nab-Paclitaxel Dose Modification Based on Gastrointestinal Toxicities in the Preceding Cycle

Toxicity	Occurrence	Adjusted Carboplatin Dose as % of Previous Dose [a]	Adjusted nab-Paclitaxel Dose as % of Previous Dose
Grade 3 diarrhea OR Grade 3 mucositis/stomatitis OR Grade 3 or 4 nausea/vomiting	First	75%	75%
	Second	50%	50%
	Third	Discontinue treatment	
Grade 4 oral mucositis/stomatitis	NA	Discontinue treatment	
Grade 4 diarrhea	NA	Discontinue treatment	

AUC = area under the concentration–time curve.

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

Nausea and/or vomiting should be controlled with adequate anti-emetics. If Grade 3 or 4 nausea/vomiting occurs despite administration of anti-emetics, the dose should be reduced by 25% for the next and subsequent courses.

If, on Day 1 of any treatment cycle, the patient has oral mucositis/stomatitis, the treatment should be withheld until the oral mucositis/stomatitis is cleared. If the oral mucositis/stomatitis has not cleared in 3 weeks, the patient's chemotherapy will be discontinued. See Table 13 for additional details on dose reductions. Dose reductions listed are permanent.

5.1.9.3 Neurological Toxicity

nab-Paclitaxel and carboplatin should be withheld for Grade 3–4 peripheral neuropathy. nab-Paclitaxel and carboplatin may be resumed at reduced doses (see Table 14) when peripheral neuropathy recovers to Grade 1 or completely resolves.

Table 14 nab-Paclitaxel and Carboplatin Permanent Dose Reductions for Neurological Toxicity

Adverse Reaction	Occurrence	Weekly nab-Paclitaxel Dose (mg/m^2)	Every-3-Week Carboplatin Dose (AUC mg•min/mL)
Grade 3 or 4 sensory neuropathy	First	75	4.5
	Second	50	3
	Third	Discontinue treatment	

AUC = area under the concentration–time curve.

5.1.9.4 Hepatic Toxicity (nab-Paclitaxel Only)

For patients with no hepatic metastases at baseline who develop severe enzyme elevations during study treatment (ALT and/or AST $\geq 5 \times$ ULN or total bilirubin $\geq 3 \times$ ULN), study treatment should be interrupted, hepatic toxicity must resolve to baseline levels prior to dosing. If nab-paclitaxel is withheld because of hepatic toxicity, carboplatin should also be withheld and administered when the nab-paclitaxel is resumed. If nab-paclitaxel is withheld, hepatic values must recover to baseline levels within 3 weeks or the patient's nab-paclitaxel treatment will be discontinued. No dose reductions for carboplatin will be made for hepatic toxicity.

For patients with mild hepatic impairment (total bilirubin > 1 to $\leq 1.5 \times$ ULN and ALT/AST $\leq 5 \times$ ULN), no dose adjustments are required. Treat with the same doses as patients with normal hepatic function.

If moderate to severe hepatic elevations (total bilirubin > 1.5–$5.0 \times$ ULN or ALT and/or AST 5–$10 \times$ ULN) occur at any time, the nab-paclitaxel dose should be permanently reduced to 80% of the starting dose (i.e., to 80 mg/m^2). nab-Paclitaxel will be discontinued for patients with total bilirubin $> 5 \times$ ULN or AST $> 10 \times$ ULN.

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

5.1.9.5 Pulmonary Events and Pneumonitis: Atezolizumab and nab-Paclitaxel, or nab-Paclitaxel without Atezolizumab

Note: When atezolizumab is administered without nab-paclitaxel, refer to the Atezolizumab Investigator's Brochure for management of pulmonary events, including pneumonitis.

Atezolizumab

- Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab and have primarily been observed in patients with underlying NSCLC.

Mild to moderate events of pneumonitis have been reported with atezolizumab. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension:

- Measurement of oxygen saturation (i.e., arterial blood gas)
- High-resolution CT scan of the chest
- Bronchoscopy with bronchoalveolar lavage and biopsy
- Pulmonary function tests (diffusion capacity of the lung for carbon monoxide [DLCO])
- Pulmonary function testing with a pulmonary embolism protocol

Patients will be assessed for pulmonary signs and symptoms throughout the study, and will also have CT scans of the chest at every tumor assessment. See Table 15 for management guidelines for pulmonary events and pneumonitis.

nab-Paclitaxel

- Interstitial pneumonitis has been observed in $<$ 1% of patients with nab-paclitaxel monotherapy and 4% with the use of nab-paclitaxel in combination with gemcitabine. Patients should be monitored closely for signs and symptoms of pneumonitis.

nab-Paclitaxel should be permanently discontinued upon ruling out infectious etiology and making a diagnosis of pneumonitis. Promptly initiate appropriate treatment and supportive measures.

Infections should be ruled out with routine microbiological and/or immunologic methods.

After ruling out an infectious etiology, high-dose IV corticosteroid therapy should be instituted without delay, with appropriate premedication and secondary pathogen coverage. Patients with an added immunological component may also require immune modulation with azathioprine or cyclophosphamide.

Table 15 details the management of pulmonary events/pneumonitis when atezolizumab and nab-paclitaxel are administered together, or when nab-paclitaxel is administered alone.

Note: When atezolizumab is administered alone, refer to the Atezolizumab Investigator's Brochure for management of pulmonary events, including pneumonitis.

Table 15 Management Guidelines for Pneumonitis: Atezolizumab and nab-Paclitaxel, or nab-Paclitaxel with or without Atezolizumab

Severity	Atezolizumab (in Combination with nab-Paclitaxel)	nab-Paclitaxel (with or without Atezolizumab)
Grade 1	• Withhold atezolizumab with close monitoring. • Resume when event improves to Grade 0. Re-evaluate on serial imaging. • Consider pulmonary consultation.	• Permanently discontinue nab-paclitaxel. • After ruling out infection, start high-dose IV corticosteroids with appropriate premedication and secondary pathogen coverage.
Grade 2	• Withhold atezolizumab. • Pulmonary and infectious disease consultation with consideration for bronchoscopy/BAL. • Start 60 mg prednisone or equivalent per day. • When improves to Grade 0 or Grade 1, then taper steroids over ≥ 1 month. • Atezolizumab may be resumed if the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to the equivalent of oral prednisone 10 mg daily or less. • Treat as Grade 3–4 if recurrent episode of pneumonitis.	• Permanently discontinue nab-paclitaxel. • After ruling out infection, start high-dose IV corticosteroids with appropriate premedication and secondary pathogen coverage.
Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Bronchoscopy/BAL is recommended. • Start 60 mg prednisone or equivalent per day. • Taper steroids over ≥ 1 month after symptoms improve to Grade 0 or Grade 1. • If not improving after 48 hours or worsening, add additional immunosuppression (e.g., infliximab, cyclophosphamide, IV Ig, or mycophenolate mofetil).	• Permanently discontinue nab-paclitaxel. • After ruling out infection, start high-dose IV corticosteroids with appropriate premedication and secondary pathogen coverage.

BAL = broncho-alveolar lavage; Ig = immunoglobulin; IV = intravenous.

5.1.9.6 Other Toxicities

For any Grade 3 or 4 toxicity not mentioned above, carboplatin or nab-paclitaxel should be withheld until the patient recovers completely or to Grade 1 toxicity. nab-Paclitaxel and carboplatin may be resumed at reduced doses (see Table 16) when toxicity recovers to Grade 1 or completely resolves. If recovery to Grade 1 toxicity does not occur within 3 weeks, the patient's chemotherapy will be discontinued. For Grade 1 and 2 toxicities, no dose reduction should be made.

Table 16 nab-Paclitaxel and Carboplatin Permanent Dose Reductions for Non-Hematologic, Non-Gastrointestinal, Non-Neurologic, and Non-Hepatic Toxicity

Adverse Reaction	Occurrence	Weekly nab-Paclitaxel Dose (mg/m^2)	Every 3-Week Carboplatin Dose (AUC mg • min/mL)
Grade 3 or 4 non-hematologic, non-GI, non-neurologic, non-hepatic toxicity	First	75	4.5
	Second	50	3
	Third	Discontinue treatment	

AUC = area under the concentration–time curve; GI = gastrointestinal.

For guidelines on the dosing of other study drugs when carboplatin or nab-paclitaxel are withheld, see Section 5.1.7.

5.1.10 Erlotinib and Pemetrexed Dose Modification and Management of Specific Adverse Events

For patients who had started switch maintenance therapy with erlotinib (allowed under Study GO29537 Protocol Versions 1–4) and for patients who receive pemetrexed, refer to the prescribing information for erlotinib and pemetrexed for dose modifications for adverse event management.

5.1.11 Potential Overlapping Toxicities

To date, on the basis of safety data from Study GP28328, the risk of overlapping toxicities between atezolizumab, carboplatin, and nab-paclitaxel is thought to be minimal. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hepatotoxicity, skin, and gastrointestinal toxicity) may not be unambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with these chemotherapeutic agents (e.g., hepatotoxicity) could be exacerbated by the immunostimulatory activity of atezolizumab.

Toxicities should initially be managed according to the recommendations in Sections 5.1.7 and 5.1.8, with dose holds and modifications (if applicable) applied to the component of the study drug judged to be the primary cause. For severe (Grade 3) or persistent Grade 1 or 2 diarrhea, an endoscopic evaluation should be considered. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology for adverse events listed above. If, in the opinion of the investigator, atezolizumab is a potential inciting factor, the dose of atezolizumab may be withheld for a maximum of 105 days beyond the last dose (see Section 5.1.7.2). Exceptions require Medial Monitor approval. Prompt symptomatic management is appropriate for mild immune-mediated adverse events. In severe cases,

immune-mediated toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or TNF-α inhibitors. These cases should be discussed with the Medical Monitor.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

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

- Confirmed treatment-emergent autoimmune conditions:

  Pneumonitis

  Grade ≥ 3 hypoxia or dyspnea

  Colitis

  Endocrinopathies: diabetes mellitus, pancreatitis, or adrenal insufficiency

  Vasculitis

  Hepatitis

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

  Systemic lupus erythematosus

  Guillain-Barré syndrome

  Skin reactions: vitiligo, pemphigoid

- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response system, or infusion-reaction syndromes
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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 treatment, all serious adverse events and adverse events of special interest, regardless of relationship to study treatment, will be reported until 90 days after the last dose of study treatment (inclusive of switch maintenance with pemetrexed or erlotinib [for patients who received switch maintenance with erlotinib under Study GO29537 Protocol Versions 1–4]) or until initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. All other adverse events, regardless of relationship to study treatment, will be reported until 30 days after the last dose of study treatment (inclusive of switch maintenance with pemetrexed or erlotinib [for patients who received switch maintenance with erlotinib under Study GO29537 Protocol Versions 1–4]) or until initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 17 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 17 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether 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. Avoid colloquialisms and abbreviations.

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

5.3.5.1 Diagnosis versus Signs and Symptoms

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

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

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

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

5.3.5.4 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

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

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

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

5.3.5.5 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.6 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

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

5.3.5.8 Preexisting Medical Conditions

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

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

5.3.5.9 Worsening of NSCLC

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

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

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

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

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

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

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

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

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

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events
- Adverse events of special interest
- Pregnancies

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

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results

- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor:	[redacted], *M.D. (Primary)*
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]
Medical Monitor:	[redacted], M.D., Ph.D. *(Secondary)*
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]

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

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study 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 (inclusive of switch maintenance with pemetrexed or erlotinib [for patients who received switch maintenance with erlotinib under Study GO29537 Protocol Versions 1–4]) or until initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. All other adverse events, regardless of relationship to study treatment, will be reported until 30 days after the last dose of study treatment (inclusive

of switch maintenance with pemetrexed or erlotinib [for patients who received switch maintenance with erlotinib under Study GO29537 Protocol Versions 1–4) or until initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first.

Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab or within 30 days after the last dose of nab-paclitaxel. 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 email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of nab-paclitaxel and/or carboplatin. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy),

either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. *When permitted by the site, the* pregnant partner *would* need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. *If* the authorization has been signed, the investigator *should* submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (as defined in Section 5.3.1), all deaths should be reported through use of the Study Discontinuation eCRF. In addition, if the investigator becomes aware of a serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

The Sponsor will promptly evaluate all serious adverse events and 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 as reference:

- Atezolizumab Investigator's Brochure
- Tarceva® (erlotinib) Summary of Product Characteristics (SmPC)/Local Label
- Abraxane® (nab-paclitaxel) Summary of Product Characteristics (SmPC)/Local Label

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 Phase III, randomized, multicenter, open-label study designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin + nab-paclitaxel compared with treatment with carboplatin + nab-paclitaxel alone in approximately 715 patients with Stage IV, non-squamous NSCLC in the first-line setting.

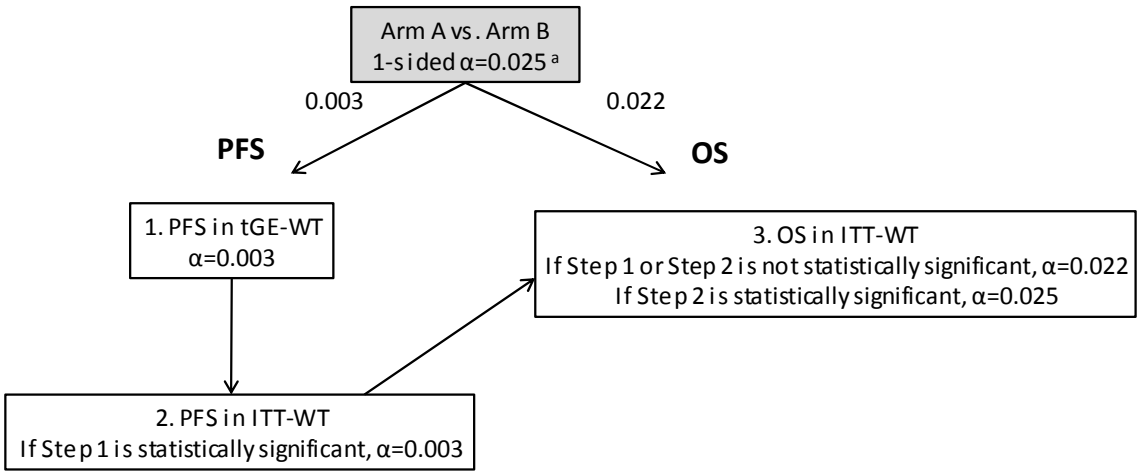
Efficacy analyses will be performed in one or more populations (tGE-WT, ITT-WT, tGE, ITT, TC2/3 or IC2/3 WT, or TC1/2/3 or IC1/2/3 WT), with patients grouped according to the treatment assigned at randomization, regardless of whether they received any assigned study treatment.

Safety analyses for the primary treatment phase will be performed on all randomized patients who received any amount of any component of protocol treatment, with patients grouped according to whether any full or partial dose of atezolizumab was received. Safety analyses for the crossover phase (for patients who entered Study GO29537 under Protocol Versions 1–4) will be performed on patients assigned to the control arm who received any amount of atezolizumab as subsequent treatment.

6.1 DETERMINATION OF SAMPLE SIZE

The primary endpoint of PFS will be analyzed in the tGE-WT population and in the ITT-WT population, and the primary endpoint of OS will be analyzed in the ITT-WT population. Analyses of PFS and OS will be conducted according to an analysis hierarchy and an α-spending algorithm to control for the type I error rate (see Figure 3) and to account for an interim OS analysis (see Section 6.8.1). The PFS and OS analysis hierarchy and α allocation, including possible α recycling, are shown in Figure 3. A detailed description of the hypothesis testing is provided in Section 6.4.1.

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



ITT = intent to treat; OS = overall survival; PFS = progression-free survival; tGE = tumor gene expression; WT = wild type

[a] To control the overall type I error rate for the one-sided test at 0.025, a one-sided type I error (α) of 0.003 and 0.022 (ratio of 3:22) will be allocated to PFS and OS, respectively, for comparison of Arm A versus Arm B.

This study will randomize approximately 715 patients. The ITT-WT population will include approximately 650 patients, assuming a prevalence of approximately 10% for sensitizing EGFR mutations or ALK translocations. The tGE-WT population will include approximately 325 patients, assuming a 50% prevalence with the chosen tGE cutoff.

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

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

- 93% power to detect an HR of 0.55, corresponding to an improvement in median PFS from 6 months to 10.9 months in the tGE-WT population with a one-sided α of 0.003
- 95% power to detect an HR of 0.65, corresponding to an improvement in median PFS from 6 months to 9.2 months in the ITT-WT population with a one-sided α of 0.003
- No interim analyses for PFS
- Dropout rate of 5% per 12 months

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

- 80% power to detect an HR of 0.75, corresponding to an improvement in median OS from 12 months to 16 months in the ITT-WT population with a one-sided α of 0.022
- One interim OS analysis performed at the time of the final PFS analysis, at which time approximately 77% of the total number of OS events required for the final analysis are expected to have occurred, as determined through use of the Lan-DeMets approximation to the O'Brien-Fleming boundary
- Dropout rate of 5% per 24 months

With these assumptions, approximately 715 patients in total will be enrolled in this study, with approximately 650 patients in the ITT-WT population. The final PFS analysis will be conducted when all of the following criteria have been met: approximately 225 PFS events have occurred in the tGE-WT population, approximately 475 PFS events have occurred in the ITT-WT population, and the last patient has been enrolled in the study. The final PFS analysis is expected to occur approximately 32 months after the first patient is enrolled. These numbers of events would allow for a minimum detectable difference corresponding to an HR of 0.68 in the tGE-WT population and 0.76 in the ITT-WT population, respectively.

With a sample size of 650 patients, approximately 457 OS events are expected to occur in the ITT-WT population. The final OS analysis is expected to occur approximately 42 months after the first patient is enrolled. This number of events would allow for a minimum detectable difference corresponding to an HR of 0.81 in the ITT-WT population.

6.2 SUMMARIES OF CONDUCT OF STUDY

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

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

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

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

6.4 EFFICACY ANALYSES

6.4.1 Co-Primary Efficacy Endpoints

The co-primary efficacy endpoints are PFS as assessed by the investigator using RECIST v1.1 and OS. PFS will be analyzed in the tGE-WT population and the ITT-WT population. OS will be analyzed in the ITT-WT population. The timing of the final PFS and OS analyses is described in Section 6.1. At least one interim OS analysis will be performed (see Section 6.8.1).

PFS is defined as the time between the date of randomization and the date of first documented disease progression or death, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

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

The following analyses will be performed for both PFS and OS. PFS and OS will be compared between treatment arms with the use of the stratified log-rank test. The HR for PFS and OS for treatment comparisons will be estimated using a stratified Cox regression model, respectively. The 95% CI for the HR will be provided.

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

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

Analyses will be conducted according to an analysis hierarchy and an α-spending algorithm to control for the type I error rate (see Figure 3 in Section 6.1) and to account for an interim analysis (see Section 6.8.1).

To control the overall type I error rate for the one-sided test at 0.025, a one-sided type I error (α) of 0.003 and 0.022 (ratio of 3:22) will be allocated to PFS and OS, respectively.

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

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

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

6.4.2.1 Progression-Free Survival and Overall Survival in Secondary Populations

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

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

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

6.4.2.2 Objective Response Rate

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

ORR is defined as the proportion of patients who had an objective response. ORR will be analyzed in the tGE-WT population and the ITT-WT population. Patients must have measurable disease at baseline to be included in the analysis. An estimate of ORR and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms will be determined using the normal approximation to the binomial distribution. The ORR will be compared between the two arms using the stratified Mantel-Haenszel test. The stratification factors of this analysis will be the same as those described in Section 6.4.1.

6.4.2.3 Duration of Response

DOR will be analyzed in the tGE-WT population and the ITT-WT population. DOR will be assessed in patients who had an objective response as determined by the investigator using RECIST v1.1. DOR is defined as the time interval from the date of the first occurrence of a complete or partial response (whichever status is recorded first) until the first date that progressive disease or death is documented, whichever occurs first. Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after date of the first occurrence of a complete or partial response, DOR will be censored at the date of the first occurrence of a complete or partial response plus 1 day.

DOR is based on a non-randomized subset of patients (specifically, patients who achieve an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes. The methodology detailed for the PFS analysis will be used for the analysis of DOR.

6.4.2.4 Overall Survival Rate at Landmark Timepoints

OS rate at 1 and 2 years will be analyzed in the tGE-WT population and the ITT-WT population. The OS rates at 1 and 2 years will be estimated using Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated using the standard error derived from the Greenwood formula. The 95% CI for the difference in OS rates between the two treatment arms will be estimated using the normal approximation method.

6.4.2.5 Patient-Reported Outcomes

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

TTD using EORTC is defined as the time from baseline to the first time the patient's score shows a ≥ 10-point increase above baseline in any of the following EORTC-transformed symptom subscale scores (whichever comes first): cough, dyspnea (single item), dyspnea (multi-item subscale), chest pain, or arm/shoulder pain. A≥10-point change in the symptoms subscale score is perceived by patients as clinically significant (Osoba et al. 1998).

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

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

6.4.3 Handling of Missing Data

For PFS, patients without a date of disease progression will be analyzed as censored observations on the date of the last tumor assessment. If no post-baseline tumor assessment is available, PFS will be censored at the date of randomization plus 1 day. Data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be handled as described in the sensitivity analysis in Section 6.7.1.4.

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

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

6.5 SAFETY ANALYSES

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

Safety analyses for patients who entered Study GO29537 under Protocol Versions 1–4 in the crossover phase will be performed on the patients assigned to the control arm who received any amount of atezolizumab as subsequent treatment.

6.5.1 Treatment Phase

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

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

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

Changes in vital signs will be summarized by treatment arm.

Deaths reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation will be summarized by treatment arm.

6.5.2 Crossover Phase (For Patients Who Entered Study GO29537 under Protocol Versions 1–4)

Crossover is no longer permitted; however, patients who were randomized to the control arm and who entered Study GO29537 under Protocol Versions 1–4 have the option for crossover to atezolizumab following disease progression according to RECIST v1.1. Drug exposure and safety data after receiving atezolizumab as subsequent treatment for the patients in the control arm will be summarized separately from the safety analyses. The analyses for drug exposure and adverse events described for that phase will be conducted.

6.6 PHARMACOKINETIC ANALYSES

PK samples will be collected in this study as outlined in Appendix 2 and Appendix 3. Atezolizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Plasma concentrations of carboplatin and nab-paclitaxel (reported as total paclitaxel) will be collected in this study as outlined in Appendix 2. The concentrations of carboplatin and paclitaxel will be summarized using descriptive statistics as described above.

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

6.7 EXPLORATORY ANALYSES

6.7.1 Exploratory Analyses of Progression-Free Survival

6.7.1.1 Progression-Free Survival Rate at Landmark Timepoints

The PFS rates at various timepoints (e.g., at 6 months and at 1 year after randomization) will be estimated using Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated using Greenwood's formula. The 95% CI for the difference in PFS rates between the two arms will be estimated using the normal approximation method.

6.7.1.2 Non–Protocol-Specified Anti-Cancer Therapy

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

6.7.1.3 Subgroup Analysis

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

6.7.1.4 Sensitivity Analyses

Sensitivity analyses will be performed to evaluate the potential impact of missing scheduled tumor assessments on the primary analysis of PFS, as determined by the investigator using a PFS event imputation rule. The following two imputation rules will be considered:

- If a patient missed two or more scheduled tumor assessments immediately prior to the date of the PFS event according to RECIST v1.1, the patient will be censored at the last tumor assessment prior to the first of these missed visits.
- If a patient missed two or more scheduled tumor assessments immediately prior to the date of the PFS event according to RECIST v1.1, the patient will be counted as having progressed on the date of the first of these missing assessments.

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

6.7.2 Exploratory Analyses of Overall Survival

6.7.2.1 Loss to Follow-Up

The impact of loss to follow-up on OS will be assessed depending on the number of patients who are lost to follow-up. If $>5\%$ of patients are lost to follow-up for OS in either treatment arm, a sensitivity analysis will be performed in which patients who are lost to follow-up will be considered as having died at the last date they were known to be alive.

6.7.2.2 Subgroup Analysis

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

6.7.2.3 Overall Survival Rate at Three-Year Landmark

The methodologies for landmark OS analysis that are outlined in Section 6.4.2.4 will be used.

6.7.2.4 Milestone Overall Survival Analysis

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

6.7.3 Exploratory Biomarker Analysis

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

6.7.4 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.

6.7.5 Patient-Reported Outcome Analyses

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

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

6.8 INTERIM ANALYSES

6.8.1 Planned Interim Analysis

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

If approximately 352 OS events have occurred in the ITT-WT population at the time of the PFS final analysis (see criteria for final PFS analysis in Section 6.1), an interim OS analysis will be conducted in the ITT-WT population. If there are significantly fewer than the expected 352 OS events at the final PFS analysis, a nominal α of 0.01% (negligible impact on overall type I error rate) will be spent on the OS analysis at the time of the

PFS final analysis and a second interim OS analysis will then be conducted after approximately 352 OS events have occurred.

The final OS analysis will be conducted when approximately 457 OS events have occurred in the ITT-WT population. This is expected to occur approximately 42 months after the first patient is enrolled.

Stopping boundaries for the interim and final OS analyses will be computed through use of the Lan-DeMets approximation to the O'Brien-Fleming boundary. The stopping boundaries are provided in Table 18.

Table 18 Analysis Timing and Stopping Boundaries for Overall Survival in the ITT-WT Population

	Stopping Boundary: HR (p-value)	
Analysis Timing	If $\alpha = 0.022$	If $\alpha = 0.025$
Interim OS analysis	HR $\leq$ 0.766 (p $\leq$ 0.0091)	HR $\leq$ 0.771 (p $\leq$ 0.0107)
Final OS analysis	HR $\leq$ 0.814 (p $\leq$ 0.0193)	HR $\leq$ 0.819 (p $\leq$ 0.0218)

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

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

6.8.2 Optional Interim Analysis

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

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

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

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

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

Once the study is complete, the ePRO data, audit trail, and study and system documentation will be archived. The Sponsor will receive all data entered by patients on the e-diary and tablet device and all study documentation.

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

7.4 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.5 USE OF COMPUTERIZED SYSTEMS

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

that shows the original data, as well as the reason for the change, the name of the person making the change, and the date of the change.

7.6 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

The Informed Consent Form will contain a separate section that addresses the use of remaining samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients

will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not provide a separate signature.

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

- A signature page for patients receiving atezolizumab who wish, if approved by the treating physician, to continue treatment beyond initial radiographic disease progression according to RECIST v1.1 and meet criteria specified in Section 4.6. This separate consent is to be signed after initial radiographic disease progression according to RECIST v1.1 has occurred and patients have discussed other available treatment options and the potential risks of continuing treatment.

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann-La Roche Ltd. Approximately 105 sites globally will participate in the study, and approximately 715 patients will be randomized.

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

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

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

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

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

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

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Assessments

Procedure	Screening Days –28 to –1	Induction Phase Cycles 1 to 4 or 6 (21-Day Cycle) [a] Day 1 (± 3 Days) [b]	Maintenance Phase (21-Day Cycle) [a] Day 1 (± 3 Days) [b]	Treatment Discontinuation Visit ≤ 30 Days after Last Dose of Study Treatment	Survival Follow-Up Every 3 Months after Disease Progression or Loss of Clinical Benefit
Informed consent	x				
Tumor tissue specimen for PD-L1 testing (15 FFPE slides required; blocks preferred) [c] Fresh or archival tissue can be used	x				
ALK and/or EGFR assessment if status is unknown (may be done locally or centrally)	x				
Demographic data	x				
Medical history and baseline conditions	x				
NSCLC cancer history	x				
Vital signs [d]	x	x [d]	x [d]	x	
Weight	x	x	x	x	
Height	x				
Complete physical examination	x				
Limited physical examination [e]		x	x	x	
ECOG performance status	x	x	x	x	
12-Lead ECG	x	x [f]	x [f]	x [f]	
Hematology [g]	x	x	x	x	
Serum chemistry [h]	x	x	x	x	
Coagulation test (aPTT or INR)	x			x	

Appendix 1
Schedule of Assessments (cont.)

Procedure	Screening Days –28 to –1	Induction Phase Cycles 1 to 4 or 6 (21-Day Cycle) a Day 1 (±3 Days) [b]	Maintenance Phase (21-Day Cycle) a Day 1 (±3 Days) [b]	Treatment Discontinuation Visit ≤ 30 Days after Last Dose of Study Treatment	Survival Follow-Up Every 3 Months after Disease Progression or Loss of Clinical Benefit
Pregnancy test (women of childbearing-potential ONLY)	x [i]	x [j]	x [j]	x [j]	
TSH, free T3, free T4 [k]	x	x [k]	x [k]	x	
HIV, HBV, HCV serology [l]	x				
Urinalysis [m]	x	x	x	x	
Determination of duration of induction treatment	x				
Induction treatment administration: Arm A: atezolizumab + carboplatin + nab-paclitaxel Arm B: carboplatin + nab-paclitaxel		x [n]			
Maintenance treatment administration: Arm A: atezolizumab Arm B: Best supportive care (switch maintenance to pemetrexed permitted)			x [n]		
Tumor response assessment	x [o]	x [p]	x [p]		x [q]
Serum sample for atezolizumab ATA assessment (atezolizumab-treated patients only) [r]		x	x	x	120 (±30) days after last dose of atezolizumab
Serum sample for PK sampling (atezolizumab-treated patients only) [r]		x	x	x	120 (±30) days after last dose of atezolizumab
Carboplatin and nab-paclitaxel PK sampling (20 patients per arm) [r]		x			

Appendix 1
Schedule of Assessments (cont.)

Procedure	Screening	Induction Phase Cycles 1 to 4 or 6 (21-Day Cycle) a	Maintenance Phase (21-Day Cycle) a	Treatment Discontinuation Visit	Survival Follow-Up
	Days –28 to –1	Day 1 (±3 Days) [b]	Day 1 (±3 Days) [b]	≤ 30 Days after Last Dose of Study Treatment	Every 3 Months after Disease Progression or Loss of Clinical Benefit
Blood samples for PD biomarkers [r]	x	x	x	x	120 (±30) days after last dose of atezolizumab
Optional blood for DNA extraction (RCR only) [r, s]		x			
Informed consent to continue treatment beyond radiographic progression (Arm A atezolizumab-treated patients)		At time of radiographic progression			
Tumor biopsy		At time of radiographic progression [t]			
Optional tumor biopsy at other timepoints (RCR only)		Any time during study treatment or during survival follow-up			
Adverse events [u]	x	x	x	x	x
Concomitant medications	From 7 days before screening	x	x	x	
Patient-reported outcomes [v]		x [v]	x [v]		x [v]
Survival and anti-cancer therapy follow-up [w]					x

Appendix 1
Schedule of Assessments (cont.)

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

Notes: Patients who are randomized to Arm B who received erlotinib switch maintenance allowed under Study GO29537 Protocol Versions 1–4,or who receive pemetrexed switch maintenance, will continue with cycle visits at the same frequency as those patients randomized to Arm A until disease progression, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

The same treatment-phase schedule of assessments and procedures will apply to the crossover patients, i.e., patients will begin on Cycle 1 (now called Cycle 1A) and will follow the same assessments and procedures as outlined in this protocol for this cycle (with the exception of an alternate schedule for PK and pharmacodynamic assessments (see Appendix 3) and a biopsy upon progression will not be requested for these patients), as well as for all subsequent cycles (i.e., Cycle 2, which will now be called Cycle 2A, etc.). In addition, patients who entered Study GO29537 under Protocol Versions 1–4 and who cross over to atezolizumab following disease progression will not follow the treatment-phase schedule for ePRO assessments during crossover. These patients will complete ePRO assessments according to the post progression schedule (i.e., SILC monthly for the first 6 months only and EORTC QLQ-C30, QLQ, LC13 and EQ-5D-3L at 3 and 6 months only).

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

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

[c] If a representative FFPE tumor specimen in paraffin block (preferred) or 15 (or more) freshly cut, unstained 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 a 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 may occur outside the 28-day screening period prior to enrollment. See Section 4.1.1, Inclusion Criteria, and Section 4.5.7.1.

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

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

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

[g] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. Hematology tests must be performed prior to Day 1 infusions and for nab-paclitaxel administration, also prior to Day 8 and Day 15 infusions. See Section 5.1.9.1 (Table 11) for dose modifications due to hematologic toxicities.

Appendix 1
Schedule of Assessments (cont.)

[h] Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total CO_2, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin. See Section 5.1.9.1 (Table 15) for carboplatin and nab-paclitaxel dose modification management due to serum chemistry toxicities.

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

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

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

[l] All patients will be tested for HIV prior to the inclusion into the study, and HIV-positive patients will be excluded from the clinical study. Patients with active hepatitis B (chronic or acute; defined as having a positive HBsAg test result at screening) will be excluded from the study. Patients with past or resolved HBV infection (defined as the presence of HBcAb and absence of HBsAg) are eligible only if their HBV DNA test is negative. Patients with HCV will be excluded from the study; patients who test positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

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

[n] For atezolizumab, the initial dose will be delivered over 60 (± 15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. For carboplatin + nab-paclitaxel, administer nab-paclitaxel over 30 minutes followed immediately by carboplatin administered over 15–30 minutes. Administer nab-paclitaxel alone on Days 8 and 15. See Section 4.3.2.2 for details. Atezolizumab will be delivered as monotherapy during the maintenance phase (Arm A only) and for patients who cross over from Arm B (allowed under Study GO29537 Protocol Versions 1–4). See Section 4.3.2.2 for details.

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

[p] Perform every 6 weeks (± 7 days) (approximately every two cycles) for 48 weeks following Cycle 1, Day 1, and then every 9 weeks (± 7 days) after the completion of the Week 48 tumor assessment, regardless of treatment delays, until radiographic disease progression (loss of clinical benefit for patients assigned to atezolizumab who continue treatment after disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. See Section 4.5.5 for details.

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

[r] See Appendix 2 for detailed schedule.

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

Appendix 1
Schedule of Assessments (cont.)

[t] A mandatory biopsy is required, 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).

[u] All serious adverse events and adverse events of special interest, regardless of relationship to study treatment, will be reported until 90 days after the last dose of study treatment (inclusive of erlotinib [allowed under Study GO29537 Protocol Versions 1–4] or pemetrexed switch maintenance for patients randomized to Arm B who receive switch maintenance) or initiation of new systemic anti-cancer therapy. All other adverse events, regardless of relationship to study treatment, will be reported until 30 days after the last dose of study treatment (inclusive of erlotinib [allowed under Study GO29537 Protocol Versions 1–4] or pemetrexed switch maintenance for patients randomized to Arm B who receive switch maintenance) or initiation of new non-protocol systemic anti-cancer therapy after last dose of study treatment. After this period, all deaths will be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment (see Section 5.6).

[v] EORTC QLQ-C30, EORTC QLQ-LC13, PGIS, and EQ-5D-3L questionnaires will be completed by the patients on the ePRO tablet at each scheduled cycle visit during the induction period and then according to the tumor assessment schedule during the treatment maintenance phase prior to administration of study drug and prior to any other study assessment(s). SILC will be completed on an ePRO device at the patient's home on a weekly basis. During survival follow-up, the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-3L will be completed at 3 and 6 months following disease progression or loss of clinical benefit (for atezolizumab-treated patients). The SILC will be completed monthly during survival follow-up for 6 months following disease progression or following loss of clinical benefit for patients treated with atezolizumab who continue after disease progression according to RECIST v1.1. The PGIS is not required during survival follow-up. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will complete the EORTC QLQ-C30, EORTC QLQ-LC13, PGIS, and EQ-5D-3L at each tumor assessment visit and will complete the SILC at home on a weekly basis, until radiographic disease progression according to RECIST v1.1 or loss of clinical benefit (for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression) as determined by the investigator (unless the patient withdraws consent or the Sponsor terminates the study). Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. Patients whose native language is not available on the ePRO device or who are deemed by the investigator incapable of inputting their ePRO assessment after undergoing appropriate training are exempted from completing all ePRO assessments.

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

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

Study Visit	Time	Arm A	Arm B
Screening	N/A	Biomarkers [b]	Biomarkers [b]
Cycle 1, Day 1 [e]	Pre-dose (same day as treatment administration)	Atezolizumab ATA Atezolizumab pharmacokinetics Carboplatin pharmacokinetics [a] nab-Paclitaxel pharmacokinetics [a] Biomarkers [d]	Carboplatin pharmacokinetics [a] nab-Paclitaxel pharmacokinetics [a] Biomarkers [d]
	30 min (±10 min) after end of atezolizumab infusion	Atezolizumab pharmacokinetics	
	5–10 min before the end of nab-paclitaxel infusion [a]	nab-Paclitaxel pharmacokinetics [a]	nab-Paclitaxel pharmacokinetics [a]
	1 hr after end of nab-paclitaxel infusion [a]	nab-Paclitaxel pharmacokinetics [a]	nab-Paclitaxel pharmacokinetics [a]
	5–10 min before the end of carboplatin infusion [a]	Carboplatin pharmacokinetics [a]	Carboplatin pharmacokinetics [a]
	1 hr after end of carboplatin infusion [a]	Carboplatin pharmacokinetics [a]	Carboplatin pharmacokinetics [a]
Cycle 2, Day 1 (±3 days)	Pre-dose (same day as treatment administration)	Atezolizumab ATA Atezolizumab pharmacokinetics Biomarkers [d]	Biomarkers [d]

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

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

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

Study Visit	Time	Arm A	Arm B
Treatment discontinuation visit	At visit	Atezolizumab ATA Atezolizumab pharmacokinetics Biomarkers [d]	Biomarkers [d]
120 ± 30 days after last dose of atezolizumab	At visit	Atezolizumab ATA Atezolizumab pharmacokinetics Biomarkers [d]	
At any timepoint during study (RCR consent required)		Optional RCR blood (DNA extraction) [c]	Optional RCR blood (DNA extraction) [c]

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

Note: Serum pharmacokinetic samples for atezolizumab; plasma pharmacokinetic samples for carboplatin, and nab-paclitaxel.

[a] At selected centers, 20 patients in each treatment arm will undergo the additional PK assessments for carboplatin and nab-paclitaxel.

[b] Whole blood for biomarkers.

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

[d] Plasma and serum for biomarkers.

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

Appendix 3
Schedule of Pharmacokinetic, Biomarker, and Anti-Therapeutic Antibody Assessments for Arm B Patients Who Cross Over to Receive Atezolizumab as Allowed under Protocol Versions 1–4

Study Visit	Time	Arm B Crossover Patients
Cycle 1A, Day 1	Pre-dose (same day as treatment administration)	Atezolizumab ATA Atezolizumab pharmacokinetics Biomarkers [a]
	30 min (±10 min) after end of atezolizumab infusion	Atezolizumab pharmacokinetics
Cycle 2A, Day 1 (±3 days)	Pre-dose (same day as treatment administration)	Atezolizumab ATA Atezolizumab pharmacokinetics Biomarkers [b]
Cycle 3A, Day 1 (±3 days)	Pre-dose (same day as treatment administration)	Atezolizumab ATA Atezolizumab pharmacokinetics Biomarkers [b]
	30 min (±10 min) after end of atezolizumab infusion	Atezolizumab pharmacokinetics
Cycles 4A, 8A, and 16A, Day 1 (±3 days)	Pre-dose (same day as treatment administration)	Atezolizumab ATA Atezolizumab pharmacokinetics Biomarkers [b]
After Cycle 16A, every eighth cycle, Day 1 (±3 days)	Pre-dose (same day as treatment administration)	Atezolizumab ATA Atezolizumab pharmacokinetics Biomarkers [b]
Treatment discontinuation visit	At visit	Atezolizumab ATA Atezolizumab pharmacokinetics Biomarkers [b]
120±30 days after last dose of atezolizumab	At visit	Atezolizumab ATA Atezolizumab pharmacokinetics Biomarkers [b]

ATA = anti-therapeutic antibody.

Notes: Serum pharmacokinetic samples for atezolizumab.

[a] Plasma, serum, and whole blood for biomarkers.

[b] Plasma and serum for biomarkers.

Appendix 4
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 4
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 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication

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

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

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

a. Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

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

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal

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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.

masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

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.

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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.

Clinical Lesions. Clinical lesions will be considered measurable only when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules).

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

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan on the basis of the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

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

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

Appendix 5
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 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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

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

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

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

RESPONSE CRITERIA

a. Evaluation of Target Lesions

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

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

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

- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

b. Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. Although some non-target lesions may actually be

measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size (< 10 mm short axis).

- Non-CR/Non-PD: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease; that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. Although it would be ideal to have objective criteria

to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. New Lesions

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

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

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

EVALUATION OF RESPONSE

a. Timepoint Response (Overall Response)

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

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

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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

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

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

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

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

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

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely

to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm; the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Appendix 5
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 6
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 6
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 6
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.

Appendix 6
Modified Response Evaluation Criteria in Solid Tumors (cont.)

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 according to 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 according to 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 6
Modified Response Evaluation Criteria in Solid Tumors (cont.)

B.3 RESPONSE CRITERIA

Timepoint Response

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

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

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

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the diameters while on study.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and selected new measurable lesions, taking as reference the smallest sum on study (nadir SLD; this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Impact of New Lesions on Modified RECIST

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall modified RECIST tumor response.

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is considered not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would only happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed but

those gave a sum of 80 mm, the patient will be assigned PD status, regardless of the contribution of the missing lesion.

Table 1 Modified RECIST Timepoint Response Definitions

% Change in Sum of the Diameters [a]	Non-Target Lesion Response Assessment	Overall Modified RECIST Timepoint Response
−100% from baseline [b]	CR	CR
−100% from baseline [b]	Non-CR or not all evaluated	PR
≤ −30% from baseline	Any	PR
> −30% to < +20%	Any	SD
Not all evaluated	Any	NE
≥ +20%from nadir SLD	Any	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; SLD = sum of the longest diameter.

[a] Percent change in sum of the diameters (including measurable new lesions when present).

[b] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm in order to meet the definition of CR.

Appendix 7
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 GO29537, the anti–PD-L1 (SP142) IHC assay will be used for investigational purposes only.

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

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

DEVICE DESCRIPTION

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

SCORING SYSTEM

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

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

Appendix 8
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 8
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 9
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 10
EQ-5D-3L

Health Questionnaire

(English version for the US)

Appendix 10
EQ-5D-3L (cont.)

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

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

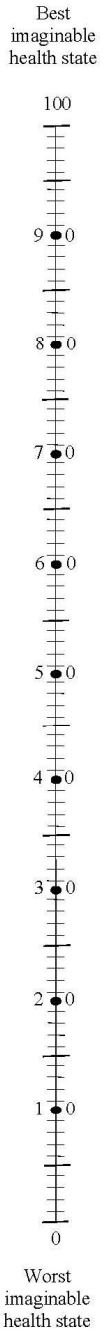
I am extremely anxious or depressed ❑

Appendix 10
EQ-5D-3L (cont.)

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

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

Your own health state today



Appendix 11
Eastern Cooperative Oncology Group Performance Status Scale

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

Appendix 12
Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

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

Appendix 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 may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty about autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

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

Appendix 14
Symptoms in Lung Cancer

Symptoms in Lung Cancer (SILC)

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

Item #	Question
1	Over the past week, how would you rate your chest pain at its worst? ☐$_0$ No pain at all ☐$_1$ Mild pain ☐$_2$ Moderate pain ☐$_3$ Severe pain ☐$_4$ Very severe pain
2	Over the past week, how often did you have chest pain? ☐$_0$ Never ☐$_1$ Rarely ☐$_2$ Sometimes ☐$_3$ Often ☐$_4$ Always
3	Over the past week, how would you rate your coughing at its worst? ☐$_0$ No coughing at all ☐$_1$ Mild coughing ☐$_2$ Moderate coughing ☐$_3$ Severe coughing ☐$_4$ Very severe coughing
4	Over the past week, how often did you cough? ☐$_0$ Never ☐$_1$ Rarely ☐$_2$ Sometimes ☐$_3$ Often ☐$_4$ Always

Appendix 14
Symptoms in Lung Cancer (cont.)

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

Appendix 14
Symptoms in Lung Cancer (cont.)

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

Appendix 15
Patient Global Impression of Severity

Patient Global Impression of Severity (PGIS)

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

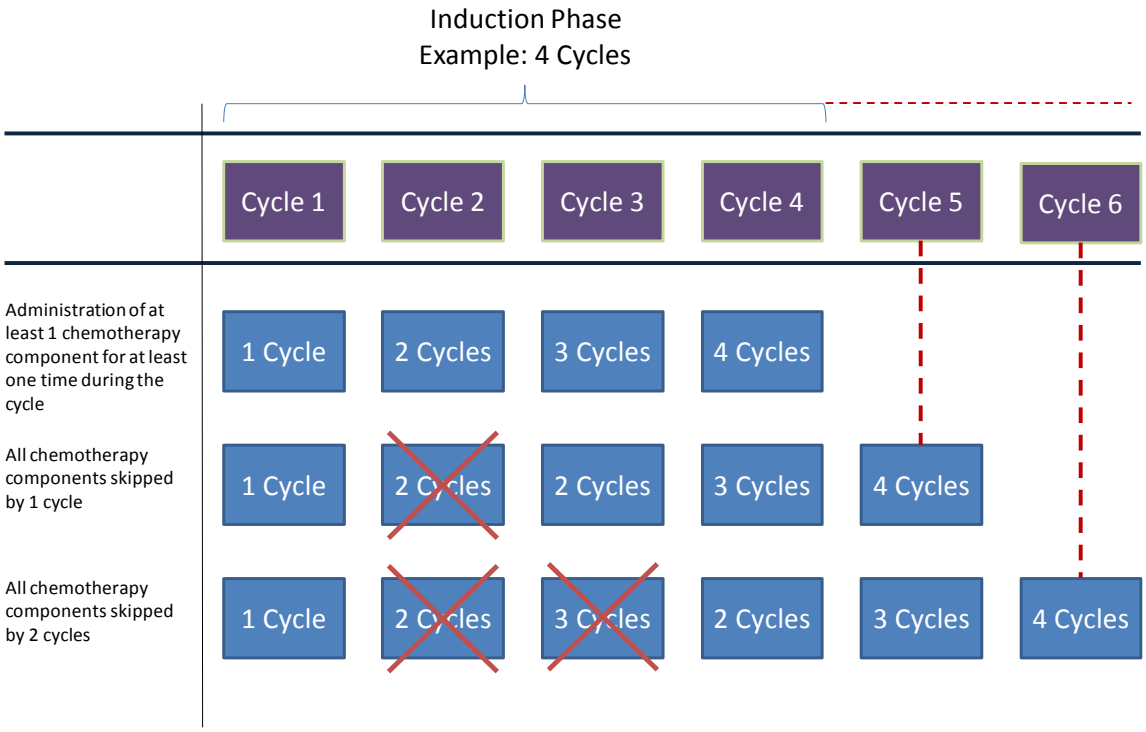
1 ☐ Not severe
2 ☐ Mildly severe
3 ☐ Moderately severe
4 ☐ Very severe
5 ☐ Extremely severe

Appendix 16
Additional Guidance on Chemotherapy Administration

For the purposes of this protocol, the Sponsor defines a chemotherapy cycle during the induction phase as the administration of at least one chemotherapy component at least once during a 21-day cycle. Cycles in which no chemotherapy component is given do not count toward the total number of induction chemotherapy cycles.

In the event that chemotherapy cannot be given, owing to toxicity, atezolizumab should be given without chemotherapy if there is no contraindication.

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



All chemotherapy components may be withheld for up to a maximum of 2 cycles. If an interruption of all chemotherapy is indicated for a third cycle, all chemotherapy should be permanently discontinued.

Within a 4-cycle induction regimen, chemotherapy may be paused for a total of two consecutive or non-consecutive cycles before chemotherapy should be permanently discontinued. Within a 6-cycle induction regimen, chemotherapy may be paused for a

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

The recommended time window for administration of all study treatment components within a cycle is 3 days. If atezolizumab was given but chemotherapy could not be administered on the same day, and the delay between the first and last component of study treatment would be more than 3 days, carboplatin should be delayed until Day 1 of the next cycle and nab-paclitaxel administered on Day 8 and/or Day 15 of the current cycle if there is no contraindication.

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

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

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

STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY EVALUATING THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (MPDL3280A, ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH CARBOPLATIN + NAB-PACLITAXEL FOR CHEMOTHERAPY–NAIVE PATIENTS WITH STAGE IV NON-SQUAMOUS NON–SMALL CELL LUNG CANCER**

PROTOCOL NUMBER: GO29537

STUDY DRUG: Atezolizumab (RO5541267)

VERSION NUMBER: 4

IND NUMBER: 117296

EUDRACT NUMBER: 2014-003206-32

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted], Ph.D.

DATE FINAL: 19 May 2017

DATE AMENDED Version 2: 17 October 2017
Version 3: 13 March 2018
Version 4: See electronic date stamp below

Name	Reason for Signing	Date and Time (UTC)
[redacted]	Company Signatory	04-May-2018 17:22:12

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

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1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study GO29537 (IMpower130), "A Phase III, Multicenter, Randomized, Open-Label Study Evaluating the Efficacy and Safety of Atezolizumab (MPDL3280A, Anti–PD-L1 Antibody) in Combination with Carboplatin + Nab-Paclitaxel for Chemotherapy–Naïve Patients with Stage IV Non-Squamous Non–Small Cell Lung Cancer." The background for the study can be found in the study protocol.

2. STUDY DESIGN

This is a randomized, Phase III, multicenter, open-label study designed to evaluate the efficacy and safety of atezolizumab in combination with carboplatin + nab-paclitaxel as compared with treatment with carboplatin + nab-paclitaxel in approximately 715 chemotherapy–naïve patients with Stage IV non-squamous non–small cell lung cancer (NSCLC).

Eligible patients were stratified by sex (male vs. female), presence of liver metastases at baseline (yes vs. no), and programmed death–ligand 1 (PD-L1) tumor expression by immunohistochemistry (IHC) (tumor cell [TC] 3 and any tumor-infiltrating immune cell [IC] vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1) tested by a central laboratory. TC0, TC1, TC2, and TC3 are defined as PD-L1 staining in $<1\%, \geq 1\%$ to $<5\%, \geq 5\%$ to $<50\%$, and $\geq 50\%$ of the TCs, respectively. IC0, IC1, IC2, and IC3 are defined as PD-L1–stained ICs covering $<1\%, \geq 1\%$ to $<5\%, \geq 5\%$ to $<10\%$, and $\geq 10\%$ of the tumor area, respectively.

Eligible patients were randomized in a 2:1 ratio to one of the following treatment regimens:

- Treatment Arm A: Atezolizumab + carboplatin + nab-paclitaxel (induction: four or six 21-day cycles); atezolizumab (maintenance: 21-day cycles)
- Treatment Arm B: Carboplatin + nab-paclitaxel (induction: four or six 21-day cycles); best supportive care, erlotinib (only for patients who started switch maintenance treatment under Versions 1–4 of the protocol) or pemetrexed

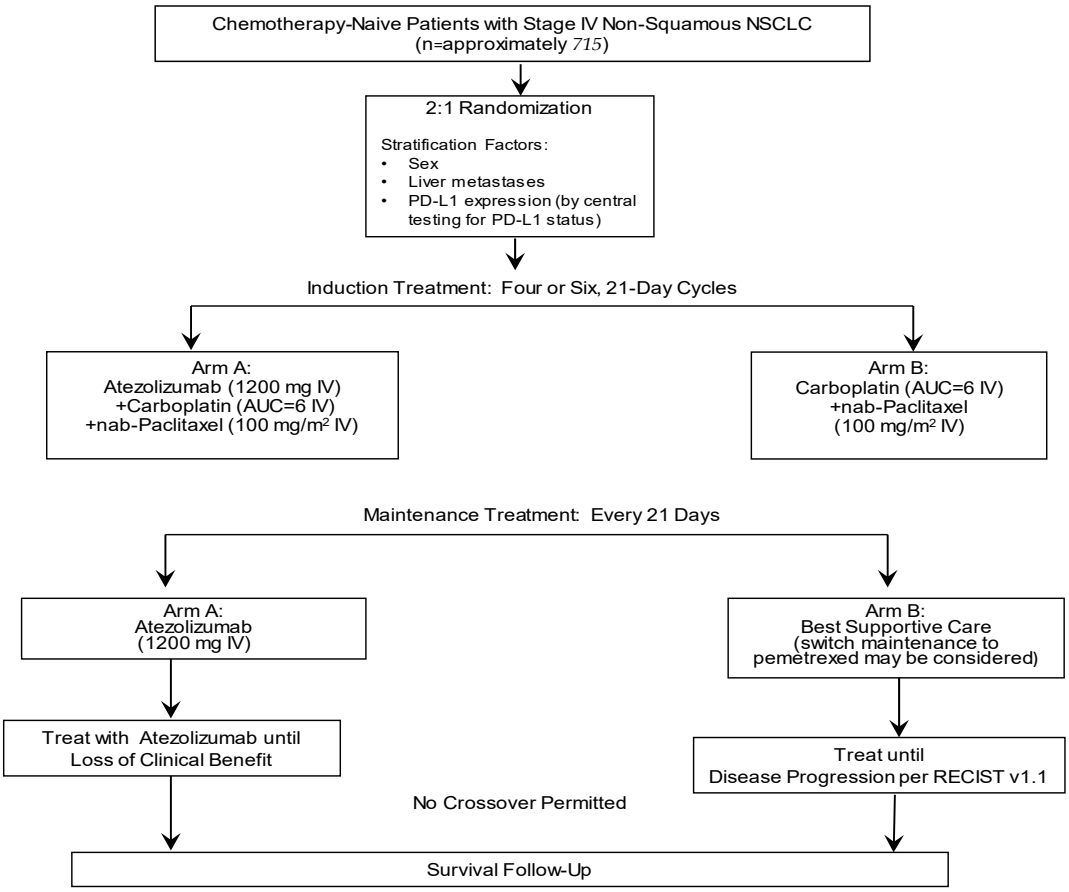
Patients who were randomized to Arm A may continue treatment with atezolizumab beyond radiographic progression by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), provided they are experiencing clinical benefit as assessed by the investigator (i.e., in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results [if available], and clinical status).

In Protocol GO29537, Versions 1–4, patients who are randomized to Arm B following disease progression will be given the option to receive atezolizumab monotherapy provided they continue to meet crossover eligibility criteria. In Protocol GO29537,

Version 5 and thereafter, crossover from the control arm to the experimental arm after the disease progression will not be permitted, with the aim to preserve the study's ability to potentially demonstrate treatment benefit of atezolizumab on overall survival (OS).

Figure 1 illustrates the study design of which details can be found in the study protocol.

Figure 1 Study Schema



AUC = area under the concentration–time curve; IV = intravenously; NSCLC = non–small cell lung cancer; PD-L1 = programmed death–ligand 1; RECIST v.1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1

Patients undergo tumor assessments at baseline and every 6 weeks (±7 days) for the first 48 weeks following Cycle 1, Day 1, regardless of dose delays. After 48 weeks, tumor assessment is required every 9 weeks (±7 days). Patients undergo tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab-treated patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity) will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab-treated patients

who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.

The co-primary efficacy endpoints are progression-free survival (PFS) as assessed by the investigator using RECIST v1.1 and OS. See Section 2.2 for details on co-primary efficacy endpoints, secondary endpoints, and other endpoints such as safety, pharmacokinetic (PK), and exploratory outcome measures.

The primary analyses of PFS and all OS analyses will be performed on all randomized patients excluding patients with an activating *EGFR* mutation or *ALK* translocation ITT–WT. *EGFR* mutations include all *EGFR*-activating mutations in exons 18 through 21. See Section 4.1 for details on analysis populations.

There are no interim analyses planned for PFS and one interim analysis planned for OS in this study. See Section 2.4 for detailed analysis timing.

An external independent Data Monitoring Committee (iDMC) will be set up to evaluate safety data on an ongoing basis.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedules of Assessments in Appendix 2 and Appendix 3.

2.2 OUTCOME MEASURES

2.2.1 Primary Efficacy Measures

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

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

2.2.2 Secondary Efficacy Measures

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

- PFS, as determined by the investigator according to RECIST v1.1, and OS in the ITT population
- PFS, as determined by the investigator according to RECIST v1.1, and OS in the PD-L1 expression population (as described in Section 4.1.1), and the aforementioned population excluding patients with an activating *EGFR* mutation or *ALK* translocation, namely, the PD-L1 expression WT population

- Objective response, defined as either complete response (CR) or partial response (PR), as determined by the investigator according to RECIST v1.1 in the same populations as defined in the PFS measure: ITT–WT, ITT, PD-L1 expression, PD-L1 expression WT; confirmation of objective response is not required
- Duration of response (DOR), defined for patients with an objective response as the time from the first documented objective response to documented disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first, in the same populations as defined in the objective response measure: ITT–WT, ITT, PD-L1 expression, PD-L1 expression WT
- OS rates at 1 and 2 years, defined as the proportion of patients alive at 1 and 2 years after randomization estimated using Kaplan-Meier (KM) methodology in the same populations as defined in the OS measure: ITT–WT, ITT, PD-L1 expression, PD-L1 expression WT
- Time to deterioration (TTD) in patient-reported lung cancer symptoms, defined as time from randomization to confirmed deterioration (10-point change) on the combined European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire–Core (EORTC QLQ-C30) and supplemental lung cancer module (EORTC QLQ-LC13) symptom subscales in the ITT–WT population
- Change from baseline in patient-reported lung cancer symptoms (cough, dyspnea, and chest pain) on the symptom severity score of the Symptoms in Lung Cancer (SILC) scale for the ITT–WT population

2.2.3 Exploratory Efficacy Measures

The exploratory efficacy measures for this study are the following:

- PFS, ORR, and DOR, as determined by the investigator according to RECIST v1.1, and OS in the T-effector high (Teff-high) population (with Teff gene signature expression in tumor tissue as described in Section 4.4.3.1, previously referred to as tGE) and the aforementioned population excluding patients with an activating EGFR mutation or ALK translocation, namely, the Teff-high WT
- PFS rates at 6 months and 1 year, defined as the proportion of patients alive and without progression as assessed by the investigator according to RECIST v1.1 at 6 months and 1 year after randomization estimated using KM methodology
- OS rate at 3 years, defined as the proportion of patients alive at 3 years after randomization estimated using KM methodology
- Status of PD-L1–, immune-, and NSCLC-related and other exploratory biomarkers in archival and/or freshly obtained tumor tissues, and blood (or blood derivatives) collected before, during, or after treatment with atezolizumab or at progression and association with disease status and/or response to atezolizumab in combination with chemotherapy
- Status of ICs and other exploratory biomarkers in mandatory biopsy specimens and blood collected at progression

- Utility scores of the Euro QoL5 Dimensions 3–Level Version (EQ-5D-3L)
- Change from baseline and the number and proportion of patients with a clinically meaningful change in patient-reported outcomes (PROs) of health-related quality of life (HRQoL), lung cancer–related symptoms, and health status as assessed by the EORTC QLQ-C30 and EORTC QLQ-LC13, as described in Section 4.4.2.6

2.2.4 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are:

- For patients randomized to atezolizumab + carboplatin + nab-paclitaxel:

  Maximum observed serum atezolizumab concentration (C_{max}) after infusion on Cycle 1, Day 1

  Minimum observed serum atezolizumab concentration (C_{min}) prior to infusion at selected cycles, at treatment discontinuation, and at 120 days (±30 days) after the last dose of atezolizumab
- Plasma concentrations for carboplatin (Arms A and B)
- Plasma concentrations for nab-paclitaxel reported as total paclitaxel (Arms A and B)
- For patients randomized to carboplatin + nab-paclitaxel who crossed over to receive open-label atezolizumab as monotherapy (allowed under Protocol GO29537, Versions 1–4):

  C_{max} of serum atezolizumab after infusion on Day 1 of the first cycle following crossover to atezolizumab as monotherapy

  C_{min} of serum atezolizumab prior to infusion on Day 1 at selected cycles following crossover to atezolizumab as monotherapy, at treatment discontinuation, and at 120 (±30 days) after the last dose of atezolizumab

2.2.5 Safety Outcome Measures

The safety outcome measures for this study are:

- Incidence, nature, and severity of adverse events graded according to the National Cancer Institute Common Terminology Criteria in Adverse Events, Version 4.0 (NCI CTCAE v4.0)
- Changes in vital signs and clinical laboratory results during and following atezolizumab administration
- Incidence of anti-drug antibody (ADA), also known as anti-therapeutic antibody (ATA), response to atezolizumab and potential correlation with PK, pharmacodynamic, safety, and efficacy parameters

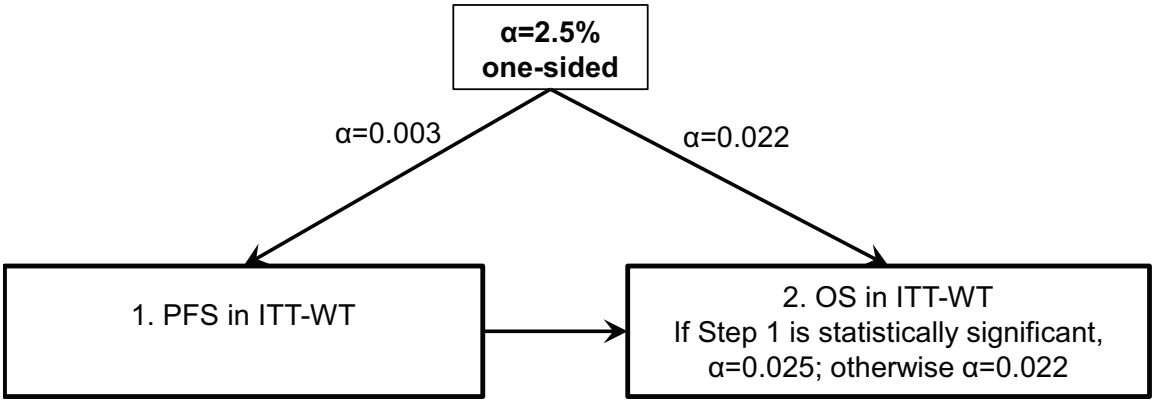
2.3 DETERMINATION OF SAMPLE SIZE

This study randomized approximately 715 patients. Patients with an activating *EGFR* mutation or *ALK* translocations will be excluded from the primary analysis populations. There are expected to be approximately 650 patients in the ITT–WT population given the approximately 10% prevalence of these genetic variations.

To control the overall type I error rate for the one-sided test at 0.025, a one-sided α of 0.003 and a one-sided α of 0.022 are allocated to PFS and OS, respectively.
The primary comparison of PFS will be tested at a one-sided α level of 0.003 in the ITT–WT population. The primary comparison of OS will be tested in the ITT–WT population at the allocated α, together with the α recycled from the PFS analysis if the PFS comparison is statistically significant.

The PFS and OS analysis hierarchy and α allocation (Burman et al. 2009), including possible α recycling, are shown in Figure 2.

Figure 2 Progression-Free Survival and Overall Survival Analysis Hierarchy, α Allocation, and α Recycling



ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival; WT = wild type.

[a] To control the overall type I error rate for the one-sided test at 0.025, a one-sided type I error (α) 0.003 and 0.022 (ratio of 3:22) will be allocated to PFS and OS, respectively, for comparison of Arm A versus Arm B.

OS will be tested using the group sequential method at the interim and final OS analyses based on the α allocated to the primary comparison of OS as described above. Statistical significance at the interim and final analyses of OS will be tested as described in Section 2.4.2.

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

The estimates of the number of events required to demonstrate efficacy with regard to PFS in the primary comparisons are based on the following assumptions:

- One-sided significance level of 0.003 in the ITT–WT population
- 95% power to detect an hazard ratio (HR) of 0.65, corresponding to an improvement in median PFS from 6 months to 9.2 months in the ITT–WT population
- No interim analysis for PFS
- Dropout rate of 5% per 12 months

The estimates of the number of events required with regard to OS in the primary comparisons are based on the following assumptions:

- One-sided significance level of 0.022 in the ITT–WT population
- 80% power to detect an HR of 0.75, corresponding to an improvement in median OS from 12 months to 16 months in the ITT–WT population
- One OS interim analyses performed when approximately 77% of the total OS events required for the final analysis have occurred using the Lan-DeMets approximation to the O'Brien-Fleming boundary
- Dropout rate of 5% per 24 months

With these assumptions, approximately 715 patients in total were planned to be randomized into this study, in order to have approximately 650 patients in the ITT–WT population. Note that the OS boundaries have been updated to use the Lan-DeMets approximation to the Pocock boundaries (described in Section 2.4.2); therefore the overall power for the OS in the ITT-WT population is reduced from 80% to 77% (Table 2).

2.4 ANALYSIS TIMING

2.4.1 Primary Analysis Timing for PFS

No interim analyses are planned for the co-primary endpoint of PFS in this study. The PFS primary analysis will be conducted at the time of the OS interim analysis (see Section 2.4.2). At this timepoint, it is expected that approximately 475 PFS events will have occurred in the ITT–WT population based on the assumptions specified in Section 2.3. These numbers of events correspond to a minimum detectable difference (MDD) in HR of approximately 0.76 in the ITT–WT population.

Table 1 Primary Analysis for Progression-Free Survival

Population	Analysis Timing (Months from FPI)	No. of Events (Event Ratio, %)	MDD in Hazard Ratio	Power, %
ITT-WT	32	475 (73)	0.76	95

FPI = first patient in; ITT = intent-to-treat; MDD = minimum detectable difference; WT = wild type.

2.4.2 Interim and Final Analysis Timing for OS

There is one interim analysis planned for the co-primary endpoint of OS.

The timing of the primary efficacy analysis will be driven by the number of events required for the OS interim analysis, which will be conducted by the Sponsor when approximately 352 OS events have occurred in the ITT–WT population. Based on the assumptions in Section 2.3, the OS interim analysis is expected to occur approximately 32 months after the first patient is randomized.

The final OS analysis will be conducted when there are approximately 457 OS events in the ITT–WT population. The OS final analysis is expected to occur approximately 42 months after the first patient is randomized.

The expected analysis timing for the OS interim and final analyses is shown in Table 2.

Table 2 Analysis for Overall Survival

	Analysis Timing		ITT-WT Population	
Type of Analysis	Months from FPI	Percentage Information, %	No. of Events (Event Ratio, %)	Power, % [a]
OS interim analysis	32	77	352 (54)	68
OS final analysis	42	100	457 (70)	77

FPI = first patient in; ITT = intent-to-treat; OS = overall survival; WT = wild type.

[a] Power is calculated using one-sided α of 0.022.

The stopping boundaries for the interim and final OS analyses considering different scenarios with α recycling are calculated using the Lan-DeMets approximation to the Pocock boundary, assuming the specified observed number of events (352 and 457, respectively), and are shown in Table 3. The p-value will be used to claim crossing of the boundaries. For example, if approximately 352 events have occurred in the ITT–WT population at the time of the OS interim analysis, statistical significance of the OS endpoint in ITT–WT population will be declared if $p \leq 0.0211$ when PFS has claimed significance in the ITT–WT population.

Table 3 Analysis Timing and Stopping Boundary for Overall Survival in the Intent-to-Treat Wild-Type Population

	Stopping Boundary in HR (p-value)	
Analysis	If $\alpha = 0.022$	If $\alpha = 0.025$
OS interim analysis	HR $\leq$ 0.790 (p-value $\leq$ 0.0185)	HR $\leq$ 0.795 (p-value $\leq$ 0.0211)
OS final analysis	HR $\leq$ 0.795 (p-value $\leq$ 0.0103)	HR $\leq$ 0.799 (p-value $\leq$ 0.0119)

HR = hazard ratio; OS = overall survival.

Note: α and p-value are one-sided.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Randomization to the treatment and control arms will occur in a 2:1 ratio using a permuted-block randomization method. Randomization will be stratified by the following factors:

- Sex (male vs. female)
- Presence of liver metastases at baseline (yes vs. no)

- PD-L1 expression by IHC (TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC 0/1/2 and IC0/1)

3.2 INDEPENDENT REVIEW FACILITY

An Independent Review Facility (IRF) will be used to conduct a blinded radiology review of the imaging data and will provide an independent assessment of tumor response and progression for all patients according to a separate IRF Charter. IRF-assessed endpoints may be used for sensitivity analyses (see Section 4.4.4).

3.3 DATA MONITORING

An external iDMC will be used to evaluate safety during the study on a periodic basis, approximately every 6 months from the point of first patient in until the time the database is locked and the study is unblinded for the primary PFS analysis and interim OS analysis. All summaries and analyses by treatment arm for the iDMC review will be prepared by an independent data coordinating center. Following the data review, the iDMC will provide a recommendation as to whether the study may continue, whether amendment(s) to the protocol should be implemented, or whether the study should be stopped. The final decision will rest with the Sponsor.

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

4. STATISTICAL METHODS

The analyses described in this SAP will supersede those specified in Protocol GO29537 for the purposes of a regulatory filing.

4.1 ANALYSIS POPULATIONS

4.1.1 Efficacy Analysis Populations

The randomized population or ITT population is defined as all randomized patients, whether or not the patient received the assigned treatment.

The ITT–WT population is defined as the ITT population excluding patients with an activating *EGFR* mutation or *ALK* translocation.

The PD-L1 expression population is defined as one of the following: PD-L1 IHC TC1/2/3 or IC1/2/3 population, defined as ITT patients with PD-L1 IHC TC1/2/3 or IC1/2/3 expression in baseline tumor tissue; PD-L1 IHC TC2/3 or IC2/3 population, defined as ITT patients with PD-L1 IHC TC2/3 or IC2/3 expression in baseline tumor tissue; PD-L1 IHC TC3 or IC3 population, defined as ITT patients with PD-L1 IHC TC3 or IC3 expression in baseline tumor tissue. The PD-L1 expression WT population is defined as the PD-L1 expression population excluding patients with an activating *EGFR* mutation or *ALK* translocation.

Analyses of primary and select secondary efficacy endpoints will be performed in the PD-L1 IHC TC1/2/3 or IC1/2/3 population and the PD-L1 IHC TC1/2/3 or IC1/2/3-WT population. Analyses of primary and select secondary efficacy endpoints may be conducted in other PD-L1 expression populations and PD-L1 expression WT populations (e.g., TC2/3 or TC2/3-WT, TC3 or IC3-WT, TC2/3 or IC2/3, TC3 or IC3, and the corresponding complementary groups, as well as TC0 and IC0-WT, TC0 and IC0).

The primary analyses of PFS and all OS analyses will be performed on the ITT−WT population. Patients are grouped according to the treatment assigned at randomization, regardless of whether they received any assigned study drug.

Objective response rate (ORR; confirmation not required) will be analyzed for patients in the aforementioned populations who have measurable disease as assessed by investigator at baseline.

DOR will be assessed in patients in the aforementioned populations who have an objective response and measurable disease as assessed by investigator at baseline.

OS rate at the 1- and 2-year landmark timepoints will be analyzed in the same populations as defined for the OS analyses.

TTD analyses will be conducted on the ITT−WT population. Change from baseline analysis in PROs will be performed for patients in the ITT−WT population who have both a non-missing baseline assessment and at least one non-missing post-baseline assessment.

4.1.2 Pharmacokinetic-Evaluable Population

The pharmacokinetic-evaluable population is defined as all patients who received any dose of atezolizumab, carboplatin, or nab-paclitaxel and who have evaluable PK samples.

4.1.3 Safety Population

The safety population includes treated patients, defined as randomized patients who received any protocol treatment. For the safety analyses, patients will be grouped according to whether any full or partial dose of atezolizumab was received, including when atezolizumab was received in error. Specifically, for patients randomized to Arm B, if atezolizumab was received in error, the patients will be grouped to Arm A for the safety analyses.

4.2 ANALYSIS OF STUDY CONDUCT

Study enrollment, major protocol deviations, including major deviations from inclusion/exclusion criteria, and reasons for study termination will be summarized overall and by treatment arm for the ITT population. Analysis of study conduct may also be summarized for the ITT−WT if needed. Study treatment administration and reasons for discontinuation from study treatment will be summarized for the safety population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic characteristics, such as age, race/ethnicity, baseline disease characteristics (e.g., Eastern Cooperative Oncology Group [ECOG] performance status), and stratification factors (sex, presence of liver metastasis at baseline, PD-L1 tumor expression by IHC) will be summarized by treatment arms for the ITT−WT population. Other populations may also be summarized as deemed needed. Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

Unless otherwise stated, baseline values are the last available data obtained prior to the patient receiving the first dose of any component of study treatment on Cycle 1, Day 1.

4.4 EFFICACY ANALYSIS

Patients will be grouped for efficacy analyses according to the treatment assigned at randomization, whether or not the assigned treatment was received.

4.4.1 Primary Efficacy Endpoint

The co-primary efficacy endpoints are PFS and OS.

PFS is defined as the time from randomization to the first documented disease progression as determined by the investigator with the use of RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who are alive and have not experienced disease progression at the time of analysis will be censored at the date of the last tumor assessment. Data for patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

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 analysis will be censored at the date last known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.

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

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

The HRs, λ_A/λ_B where λ_A, and λ_B represent the hazard of having a PFS event in Arm A and Arm B, respectively, comparing the treatment effect between the two treatment arms will be estimated using a stratified Cox regression model with the same stratification variables used for the stratified log-rank test, and the 95% CI will be provided.

For PFS and OS analyses in the ITT−WT population, the stratification factors will be sex (male vs. female), presence of liver metastases at baseline (yes vs. no), and PD-L1 tumor expression by IHC ([TC3 and any IC, TC0/1/2 and IC2/3 combined] vs. TC0/1/2

and IC0/1). The stratification factors will be those used during randomization as recorded in the interactive voice/web response system. Due to the potential risk of over-stratification (Akazawa et al. 1997), if at least one stratum (i.e., a combination of stratification factor levels across sex, presence of liver metastasis at baseline, and PD-L1 tumor expression by IHC per IxRS) has less than 15 events (PFS or OS events), the stratification factor (one of three stratification factors: sex, presence of liver metastasis at baseline, and PD-L1 tumor expression by IHC 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 15 events (PFS or OS events). The final set of stratification factors used in stratified analyses will be applied to all endpoints where stratified analyses are planned. The analyses based on stratification factors as recorded on the electronic Case Report Form (eCRF) may also be provided. Results from an unstratified analysis will also be provided.

Treatment comparisons will be conducted by comparing Arm A versus Arm B based on stratified log-rank tests in the ITT–WT population for the PFS and the OS endpoints. For each comparison, analyses will be conducted according to an analysis hierarchy and an α–spending algorithm to control for the type I error rate (see Figure 2 in Section 2.3) and to account for an interim analysis (see Section 2.4.2).

To control the overall type I error rate for the one-sided test at 0.025, the hypothesis testing will be done at the specified significance levels in the order described below:

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

KM methodology will be used to estimate median PFS and OS and to construct survival curves for each treatment arm for a visual description of the difference among arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS and OS (Brookmeyer and Crowley 1982).

Follow-up for OS, defined as the time from randomization to death or last known date alive, will be summarized for all patients included in the analysis (whether patient is alive or has died). Follow-up will be summarized using the KM method with data for patients who died censored at the date of death.

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 PFS and OS in the ITT Population

PFS and OS in the ITT populations will be analyzed using the same methods as described in Section 4.4.1. PFS and OS in patients with an activating *EGFR* mutation or *ALK* translocation may be analyzed using the same methods to provide the evaluation of the population complementary to the ITT-WT population.

If the difference in OS between Arm A and Arm B in the ITT–WT population is statistically significant, a comparison of Arm A versus Arm B will be conducted in the ITT population, similarly as shown in Figure 2. The α allocation will follow the same α-spending algorithm and allocation ratio (3:22) described for analysis of the co-primary efficacy endpoints as described in Section 2.3.

4.4.2.2 PFS and OS in PD-L1 Expression and PD-L1 Expression WT Populations

PFS and OS in the TC1/2/3 or IC1/2/3–WT, and the TC1/2/3 or IC1/2/3 populations will be analyzed using similar methods as described in Section 4.4.1. Analyses of PFS and OS may be conducted in other PD-L1 expression populations and PD-L1 expression WT populations (e.g., TC2/3 or TC2/3-WT, TC3 or IC3-WT, TC2/3 or IC2/3, TC3 or IC3, and the corresponding complementary groups, as well as TC0 and IC0-WT, TC0 and IC0).

4.4.2.3 Objective Response Rate

ORR (confirmation not required) is defined as the proportion of patients with an objective response, either CR or PR, with the use of RECIST v1.1, as determined by the investigator. Patients not meeting these criteria, including those without any post-baseline assessment, will be considered non-responders. Confirmation of response according to RECIST v1.1 is not required, but for exploratory purposes, ORR with confirmation may be reported. ORR will be compared between treatment arms using the stratified Cochran-Mantel-Haenszel test. The 95% CI for the difference in ORRs between the two treatment arms will be computed using the normal approximation to the binomial distribution. An estimate of ORR and its 95% CI will be calculated for each treatment arm using the Clopper-Pearson method.

4.4.2.4 Duration of Response

DOR is defined for patients with an objective response as the time from the first documented objective response to documented disease progression as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who are alive and who have not experienced disease progression at the time of analysis will be censored at the date of the last tumor assessment. If no tumor assessments were performed after the date of the first occurrence of the objective response (CR or PR), DOR will be censored at the date of the first occurrence of the objective response. Because the determination of DOR is based on a non-randomized subset of patients, formal hypothesis testing will not be performed. DOR will be

estimated using KM methodology. Comparisons between treatment arms will be made using the stratified and unstratified log-rank test for descriptive purposes only.

Confirmation of response according to RECIST v1.1 will not be required, but for exploratory purposes, DOR for patients with confirmed response may be reported.

4.4.2.5 OS Rate at the 1- and 2-Year Landmark Timepoints

The OS rate at the 1- and 2-year landmark time points after randomization will be estimated for each treatment arm using KM methodology, along with 95% CI calculated with the standard error derived from the Greenwood formula. The 95% CI for the difference in OS rates between the two treatment arms will be estimated using the normal approximation method, with standard errors computed using the Greenwood method.

4.4.2.6 Patient-Reported Outcomes

Through the use of the SILC scale, the EORTC QLQ-C30, and EORTC QLQ-LC13, lung cancer symptom data will be collected about symptoms commonly associated with cancer treatments, and disease and treatment impact on patients' functioning.

The EORTC QLQ-C30 and EORTC QLQ-LC13 will be scored according to the EORTC scoring manual (Fayers et al. 2001). The QLQ-C30 and QLQ-LC13 consist of both multi-item scales and single-item measures such as functional scales, symptom scales, and a global health status/quality-of-life scale.

For multi-item subscales, if $\leq 50\%$ of items within the multi-item subscale are missing at a given timepoint, the multi-item score will be calculated on the basis of the non-missing items. If $> 50\%$ of items are missing or if a single-item measure is missing, the subscale is missing.

All EORTC scales and single-item measures will be linearly transformed so that each score has a range of $0 - 100$. A high score for a functional scale represents a high or healthy level of functioning, and a high score for the global health status and HRQoL represents a high HRQoL; however, a high score for a symptom scale or item represents a high level of symptomatology or problems.

The SILC questionnaire comprises three individual symptoms (dyspnea, cough, chest pain) and will be scored at the individual symptom level, thus will have a dyspnea score, chest pain score, and cough score. Each individual symptom score will be calculated as the average of responses for the symptom items (e.g., Chest Pain Score = mean [item 1; item 2]). An increase in score is suggestive of a worsening in symptomology (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.

Time to Deterioration in Patient-Reported Outcomes

TTD with use of the EORTC is defined as the time from baseline to the first confirmed clinically meaningful deterioration in the EORTC symptom score.

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. In this instance, symptom deterioration will be determined as confirmed clinically meaningful deterioration in any of the listed symptom scores, whichever occurs first (cough, chest pain, and dyspnea multi-item scale). Confirmed clinically meaningful deterioration in lung cancer symptoms is defined as a $\geq$10-point increase above baseline in a symptom score that must be held for at least two consecutive assessments or an initial $\geq$10-point increase above baseline followed by death within 3 weeks from the last assessment. A $\geq$10-point change in the EORTC scale score is perceived by patients as clinically significant (Osoba et al. 1998).

TTD analyses will be performed for the ITT–WT population and will include all data collected through disease progression and survival follow up. TTD analyses may be performed for the ITT population when a PFS or an OS benefit has been demonstrated for the ITT population. The methodologies that are outlined for the analysis of OS will be used for the analyses of TTD for prespecified symptoms of the EORTC QLQ-C30 and EORTC QLQ-LC13 measures. TTD of prespecified symptoms will be summarized using the KM method. Comparison of TTD using the EORTC QLQ-C30 and EORTC QLQ-LC13 measures between treatment arms will be performed using the stratified log-rank test; the stratified HRs and 95% CIs will also be reported. If no baseline or post-baseline assessment is performed, patients will be censored at the randomization date plus 1 day. Patients without deterioration at the time of analysis will be censored at the last time they were known to have not deteriorated. There will be no imputation for missing baseline or post-baseline data for the TTD analysis.

Change from Baseline per SILC Scale

Summary statistics (mean, SD, median, 25th and 75th percentiles, and range) of the change from baseline per SILC scale may be provided. The analysis may be performed for patients in the ITT–WT population with a non-missing baseline and a non-missing post-baseline PRO assessment. Graphs of the mean changes and standard errors over time from the baseline assessment for the total score and subscales may be provided for each treatment arm.

The analysis of SILC change from baseline may be performed at all on-treatment timepoints, as well as at the time of disease progression per RECIST v1.1 (PRO assessment completed within $\pm$7 days of date of radiographic disease progression), at the last dose of treatment received before treatment discontinuation for any cause, and at the survival follow-up visits through 6 months.

4.4.3 Exploratory Efficacy Endpoints

4.4.3.1 PFS, OS, ORR, and DOR in Teff-High and Teff-High WT Populations

The Teff-high (−1.91) population is defined as the ITT patients with a Teff signature score ≥ −1.91 in baseline tumor tissues. The Teff-high (−0.91) population is defined as ITT patients with a Teff signature score ≥−0.91 in baseline tumor tissues. The Teff-high (−2.38) population is defined as ITT patients with a Teff signature score ≥−2.38 in baseline tumor tissues. The Teff-high (−2.93) population is defined as ITT patients with a Teff signature score ≥−2.93 in baseline tumor tissues. The Teff signature score is derived from the average expression of PD-L1 (CD274), CXCL9, and interferon-gamma (IFN-γ) genes relative to a reference gene using RNA isolated from the patient's formalin−fixed paraffin-embedded tumor tissue, as measured using a quantitative real-time polymerase chain reaction on a Roche Molecular System Cobas 4800 platform.

The Teff-high WT population is defined as either of the above-described Teff populations excluding patients with an activating *EGFR* mutation or *ALK* translocation.

Analyses of PFS, ORR, and DOR, as assessed by investigator using RECIST v1.1, and OS in the Teff-high and Teff-high WT populations may not be included in the Clinical Study Report (CSR) for this study.

4.4.3.2 Progression-Free Survival Rates at 6 Months and 1 Year

PFS rates at 6 months and 1 year will be estimated and analyzed using the same method as described in Section 4.4.2.5.

4.4.3.3 Overall Survival Rate at 3 Years

OS rate at 3 years will be estimated and analyzed using the same method as described in Section 4.4.2.5.

4.4.3.4 EQ-5D-3L Health Status Data

The EQ-5D-3L questionnaire will also be collected to generate HRQoL and utility scores for use in economic models for reimbursement.

Health status is assessed by the EQ-5D-3L. For the EQ-5D-3L health-state profiles, descriptive statistics that summarize the proportions of patients who reported having "no," "some," or "extreme" problems at each timepoint will be reported. Frequencies and percentages of missing data will also be reported at each timepoint. Patients without post-baseline assessments will be excluded from this analysis. A single summary index from the EQ-5D-3L health status will be used in this study for economic modeling. This analysis will not be included in the CSR for this study.

4.4.3.5 Additional Patient-Reported Outcome Analyses

EORTC score changes from baseline will be descriptively analyzed using means, SDs, medians, and range by treatment arm for patients with a baseline assessment and at

least one post-baseline assessment. The analyses will be performed at timepoints similar to those used for the analyses of change from baseline per SILC scale.

TTD may also be documented for each of the following individual lung cancer symptoms (i.e., cough, dyspnea, chest pain) with use of the EORTC.

To help interpret the results from the change from baseline analyses, the number and proportion of patients with a clinically meaningful change may be summarized by treatment arm, for the EORTC QLQ-C30 global health status and physical function scale scores and for the SILC cough, chest pain, and dyspnea scale scores at each cycle post-baseline.

Compliance rates will be summarized by listing the number and proportion of patients in the PRO-evaluable subset who completed the PRO assessments at each timepoint by treatment arm. Reasons for non-completion will be summarized if available in the CRF.

These additional PRO analyses may not be included in the CSR for this study.

4.4.4 Sensitivity Analyses

4.4.4.1 Missing Tumor Assessment

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

- Patients who missed two or more scheduled assessments immediately prior to the date of disease progression per RECIST v1.1 or death will be censored at the last tumor assessment prior to the missed visits.
- Patients who missed two or more scheduled assessments immediately prior to the date of disease progression per RECIST v1.1 or death will be counted as having progressed on the date of the first of these missing assessments.

Statistical methodologies analogous to those used in the primary analysis of PFS as specified in Section 4.4.4.1 will be used for this sensitivity analysis.

4.4.4.2 Non-Proportional Hazard Non–Protocol-Specified Anti-Cancer Therapy

The impact of non–protocol-specified anti-cancer therapy (NPT) on PFS as determined by the investigator will be assessed, depending on the number of patients who received NPT before a PFS event. If $>5\%$ of patients received NPT before a PFS event in the control arm, a sensitivity analysis may be performed for the comparisons between two treatment arms in which data from patients who receive NPT before a PFS event will be censored at the last tumor assessment date before receipt of NPT.

The impact of subsequent NPT on OS will be assessed depending on the number of patients who received NPT. If > 10% of patients received a NPT in the control arm, the following analyses may be performed to compare treatment arms:

- The discount method uses a 'discounted' survival time after switching for patients who switch treatments based on a user-specified assumption for the effect on OS. OS may be discounted according to a range of possible effects on OS of the subsequent NPT after treatment switching occurred (e.g., 10%, 20%, 30%, etc.).
- Rank preserving structural failure time provides an estimate of the OS time for the control group had NPT not occurred (Robins and Tsiatis 1991). It estimates OS measured from the time of NPT by applying an estimate of the benefit of the NPT. The total OS time (sum of time to NPT and the estimated survival time after NPT started) may then be analyzed using the same methodology as for the primary analysis of OS.
- The inverse probability of censoring weighting method censors patients at start of NPT and uses the control arm patients to create weights that represent how NPT treated patient is like a non–NPT-treated patient (Robins and Finkelstein 2000). These time-varying weights are included into the OS analysis to correct the effect of NPT by giving increased weight to non-censored patients with similar characteristics to censored patients.

Delayed Clinical Effect

If a delayed separation of the KM curves is observed at the beginning of the curves and the delay is ≥ 3 months, the following analyses may be conducted to assess a potential delayed clinical effect for the treatment group.

- **Weighted Log-Rank Analysis**

  Where the delayed clinical effect is > 10% of the median survival time of the control group, an analysis of OS may be performed using the weighted log-rank test based on the Rho-Gamma weight function family (Fleming and Harrington 1991) or piece-wise linear weight functions (Lin and Leon 2017) that weight more on late events to account for the delayed clinical effect (Fine et al. 2007). In addition, in order to enhance clinical interpretation of the treatment effect that varies over time, hazard ratio estimates may also be provided based on the corresponding Cox models (Lin and Leon 2017), for example, the models that assume a minimal treatment effect during the first few months (e.g., 3 months, 6 months) then a full treatment effect afterwards.

4.4.4.3 Loss to Follow-up

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

4.4.4.4 Progression-Free Survival by Independent Review Facility

PFS as assessed by the IRF is defined as the time from randomization to the first documented disease progression as determined by the IRF using RECIST v1.1 or death from any cause, whichever occurs first.

PFS as assessed by the IRF may be examined as a sensitivity analysis using the same methods that will be used for PFS as assessed by the investigator.

4.4.5 Subgroup Analyses

The consistency of PFS and OS results in subgroups will be examined in the populations where PFS and/or OS benefit has been demonstrated. The subgroups are defined by the following:

- Demographics (age, sex, race/ethnicity)
- Baseline disease characteristics (e.g., ECOG performance status; presence of liver metastases at baseline; smoking status; metastatic sites such as brain, bone, etc.; *EGFR* mutation status; *KRAS* mutation status)
- PD-L1 IHC status (e.g., TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3, and their corresponding complementary groups as determined by the SP142 assay; subgroups with PD-L1 expression on at least 1%, 25%, or 50% of TC [and their corresponding complementary subgroups] as determined by the SP263 assay may also be performed pending data availability)
- Intended cycles during induction phase (4 cycles vs. 6 cycles)

Summaries of PFS and OS, including the unstratified HR estimated from a Cox proportional hazards model and KM estimates of median PFS and OS, will be produced separately for each level of the subgroup for the comparisons between treatment arms and displayed in a forest plot (Lewis and Clarke 2001). KM plots of PFS and/or OS will also be produced for selected subgroups.

Summaries of ORR by subgroup will also be provided.

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Atezolizumab PK samples will be collected in this study as outlined in Appendix 3. Atezolizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Plasma concentrations of carboplatin and nab-paclitaxel will be collected in this study as outlined in Appendix 3. The concentrations of carboplatin and nab-paclitaxel will be summarized using descriptive statistics as described above.

Additional PK analyses will be conducted, as appropriate, based on the availability of data. These additional analyses may not be included in the CSR for this study.

4.6 EXPLORATORY BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with response to study drug, including efficacy (PFS, OS, and/or ORR). The biomarkers include but are not limited to tumor mutational burden (in blood and/or tumor tissue). Additional predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and/or blood may be examined for their association with disease status and/or clinical outcomes. These exploratory analyses will not be included in the CSR for this study.

4.7 SAFETY ANALYSES

The safety population includes treated patients, defined as randomized patients who received any protocol treatment. For the safety analyses, patients will be grouped according to whether any full or partial dose of atezolizumab was received, including when atezolizumab was received in error. Specifically, for patients randomized to Arm B, if atezolizumab was received in error, the patients will be grouped to Arm A for the safety analyses.

Patients who were consented prior to approval of Protocol GO29537, Version 5 and are randomized to carboplatin + nab-paclitaxel will be given the option to cross over to receive atezolizumab as monotherapy upon progressive disease per RECIST v1.1, provided they continue to meet eligibility criteria. Safety data observed after those patients who crossed over from Arm B to receive atezolizumab (as allowed under previous protocol versions) may be summarized separately.

4.7.1 Exposure of Study Medication

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

4.7.2 Adverse Events

Verbatim description of adverse events will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms. Adverse events will be graded by the investigator in accordance with the NCI CTCAE v4.0. Treatment-emergent adverse events will be summarized by mapped term, appropriate thesaurus level, NCI CTCAE grade, and treatment arm. Multiple occurrences of the same event will be counted once at the maximum grade. Adverse events, serious adverse events, treatment-related serious adverse events, severe adverse events (Grade ≥ 3), adverse events of special interest, immune-mediated adverse events, and adverse events that lead to study drug discontinuation or interruption will be summarized.

“Treatment emergent” is defined for all events with onset on or after the first study drug treatment up to the data cutoff date.

Listings of adverse events will include all adverse events with onset on or after the first study drug treatment up to the data cutoff date.

Deaths during the study treatment period and those reported during the follow-up period after treatment completion or discontinuation and causes of death will be summarized by treatment arm.

4.7.3 Laboratory Data

Change from baseline and values outside the normal ranges may also be summarized. Additionally, selected laboratory data will be classified according to NCI CTCAE and will be summarized by grade. Shift tables from baseline to the highest NCI CTCAE grade during the study post-baseline will be presented.

4.7.4 Vital Signs

Changes in selected vital signs will be summarized by treatment arm.

4.7.5 Anti-Drug Antibody

Incidence of ADAs against atezolizumab will be summarized. The analyses of PK, key efficacy, and safety by ADA status will be conducted to explore the potential impact of immunogenicity as appropriate.

4.8 MISSING DATA

Please refer to Sections 4.4.1 and 4.4.2 for methods of handling missing data for the primary and secondary efficacy endpoints.

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Appendix 1 Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY EVALUATING THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (MPDL3280A, ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH CARBOPLATIN + NAB-PACLITAXEL FOR CHEMOTHERAPY-NAIVE PATIENTS WITH STAGE IV NON-SQUAMOUS NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO29537
VERSION NUMBER:	6
EUDRACT NUMBER:	2014-003206-32
IND NUMBER:	117296
TEST PRODUCT:	Atezolizumab (MPDL3280A, RO5541267)
PHASE:	III
INDICATION:	Non-squamous non–small cell lung cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

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

The term "tumor gene expression" (tGE) refers to randomized patients with a defined level of expression of a programmed death–ligand 1 (PD-L1) and T-effector gene signature in tumor tissue, as analyzed through use of a centrally performed RNA-based assay.

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

Efficacy Objectives

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

- To evaluate the efficacy of atezolizumab + carboplatin + nab-paclitaxel compared with carboplatin + nab-paclitaxel as measured by investigator-assessed progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) *in the tGE-WT population and the intent-to-treat wild-type (ITT-WT) population*
- To evaluate the efficacy of atezolizumab + carboplatin + nab-paclitaxel compared with carboplatin + nab-paclitaxel as measured by overall survival (OS) *in the ITT-WT population*

The secondary efficacy objectives for this study are the following:

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

- *To evaluate the efficacy of atezolizumab as measured by investigator-assessed PFS according to RECIST v1.1 and OS in the tGE population and the ITT population*
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed objective response rate according to RECIST v1.1 for both the *tGE-WT population and the ITT-WT population*
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed duration of response according to RECIST v1.1 for both the *tGE-WT population and the ITT-WT population*
- To evaluate the OS rate at 1 and 2 years in each treatment arm *in the tGE-WT population and the ITT-WT population*
- To determine the impact of atezolizumab as measured by time to deterioration (TTD) in patient-reported lung cancer symptoms of cough, dyspnea (single-item and multi-item subscales), chest pain, or arm/shoulder pain, using the European Organisation for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire–Core 30 (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13) in *the tGE-WT population and the ITT-WT population*
- To determine the impact of atezolizumab as measured by change from baseline (i.e., improvement or deterioration based upon presenting symptomatology) *in* patient-reported lung cancer symptom (chest pain, dyspnea, and cough) score using the Symptoms in Lung Cancer (SILC) scale symptom severity score *in the tGE-WT population and the ITT-WT population*

Safety Objectives

The safety objectives for this study are the following:

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

Pharmacokinetic Objectives

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

- To characterize the pharmacokinetics of atezolizumab when given in combination with carboplatin and nab-paclitaxel
- To characterize the pharmacokinetics of carboplatin when given in combination with nab-paclitaxel with and without atezolizumab
- To characterize the pharmacokinetics of nab-paclitaxel when given in combination with carboplatin with and without atezolizumab

Exploratory Objectives

The exploratory objectives for this study are the following:

- To evaluate PFS at 6 months and at 1 year in each treatment arm
- To evaluate the OS rate at 3 years in each treatment arm
- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status, mechanisms of resistance, and/or response to study treatment
- To evaluate the utility of biopsy at the time of apparent disease progression to distinguish apparent increases in tumor volume related to the immunomodulatory activity of atezolizumab (i.e., pseudoprogression/tumor immune infiltration) from true disease progression
- To evaluate and compare patient's health status as assessed by the EuroQoL 5 Dimensions 3-Level (EQ-5D-3L) questionnaire to generate utility scores for use in economic models for reimbursement

- To determine the impact of atezolizumab as measured by change from baseline in patient-reported outcomes of health-related quality of life, lung cancer-related symptoms, and functioning as assessed by the EORTC QLQ-C30 and QLQ-LC13

Study Design

Description of Study

This is a randomized, Phase III, multicenter, open-label study (IMpower130) designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin + nab-paclitaxel compared with treatment with carboplatin + nab-paclitaxel in approximately 715 chemotherapy–naive patients with Stage IV non-squamous non–small cell lung cancer (NSCLC).

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

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

Treatment Arm B: Carboplatin + nab-paclitaxel (Induction: four or six 21-day cycles); best supportive care or pemetrexed (Maintenance: 21-day cycles)

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

Following the induction phase, patients who are randomized to atezolizumab *(Arm A) may continue treatment with atezolizumab beyond radiographic disease progression according to RECIST v1.1*, provided they are experiencing clinical benefit as assessed by the investigator (i.e., in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results [if available], and clinical status). Patients randomized to carboplatin + nab-paclitaxel (Arm B) will be offered best supportive care provided they have non-progressive disease. Switch maintenance to pemetrexed is also permitted for patients randomized to Arm B. Switch maintenance must be administered within 6 weeks of Day 1 of the last induction cycle.

Patients who *entered Study GO29537 under Protocol Versions 1 – 4* and are randomized to carboplatin + nab paclitaxel will be given the option to cross over to receive atezolizumab as monotherapy upon progressive disease per RECIST v1.1, provided they continue to meet eligibility criteria. Safety data for patients who crossed over from Arm B to receive atezolizumab as allowed under *Protocol Versions 1 – 4* will be summarized for exploratory purposes.

For Atezolizumab-Treated Patients Only

During treatment (induction or maintenance), patients receiving atezolizumab (including patients in Arm B who *entered Study GO29537 under Protocol Versions 1 – 4 and* crossed over to receive atezolizumab *after disease progression according to RECIST v1.1*) who show evidence of clinical benefit will be permitted to continue atezolizumab after the criteria per RECIST v1.1 for progressive disease are met if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values, e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

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

Treatment with *induction* chemotherapy (Arms A and B) and pemetrexed (Arm B) as switch maintenance *must* be discontinued in all patients who exhibit evidence of progressive disease *according to RECIST v1.1*.

Patients will undergo tumor assessments at baseline and every 6 weeks for the first 48 weeks following Cycle 1, Day 1, regardless of dose delays. After 48 weeks, tumor assessment will be required every 9 weeks. Patients will undergo tumor assessments until radiographic disease progression 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), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. Patients who discontinue treatment for reasons other than radiographic disease progression *according to RECIST v1.1* (e.g., toxicity*, symptomatic deterioration*) will continue scheduled tumor assessments until radiographic disease progression 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), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.

All primary imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints. *The independent reviews of the stored scans will be performed when requested.*

Patients in all treatment arms will undergo a mandatory tumor biopsy sample collection, unless not clinically feasible as assessed and documented by investigators, at the first evidence of radiographic disease progression. These data will be used to explore whether radiographic findings are consistent with the presence of tumor. Additionally, these data will be analyzed to evaluate the association between changes in tumor tissue and clinical outcome and to understand further the potential mechanisms of progression and resistance to atezolizumab as compared with such mechanisms after treatment with chemotherapy alone. This exploratory biomarker evaluation will not be used for any treatment-related decisions. Patients in Arm A and patients in Arm B (*who entered Study GO29537 under Protocol Versions 1 –4*) who are unable to undergo biopsy sample collection but who otherwise meet the criteria listed above may continue*/crossover* to receive atezolizumab.

Number of Patients

Approximately 105 sites globally will participate in the study, and approximately 715 patients will be randomized.

Target Population

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

Inclusion Criteria

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

- Signed Informed Consent Form
- Male or female, 18 years of age or older
- ECOG performance status of 0 or 1
- Histologically or cytologically confirmed, Stage IV non-squamous NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 7th edition)

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

- No prior treatment for Stage IV non-squamous NSCLC

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

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

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

  Patients who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomization since the last chemotherapy, radiotherapy, or chemoradiotherapy cycle.
- Patients with a history of treated asymptomatic central nervous system (CNS) metastases are eligible, provided they meet all of the following criteria:

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

  No ongoing requirement for corticosteroids as therapy for CNS disease

  No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomization

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

  Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to randomization, if all other criteria are met.
- Known PD-L1 tumor status as determined by an IHC assay performed by a central laboratory on previously obtained archival tumor tissue or tissue obtained from a biopsy at screening

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

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

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

  For core-needle biopsy specimens, preferably at least three cores embedded in a single paraffin block, should be submitted for evaluation.
- Measurable disease, as defined by RECIST v1.1

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

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

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

  Lymphocyte count $\geq$ 500/μL

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

  Hemoglobin $\geq$ 9.0 g/dL

  Patients may be transfused to meet this criterion.

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

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

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

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

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

  Serum bilirubin $\leq 1.25 \times$ ULN

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

  Serum creatinine $\leq 1.5 \times$ ULN
- For female patients of childbearing potential agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate [$<$ 1% per year] when used consistently and correctly, and to continue its use for 5 months after the last dose of atezolizumab or for 30 days after the last dose of nab-paclitaxel, whichever is later. For male patients with female partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate [$<$ 1% per year] when used consistently and correctly, and to continue its use for 6 months after the last dose of nab-paclitaxel and/or carboplatin, whichever is later. 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, intrauterine hormone-releasing system, bilateral tubal occlusion or vasectomized partner (on the understanding that this is the only one partner during the whole study duration), and sexual abstinence. Male patients should not donate sperm during this study and for at least 6 months after the last dose of nab-paclitaxel and/or carboplatin, whichever is later.
- Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drug. The same rules are valid for male patients involved in this clinical study if they have a partner of childbirth potential. Male patients must always use a condom.
- Women who are not postmenopausal ($\geq$ 12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.

Exclusion Criteria

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

Cancer-Specific Exclusions

- Active or untreated CNS metastases as determined by computed tomography 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 locoregional therapy, if appropriate, prior to randomization.

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

  Patients with indwelling catheters (e.g., PleurX®) are allowed.

- Uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > ULN)

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

- Malignancies other than NSCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
- Known tumor PD-L1 expression status as determined by an IHC assay from other clinical studies (e.g., patients whose PD-L1 expression status was determined during screening for entry into a study with anti–PD-1 or anti–PD-L1 antibodies but were not eligible are excluded)

General Medical Exclusions

- Women who are pregnant, lactating, or intending to become pregnant during the study
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

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

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

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

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

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

No acute exacerbations of underlying condition within the previous 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high-potency or oral steroids)

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

- Positive test for HIV

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

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

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible only if they are negative for HBV DNA.

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

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

- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within the 3 months prior to randomization, unstable arrhythmias, or unstable angina

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction $<$ 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

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

Exclusion Criteria Related to Medications

- Any approved anti-cancer therapy, including hormonal therapy within 21 days prior to initiation of study treatment; the following exceptions are allowed:

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

Patients who have had prior anti–cytotoxic T-lymphocyte-associated protein 4 (anti–CTLA-4) treatment may be enrolled, provided the following requirements are met:

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

No history of severe immune-mediated adverse effects from anti–CTLA-4 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grades 3 and 4)

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

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

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

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

Exclusions Related to Chemotherapy

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

Length of Study

The final PFS analysis will be conducted when *all of the following criteria have been met: approximately 225 PFS events have occurred in the tGE-WT population, approximately 475 PFS events have occurred in the ITT-WT population, and the last patient has been enrolled in the study.* This is expected to occur approximately *32* months after the first patient is enrolled.

The final OS analysis will be conducted when approximately *457* OS events *have occurred* in the *ITT-WT* population. *This is expected to occur approximately 42 months after the first patient is enrolled.*

End of Study

The end of study is defined as when the required number of deaths for the final analysis of OS has been observed. Additionally, the Sponsor may decide to terminate the study at any time. *If the Sponsor decides to terminate the study, patients who are still receiving study treatment or undergoing survival follow-up may be enrolled into an extension study or a non-interventional study.*

Outcome Measures

Efficacy Outcome Measures

The co-primary 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 according to RECIST v1.1 or death from any cause, whichever occurs first *in the tGE-WT population and the ITT-WT population*
- OS, defined as the time from randomization to death from any cause*, in the ITT-WT population*

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

- *OS in the tGE-WT population*
- *PFS, as determined by the investigator according to RECIST v1.1, and OS in the TC2/3 or IC2/3 WT population and the TC1/2/3 or IC1/2/3 WT population*
- *PFS, as determined by the investigator according to RECIST v1.1, and OS in the tGE population and the ITT population*
- Objective response, defined as a partial response or a complete response as determined by the investigator according to RECIST v1.1 *for the tGE-WT population and the ITT-WT population*
- DOR, defined as the time interval from first occurrence of a documented objective response to the time of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first *for the tGE-WT population and the ITT-WT population*
- OS rates at 1 and 2 years *for the tGE-WT population and the ITT-WT population*
- TTD in patient-reported lung cancer symptoms, defined as time from randomization to deterioration (10-point change) on each of the EORTC QLQ-C30 and EORTC QLQ-LC13 symptom subscales (cough, dyspnea [single item], dyspnea [multi-item subscale], chest pain, and arm/shoulder pain) *in the tGE-WT population and the ITT-WT population*
- Change from baseline in patient-reported lung cancer symptoms (chest pain, dyspnea, and cough) on the symptom severity score of the SILC scale *in the tGE-WT population and the ITT-WT population*

Safety Outcome Measures

The safety outcome measures for this study are the following:

- Incidence, nature, and severity of adverse events graded according to the NCI CTCAE v4.0
- Changes in vital signs, physical findings, and clinical laboratory results during and following atezolizumab administration
- Incidence of ATA response to atezolizumab and potential correlation with PK, pharmacodynamic, safety, and efficacy parameters

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are the following:

- For patients randomized to atezolizumab + carboplatin + nab-paclitaxel:

  Maximum observed serum atezolizumab concentration (C_{max}) after infusion on Cycle 1, Day 1

  Minimum observed serum atezolizumab concentration (C_{min}) prior to infusion at selected cycles, at treatment discontinuation, and at 120 days (±30 days) after the last dose of atezolizumab

  Plasma concentrations for carboplatin (Arms A and B)

  Plasma concentrations for nab-paclitaxel reported as total paclitaxel (Arms A and B)

- For patients randomized to carboplatin + nab-paclitaxel who crossed over to receive open-label atezolizumab as monotherapy (allowed under *Study GO29537 Protocol, Versions 1–4*):

  C_{max} of serum atezolizumab after infusion on Day 1 of the first cycle following crossover to atezolizumab as monotherapy

  C_{min} of serum atezolizumab prior to infusion on Day 1 at selected cycles following crossover to atezolizumab as monotherapy, at treatment discontinuation, and at 120 (±30 days) after the last dose of atezolizumab

Exploratory Outcome Measures

The exploratory outcome measures for this study are the following:

- PFS at 6 months and at 1 year
- OS rate at 3 years
- Status of PD-L1–, immune-, and NSCLC-related and other exploratory biomarkers in archival and/or freshly obtained tumor tissues and blood (or blood derivatives) collected before, during, or after treatment with atezolizumab or at progression and association with disease status and/or response to atezolizumab in combination with chemotherapy
- Status of ICs and other exploratory biomarkers in mandatory biopsy specimens and blood collected at progression
- Utility scores of the EQ-5D-3L
- Change from baseline in patient-reported outcomes of health-related quality-of-life, lung cancer-related symptoms, and functioning as assessed by the EORTC QLQ-C30 and QLQ-LC13

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal products (IMPs) for this study are atezolizumab and erlotinib.

Atezolizumab (1200 mg IV) will be administered on Day 1 of each 21–day cycle. Atezolizumab will be administered to patients who are randomized to Arm A and to patients in Arm B who cross over at progression.

Switch maintenance treatment with erlotinib is no longer permitted. However, patients who had already started switch maintenance treatment with erlotinib under *Protocol Versions 1–4* may be allowed to continue treatment with erlotinib upon discussion of the risks, potential benefits and alternative treatment options with the investigator. For those patients who receive switch maintenance, institutions should follow the dosage and administration instructions in the prescribing information.

Comparator

Nab-paclitaxel (100 mg/m^2 IV) will be administered on Days 1, 8, and 15 of each 21-day cycle for four or six cycles during the induction phase. Nab-paclitaxel will be considered an IMP for study purposes in countries where nab-paclitaxel is considered an IMP by local regulations.

Non-Investigational Medicinal Products

Comparator

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

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

Statistical Methods

Primary Analysis

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

is described below (see "Determination of Sample Size"). At least one interim OS analysis will be performed.

PFS is defined as the time between the date of randomization and the date of first documented disease progression or death, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

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

The following analyses will be performed for both PFS and OS. PFS and OS will be compared between treatment arms with the use of the stratified log-rank test. The hazard ratio (HR) for PFS and OS for treatment comparisons will be estimated using a stratified Cox regression model, respectively. The 95% CI for the HR will be provided.

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

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

Analyses will be conducted according to an analysis hierarchy and an α-spending algorithm to control for the type I error rate and to account for an interim analysis.

To control the overall type I error rate for the one-sided test at 0.025, a one-sided type I error (α) of 0.003 and 0.022 (ratio of 3:22) will be allocated to PFS and OS, respectively.

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

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

Determination of Sample Size

This study will randomize approximately 715 patients. The ITT-WT population will include approximately 650 patients, assuming a prevalence of approximately 10% for sensitizing EGFR mutations or ALK translocations. The tGE-WT population will include approximately 325 patients, assuming a 50% prevalence with the chosen tGE cutoff.

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

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

- *93*% power to detect an HR of 0.55, corresponding to an improvement in median PFS from 6 months to 10.9 months in the *tGE-WT* population with a one-sided α of 0.003
- *95*% power to detect an HR of 0.65, corresponding to an improvement in median PFS from 6 months to 9.2 months in the ITT-*WT* population with a one-sided α of 0.003
- No interim analyses for PFS
- Dropout rate of 5% per 12 months

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

- *80*% power to detect an HR of 0.75, corresponding to an improvement in median OS from 12 months to 16 months in the ITT-*WT* population with a one-sided α of *0.022*
- *One interim OS analysis performed at the time of the final PFS analysis, at which time approximately 77% of the total number of OS events required for the final analysis are expected to have occurred as determined through use of the Lan-DeMets approximation to the O'Brien-Fleming boundary*
- Dropout rate of 5% per 24 months

With these assumptions, approximately 715 patients in total will be enrolled in this study, with approximately 650 patients in the ITT-WT population. The final PFS analysis will be conducted when all of the following criteria have been met: approximately 225 PFS events have occurred in the tGE-WT population, approximately 475 PFS events have occurred in the ITT-WT population, and the last patient has been enrolled in the study. The final PFS analysis is expected to occur approximately 32 months after the first patient is enrolled. These numbers of events would allow for a minimum detectable difference corresponding to an HR of 0.68 in the tGE-WT population and 0.76 in the ITT-WT population, respectively.

With a sample size of 650 patients, approximately 457 OS events are expected to occur in the ITT-WT population. The final OS analysis is expected to occur approximately 42 months after the first patient is enrolled. This number of events would allow for a minimum detectable difference corresponding to an HR of 0.81 in the ITT-WT population.

Interim Analyses

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

If approximately 352 OS events have occurred in the ITT-WT population at the time of the PFS final analysis, an interim OS analysis will be conducted in the ITT-WT population. If there are significantly fewer than the expected 352 OS events at the final PFS analysis, a nominal α of 0.01% (negligible impact on overall type I error rate) will be spent on the OS analysis at the time of the PFS final analysis and a second interim OS analysis will then be conducted after approximately 352 OS events have occurred.

The final OS analysis will be conducted when approximately 457 OS events have occurred in the ITT-WT population. This is expected to occur approximately 42 months after the first patient is enrolled.

Appendix 2 Schedule of Assessments

Procedure	Screening Days –28 to –1	Induction Phase Cycles 1 to 4 or 6 (21-Day Cycle) [a] Day 1 (±3 Days) [b]	Maintenance Phase (21-Day Cycle) [a] Day 1 (±3 Days) [b]	Treatment Discontinuation Visit ≤30 Days after Last Dose of Study Treatment	Survival Follow-Up Every 3 Months after Disease Progression or Loss of Clinical Benefit
Informed consent	x				
Tumor tissue specimen for PD-L1 testing (15 FFPE slides required; blocks preferred) [c] Fresh or archival tissue can be used	x				
ALK and/or EGFR assessment if status is unknown (may be done locally or centrally)	x				
Demographic data	x				
Medical history and baseline conditions	x				
NSCLC cancer history	x				
Vital signs [d]	x	x [d]	x [d]	x	
Weight	x	x	x	x	
Height	x				
Complete physical examination	x				
Limited physical examination [e]		x	x	x	
ECOG performance status	x	x	x	x	
12-Lead ECG	x	x [f]	x [f]	x [f]	
Hematology [g]	x	x	x	x	
Serum chemistry [h]	x	x	x	x	
Coagulation test (aPTT or INR)	x			x	

Appendix 2 Schedule of Assessments (cont.)

Procedure	Screening Days –28 to –1	Induction Phase Cycles 1 to 4 or 6 (21-Day Cycle) a Day 1 (±3 Days) [b]	Maintenance Phase (21-Day Cycle) a Day 1 (± 3 Days) [b]	Treatment Discontinuation Visit ≤ 30 Days after Last Dose of Study Treatment	Survival Follow-Up Every 3 Months after Disease Progression or Loss of Clinical Benefit
Pregnancy test (women of childbearing-potential ONLY)	x [i]	x [j]	x [j]	x [j]	
TSH, free T3, free T4 [k]	x	x [k]	x [k]	x	
HIV, HBV, HCV serology [l]	x				
Urinalysis [m]	x	x	x	x	
Determination of duration of induction treatment	x				
Induction treatment administration: Arm A: atezolizumab + carboplatin + nab-paclitaxel Arm B: carboplatin + nab-paclitaxel		x [n]			
Maintenance treatment administration: Arm A: atezolizumab Arm B: Best supportive care (switch maintenance *to pemetrexed* permitted)			x [n]		
Tumor response assessment	x [o]	x [p]	x [p]		x [q]
Serum sample for atezolizumab ATA assessment (atezolizumab-treated patients only) [r]		x	x	x	120 (±30) days after last dose of atezolizumab
Serum sample for PK sampling (atezolizumab-treated patients only) [r]		x	x	x	120 (±30) days after last dose of atezolizumab
Carboplatin and nab-paclitaxel PK sampling (20 patients per arm) [r]		x			

Appendix 2 Schedule of Assessments (cont.)

Procedure	Screening Days –28 to –1	Induction Phase Cycles 1 to 4 or 6 (21-Day Cycle) a Day 1 (± 3 Days) [b]	Maintenance Phase (21-Day Cycle) a Day 1 (± 3 Days) [b]	Treatment Discontinuation Visit ≤ 30 Days after Last Dose of Study Treatment	Survival Follow-Up Every 3 Months after Disease Progression or Loss of Clinical Benefit
Blood samples for PD biomarkers [r]	x	x	x	x	120 (± 30) days after last dose of atezolizumab
Optional blood for DNA extraction (RCR only) [r, s]		x			
Informed consent to continue treatment beyond radiographic progression (Arm A atezolizumab-treated patients)		At time of radiographic progression			
Tumor biopsy		At time of radiographic progression [t]			
Optional tumor biopsy at other timepoints (RCR only)		Any time during study treatment or during survival follow-up			
Adverse events [u]	x	x	x	x	x
Concomitant medications	From 7 days before screening	x	x	x	
Patient-reported outcomes [v]		x [v]	x [v]		x [v]
Survival and anti–cancer therapy follow-up [w]					x

Appendix 2 Schedule of Assessments (cont.)

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

Notes: Patients who are randomized to Arm B who received erlotinib switch maintenance allowed under *Study GO29537 Protocol Versions 1 −4,* or who receive pemetrexed switch maintenance, will continue with cycle visits at the same frequency as those patients randomized to Arm A until disease progression, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

The same treatment-phase schedule of assessments and procedures will apply to the crossover patients, i.e., patients will begin on Cycle 1 (now called Cycle 1A) and will follow the same assessments and procedures as outlined in this protocol for this cycle (with the exception of an alternate schedule for PK and pharmacodynamic assessments (see Appendix 3 of Protocol GO29537) and a biopsy upon progression will not be requested for these patients), as well as for all subsequent cycles (i.e., Cycle 2, which will now be called Cycle 2A, etc.). In addition, patients who *entered Study GO29537 under Protocol Versions 1 −4 and who* cross over to atezolizumab following disease progression will not follow the treatment-phase schedule for ePRO assessments during crossover. These patients will complete ePRO assessments according to the post progression schedule (i.e., SILC monthly for the first 6 months only and EORTC QLQ-C30*, QLQ,* LC13 *and EQ-5D-3L* at 3 and 6 months only).

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

[b] Cycle 1, Day 1, must be performed within 5 days after the patient is randomized. Screening assessments performed ≤ 96 hours before Cycle 1, Day 1 are not required to be repeated for Cycle 1, Day 1. In addition, ECOG performance status, limited physical examination, and local laboratory tests may be performed ≤ 96 hours before Day 1 of each cycle as specified in Section 4.5.12.2 of Protocol GO29537.

[c] If a representative FFPE tumor specimen in paraffin block (preferred) or 15 (or more) freshly cut, unstained 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 a 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 may occur outside the 28-day screening period prior to enrollment. See Section 4.1.1 of Protocol GO29537, Inclusion Criteria, and Section 4.5.7.1 of Protocol GO29537.

[d] Vital signs include *pulse* rate, respiratory rate, blood pressures, and temperature. Vital signs should be recorded as described in Section 4.5.4 of Protocol GO29537.

[e] Symptom-directed physical examinations; see Section 4.5.3 of Protocol GO29537 for details.

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

[g] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. Hematology tests must be performed prior to Day 1 infusions and for nab-paclitaxel administration, also prior to Day 8 and Day 15 infusions. See Section 5.1.9.1 (Table 11) of Protocol GO29537 for dose modifications due to hematologic toxicities.

Appendix 2 Schedule of Assessments (cont.)

[h] Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total CO_2, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin. See Section 5.1.9.1 of Protocol GO29537 for carboplatin and nab-paclitaxel dose modification management due to serum chemistry toxicities.

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

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

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

[l] All patients will be tested for HIV prior to the inclusion into the study, and HIV-positive patients will be excluded from the clinical study. *Patients with active hepatitis B (chronic or acute; defined as having a positive HBsAg test result at screening) will be excluded from the study. Patients with past or resolved HBV infection (defined as the presence of HBcAb and absence of HBsAg) are eligible only if their HBV DNA test is negative. Patients with HCV will be excluded from the study; patients who test positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.*

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

[n] For atezolizumab, the initial dose will be delivered over 60 (± 15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. For carboplatin + nab-paclitaxel, administer nab-paclitaxel over 30 minutes followed immediately by carboplatin administered over 15 – 30 minutes. Administer nab-paclitaxel alone on Days 8 and 15. *See Section 4.3.2.2* of Protocol GO29537 *for details.* Atezolizumab will be delivered as monotherapy during the maintenance phase (Arm A only) and for patients who cross over from Arm B *(*allowed under *Study GO29537 Protocol, Versions 1 – 4).* See Section 4.3.2.2 of Protocol GO29537 for details

[o] CT scans (with oral/IV contrast unless contraindicated) or MRI of the chest and abdomen. A CT or MRI scan of the pelvis is required at screening and as clinically indicated or as per local standard of care at subsequent response evaluations. A CT (with contrast) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients. See Section 4.5.5 of Protocol GO29537 for details.

[p] Perform every 6 weeks (±7 days) (approximately every two cycles) for 48 weeks following Cycle 1, Day 1, and then every 9 weeks (±7 days) after the completion of the Week 48 tumor assessment, regardless of treatment delays, until radiographic disease progression (loss of clinical benefit for patients assigned to atezolizumab who continue treatment after disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. See Section 4.5.5 of Protocol GO29537 for details.

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

[r] See Appendix 2 of Protocol GO29537 for detailed schedule.

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

Appendix 2 Schedule of Assessments (cont.)

[t] A mandatory biopsy is required, 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 of Protocol GO29537).

[u] All serious adverse events and adverse events of special interest, regardless of relationship to study treatment, will be reported until 90 days after the last dose of study treatment (inclusive of erlotinib [allowed under *Study GO29537 Protocol Versions 1–4*] or pemetrexed switch maintenance for patients randomized to Arm B who receive switch maintenance) or initiation of new systemic anti-cancer therapy. All other adverse events, regardless of relationship to study treatment, will be reported until 30 days after the last dose of study treatment (inclusive of erlotinib [allowed under *Study GO29537 Protocol Versions 1 –4]* or pemetrexed switch maintenance for patients randomized to Arm B who receive switch maintenance) or initiation of new non-protocol systemic anti-cancer therapy after last dose of study treatment. After this period, *all deaths will be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment (see Section 5.6 of Protocol GO29537*).

[v] EORTC QLQ-C30, EORTC QLQ-LC13, PGIS, and EQ-5D-3L questionnaires will be completed by the patients on the ePRO tablet at each scheduled -cycle visit during the induction period and then according to the tumor assessment schedule during the treatment maintenance phase prior to administration of study drug and prior to any other study assessment(s). SILC will be completed on an ePRO device at the patient's home on a weekly basis. During survival follow-up, the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-3L will be completed at 3 and 6 months following disease progression or loss of clinical benefit (for atezolizumab-treated patients). The SILC will be completed monthly during survival follow-up for 6 months following disease progression or following loss of clinical benefit for patients treated with atezolizumab who continue after disease progression according to RECIST v1.1. The PGIS is not required during survival follow-up. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will complete the EORTC QLQ-C30, EORTC QLQ-LC13, PGIS, and EQ-5D-3L at each tumor assessment visit and will complete the SILC at home on a weekly basis, until radiographic disease progression according to RECIST v1.1 or loss of clinical benefit (for atezolizumab-treated patients who had continued treatment *with atezolizumab* after radiographic disease progression) as determined by the investigator (unless the patient withdraws consent or the Sponsor terminates the study). Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. Patients whose native language is not available on the ePRO device or who are deemed by the investigator incapable of inputting their ePRO assessment after undergoing appropriate training are exempted from completing all ePRO assessments.

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

Appendix 3 Schedule of Pharmacokinetic, Biomarker, and Anti-Drug Antibody Assessments

Study Visit	Time	Arm A	Arm B
Screening	N/A	Biomarkers [b]	Biomarkers [b]
Cycle 1, Day 1 [e]	Pre-dose (same day as treatment administration)	Atezolizumab ATA Atezolizumab pharmacokinetics Carboplatin pharmacokinetics [a] Nab-Paclitaxel pharmacokinetics [a] Biomarkers [d]	Carboplatin pharmacokinetics [a] Nab-Paclitaxel pharmacokinetics [a] Biomarkers [d]
	30 min (±10 min) after end of atezolizumab infusion	Atezolizumab pharmacokinetics	
	5 – 10 min before the end of nab-paclitaxel infusion [a]	Nab-Paclitaxel pharmacokinetics [a]	Nab-Paclitaxel pharmacokinetics [a]
	1 hr after end of nab-paclitaxel infusion [a]	Nab-Paclitaxel pharmacokinetics [a]	Nab-Paclitaxel pharmacokinetics [a]
	5 – 10 min before the end of carboplatin infusion [a]	Carboplatin pharmacokinetics [a]	Carboplatin pharmacokinetics [a]
	1 hr after end of carboplatin infusion [a]	Carboplatin pharmacokinetics [a]	Carboplatin pharmacokinetics [a]
Cycle 2, Day 1 (±3 days)	Pre-dose (same day as treatment administration)	Atezolizumab ATA Atezolizumab pharmacokinetics Biomarkers [d]	Biomarkers [d]

Appendix 3 Schedule of Pharmacokinetic, Biomarker, and Anti-Drug Antibody Assessments (cont.)

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

Appendix 3 Schedule of Pharmacokinetic, Biomarker, and Anti-Drug Antibody Assessments (cont.)

Study Visit	Time	Arm A	Arm B
Treatment discontinuation visit	At visit	Atezolizumab ATA Atezolizumab pharmacokinetics Biomarkers [d]	Biomarkers [d]
120 ± 30 days after last dose of atezolizumab	At visit	Atezolizumab ATA Atezolizumab pharmacokinetics Biomarkers [d]	
At any timepoint during study (RCR consent required)		Optional RCR blood (DNA extraction) [c]	Optional RCR blood (DNA extraction) [c]

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

Note: Serum pharmacokinetic samples for atezolizumab; plasma pharmacokinetic samples for carboplatin, and nab-paclitaxel.

[a] At selected centers, 20 patients in each treatment arm will undergo the additional PK assessments for carboplatin and nab-paclitaxel.

[b] Whole blood for biomarkers.

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

[d] Plasma and serum for biomarkers.

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