Official Title: **A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (MPDL3280A, ANTI−PD-L1 ANTIBODY) IN COMBINATION WITH CARBOPLATIN OR CISPLATIN+PEMETREXED COMPARED WITH CARBOPLATIN OR CISPLATIN+PEMETREXED IN PATIENTS WHO ARE CHEMOTHERAPY-NAIVE AND HAVE STAGE IV NON-SQUAMOUS NON−SMALL CELL LUNG CANCER**

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PROTOCOL

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (MPDL3280A, ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH CARBOPLATIN OR CISPLATIN+PEMETREXED COMPARED WITH CARBOPLATIN OR CISPLATIN+PEMETREXED IN PATIENTS WHO ARE CHEMOTHERAPY-NAIVE AND HAVE STAGE IV NON-SQUAMOUS NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO29438
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TEST PRODUCT:	Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 19 September 2015
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PROTOCOL AMENDMENT APPROVAL

CONFIDENTIAL

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PROTOCOL AMENDMENT, VERSION 5: RATIONALE

Protocol GO29438 has been amended to reflect changes in the statistical methodology. Changes to the protocol, along with a rationale for each change, are summarized below.

The following statistical testing procedures have been revised:

- The timing of the primary analysis of progression-free survival (PFS) and the definition of end of study have been updated. The primary efficacy analysis will be performed when approximately 458 PFS events have occurred in the intent-to-treat (ITT) population, and at least 10 months after the last patient is enrolled during the global enrollment phase, whichever occurs later. The study will end when the required number of deaths for the final analysis of overall survival (OS) has been observed among patients enrolled during the global enrollment phase, [redacted], or the last patient has been enrolled in the study, whichever occurs later (Sections 3.2 and 6.1).
- The testing hierarchy and α-spending algorithm have been adjusted. The statistical testing procedures have been amended to reflect the change in the analysis populations (throughout Section 6).
- To focus the efficacy analyses on more meaningful endpoints, all objectives and outcome measures (secondary and exploratory) based on the review by the Independent Review Facility (IRF) and associated language have been removed (Sections 2.1.2, 2.4, 3.1, 3.3.3, 3.3.4, 3.4.1.2, 3.4.4, 6.4.2.5, and 6.7.2). The rationale for this change is the high concordance between investigator and IRF assessments of response[1]. However, all imaging data will be collected by the IRF to enable assessment upon request. In addition, exploratory efficacy analyses based on response assessments according to modified Response Evaluation Criteria in Solid Tumors (modified RECIST) have been removed from the protocol (Sections 2.4, 3.3.5, 3.4.4, 6.7.1 and 6.7.3), as well as investigator assessment of time to response (TTR) and time in response (TIR) (both secondary endpoints), and disease control rate (an exploratory endpoint) per RECIST, Version 1.1 (RECIST, v1.1) (Sections 2.1.2, 3.4.4, 3.4.1.2, 6.4.2.3, and 6.4.2.4).

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[1] Amit O, Mannino F, Stone AM, et al. Blinded independent central review of progression in cancer clinical trials: results from a meta-analysis. Eur J Cancer 2011;47:1772− 8. Epub: 21 March 2011.

- A secondary efficacy objective and outcome measure for patient-reported lung cancer symptoms using Symptoms in Lung Cancer (SILC) scale symptom severity scores has been updated so that it will be measured from baseline instead of time to deterioration (TTD) to align with other first-line atezolizumab protocols (Sections 2.1.2 and 3.4.1.2). Sections 3.3.6 and 6.4.2.4 have been updated accordingly.
- An exploratory objective and outcome measure for OS and investigator-assessed PFS according to RECIST v1.1 in subgroups based on demographic and baseline characteristics have been added to account for the analyses described in Section 6.7.1 (see also Sections 2.4 and 3.4.4).
- An exploratory objective and outcome measure for milestone survival have been added to account for the analyses described in Section 6.7.2; it had been unintentionally omitted from this section in previous versions (see also Sections 2.4 and 3.4.4).
- Details regarding the analysis of objective response rate have been added (Section 6.4.2.1).
- On the basis of updated United States (U.S.) Food and Drug Administration (FDA) guidance, the additional censoring rule for the primary endpoint of PFS for U.S. registration purposes has been removed from the primary analysis[2] (Sections 6.4.1 and 6.4.3) and added as the sensitivity analysis (Section 6.7.1.4).
- Exploratory analyses on the impact of non–protocol-specified anti-cancer therapy and the proportional hazards assumption on OS have been added (Section 6.7.2.5).
- Statistical methods for exploratory patient-reported outcome (PRO) measures were added (Sections 6.7.4 and 6.7.5).
- Language has been added to clarify the time of analysis for the [redacted] (Section 6.9).

This amendment also includes the following changes:

- Language has been added to state that atezolizumab is approved for the treatment of patients with metastatic non–small cell lung cancer after prior chemotherapy in certain countries (Section 1.2).
- Information on a clinical trial for atezolizumab (Study GO28753) has been added to the Ongoing Clinical Studies section (Section 1.3.1).

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[2] [FDA] U.S. Food and Drug Administration. Clinical trial endpoints for the approval of non−small cell lung cancer drugs and biologics: guidance for industry. Fed Regist 2015;80:22526−7.

- The definition of the end of study has been clarified that if the Sponsor decides to terminate the study, patients who are still receiving study treatment or who are in survival follow-up may be enrolled in an extension study or a non-interventional study (Section 3.2).
- The secondary efficacy outcome regarding TTD, defined as time from randomization to deterioration (10-point change) on each of the European Organization for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire–Core 30 (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13) symptom subscales has been updated to align with other first-line atezolizumab protocols (Section 3.4.1.2).
- The exploratory objective to evaluate the PFS rate at 6-month and 1-year landmark timepoints was added to be consistent with Section 3.4.4; it had been unintentionally omitted from this section (Section 2.4).
- Language regarding the [redacted] has been clarified (Sections 4.1.1 and 6).
- Language has been added to clarify that patients with a history of irradiated brain metastases at screening are not required to repeat imaging brain scans at subsequent, post-screening tumor evaluations, unless clinically indicated (Section 4.5.5).
- Language has been updated to clarify that tumor assessments will continue for patients who discontinue treatment for reasons other than disease progression per RECIST v1.1 and for patients who start a new anti-cancer therapy in the absence of disease progression per RECIST v1.1 and to clarify how long tumor assessments will then be continued (Sections 4.5.5, 4.5.12.2, and 4.5.12.4).
- Language has been added to clarify that all patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from the study. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator (Section 4.5.12.4).
- The adverse event reporting period has been clarified to indicate that all deaths, regardless of cause, will be reported, as already noted in Section 5.3.5.7, and to clarify the process for reporting such events (Sections 5.1, 5.1.5.1, 5.3.1, 5.3.5.7, 5.4.2.2, and 5.6; Section 5.5.3 was deleted).
- The protocol has been modified to prohibit use of the term "sudden death" on the Adverse Event eCRF, unless it is combined with the presumed cause of death (e.g., "sudden cardiac death") (Section 5.3.5.7).
- Guidance on reporting death attributed to progressive disease was updated with instructions to record such death on the Death Attributed to Progressive Disease eCRF (Section 5.3.5.7).
- Language for reporting adverse events due to worsened preexisting medical conditions has been updated with an additional example (Section 5.3.5.8).

- Language has been modified to clarify the reporting of adverse events leading to hospitalization (Section 5.3.5.10).
- Language has been added to clarify that adverse event reports will not be derived from PRO data by the Sponsor and sites are not expected to review the PRO data for adverse events (Section 5.3.5.12).
- The Medical Monitor has changed and the contact information updated (Section 5.4.1).
- Language at the beginning of the efficacy analyses section was deleted because the information is found elsewhere in the protocol (Section 6.4).
- Language has been added to clarify that the Sponsor or a designee will review all protocol deviations, and prospective requests to deviate from the protocol are not allowed (Section 9.2).
- The web site URL for the "Roche Global Policy on Sharing of Clinical Trials Data" has been corrected (Section 9.5).
- The list of references has been revised (Section 10).
- Minor changes have been made to the following sections for clarification and/or to align with other atezolizumab studies: Sections 3.1.1, 4.4.3, 4.5.4, 4.5.10, 6, 6.4.2.4, 6.5, 6.7.1.1, and 6.7.3.
- Reference to heart rate in vital signs has been changed to pulse rate to ensure consistency between the protocol and the electronic Case Report Form (eCRF) (Table 10, and Appendix 1).
- Appendix 1 has been amended to reflect changes in the protocol.
- Guidelines for managing patients who experience atezolizumab-associated adverse events have been revised to include guidelines for hypophysitis and myocarditis and have been provided in an appendix so there is no longer a need to consult the Atezolizumab Investigator's Brochure for management guidelines (Appendix 15). Appropriate cross-references have been added and previous references to the Atezolizumab Investigator’s Brochure have been updated accordingly (Sections 4.3.2.1, 4.4.2, 5.1, 5.1.1, 5.1.6.1, and 5.1.6.2).

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

PROTOCOL AMENDMENT, VERSION 5: SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.2: BACKGROUND ON ATEZOLIZUMAB

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

SECTION 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). Safety and efficacy data are summarized below from the following studies:

- *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.*

SECTION 2.1.2: Secondary Efficacy Objectives

The secondary efficacy objectives for this study are:

- ~~To evaluate the efficacy of atezolizumab as measured by an Independent Review Facility (IRF) assessed PFS according to RECIST v1.1~~
- ~~To evaluate the efficacy of atezolizumab as measured by investigator assessed time to response (TTR) according to RECIST v1.1~~
- ~~To evaluate the efficacy of atezolizumab as measured by investigator assessed time in response (TIR) according to RECIST v1.1~~
- To determine the impact of atezolizumab as measured by *the change from baseline*~~TTD~~ in patient-reported lung cancer symptoms (chest pain, dyspnea, and cough) scores using the Symptoms in Lung Cancer (SILC) scale symptom severity scores

SECTION 2.4: EXPLORATORY OBJECTIVES

The exploratory objectives for this study are:

- ~~To evaluate ORR, DCR, DOR, TTR, and TIR according to RECIST v1.1 as assessed by the IRF~~
- ~~To evaluate investigator assessed DCR according to RECIST v1.1~~

- ~~To evaluate investigator assessed PFS, ORR, DCR, DOR, TTR, and TIR according to modified RECIST for the atezolizumab-containing treatment arms~~
- *To evaluate the PFS rate at 6-month and 1-year landmark timepoints*
- *To evaluate the efficacy of atezolizumab as measured by OS and investigator-assessed PFS according to RECIST v1.1 in subgroups based on demographic and baseline characteristics*
- *To evaluate the efficacy of atezolizumab as measured by milestone survival*

SECTION 3.1: DESCRIPTION OF STUDY

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

SECTION 3.1.1: Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will be used to evaluate safety *data* ~~during the study. Unblinded safety data will be reviewed by the iDMC after~~*when* a minimum of 12 patients receiving cisplatin-based chemotherapy ~~have~~ *has* been enrolled into each treatment arm with a minimum follow-up of approximately 60 days*, and then* ~~.~~ ~~Subsequently, the iDMC will review safety data~~ approximately every 6 months *thereafter until the study* ~~*data are*~~*is* ~~*unblinded*~~*unblinded for primary efficacy analyses or the study is terminated by the Sponsor*~~. The safety data will include disposition, demographic data, adverse events, serious adverse events, and relevant laboratory data~~.

The Sponsor will remain blinded to the efficacy results until the final PFS analysis. All summaries and analyses by treatment arm for the iDMC review will be prepared by an external independent Data Coordinating Center (iDCC). *The safety data will include disposition, demographic data, adverse event data (e.g. serious adverse events and adverse events of special interest), study conduct data, and relevant laboratory data. Efficacy data (excluding data on deaths) will not be included in the iDMC safety data reviews.* Following the *safety* data 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~~.

SECTION 3.2: END OF STUDY AND LENGTH OF STUDY

The end of this study ~~is defined as when approximately 414 deaths have occurred in the ITT population enrolled in the global phase or~~ [redacted]

[redacted]~~. In addition, the Sponsor may decide to terminate the study at any time~~*will occur when all of the following criteria have been met:*

- *The required number of deaths for the final analysis of OS has been observed among patients enrolled during the global enrollment phase (see Section 6.8.1).*
- [redacted] *(see Section 6.9)*
- *The last patient has been enrolled in the study (i.e., global enrollment phase* [redacted]

~~If no patients are enrolled in the~~ [redacted]~~, the total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 45 months.~~*In addition, the Sponsor may decide to terminate the study at any time. If the Sponsor decides to terminate the study, patients who are still receiving study treatment or undergoing survival follow-up may be enrolled in an extension study or a non-interventional study.*

SECTION 3.3.3: Rationale for Open-Label Study

Adequate steps have been taken to ensure the validity of data in an open-label study design. This includes ~~performing a supportive analysis of efficacy on the basis of determined progression by an IRF,~~ performing a sensitivity analysis to demonstrate the robustness of the co-primary endpoints, 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 co-primary endpoints prior to study start, including predefined methods for handling missing data and censoring rules. Final efficacy analyses will only be performed at the prespecified analysis timepoints in the protocol.

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

However, given that the majority of patients in this study will likely receive subsequent therapies and/or palliative care (Temel et al. 2010), the OS analysis may be confounded (Miller et al. 2012). Therefore, investigator-assessed PFS ~~(which will be supported by an IRF-assessed PFS analysis, one of the secondary endpoints of the study)~~ is being retained as a co-primary endpoint, and crossover from the control arm to the experimental arm will not be permitted with the aim of preserving the study's ability to potentially demonstrate treatment benefit of atezolizumab on OS.

… To ensure the validity of investigator-assessed PFS as a co-primary endpoint, a number of measures have been implemented: ~~full IRF assessment to support the analysis of the co-primary endpoint,~~ a substantial, clinically meaningful target magnitude of benefit (target HR of 0.65 in the ITT 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).

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

~~In addition, while the primary endpoint measures of efficacy (PFS) comparing the atezolizumab-containing treatment arm to the control arm will be using RECIST v1.1, exploratory analyses of PFS, ORR, DCR, DOR, TIR, and TTR using modified RECIST (see Section 2.3) will be performed for patients randomized to receive atezolizumab. Modified RECIST allow for the incorporation of new lesions into the calculation of total tumor burden after baseline. Tumor assessments will be performed according to RECIST and modified RECIST for patients in the atezolizumab-containing treatment arms (Arm A) and only according to RECIST v1.1 for patients in the control arm (Arm B).~~

SECTION 3.3.6: Rationale for Patient-Reported Outcome Assessments

In addition, the SILC scale will be used to assess the effect and impact of atezolizumab ~~on TTD~~*as measured by the change from baseline in patient-reported* ~~of~~ specific lung cancer symptoms (chest pain, dyspnea, and cough) in patients with Stage IV, non-squamous NSCLC in the first-line setting.

SECTION 3.4.1.2: Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are:

- ~~TTR, defined as the time from randomization to first occurrence of a documented objective response as determined by the investigator according to RECIST v1.1~~
- ~~TIR, defined as 1 day for non-responders and defined the same as DOR for responders~~
- ~~PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the IRF using RECIST v1.1 or death from any cause, whichever occurs first~~
- OS ~~rates~~ at 1- and 2 -year *landmark timepoints*
- TTD in patient-reported lung cancer symptoms, defined as time from randomization to deterioration (10-point change) on each of the EORTC QLQ-C30 and EORTC QLQ-LC13 symptom subscales ~~maintained for two assessments or one assessment followed by death from any cause within 3 weeks~~
- ~~TTD~~ *Change from baseline* in patient-reported lung cancer symptoms (cough, dyspnea, or chest pain~~, whichever occurs first)~~ with use of the SILC scale symptom score~~, defined as time from randomization to the first deterioration maintained for two assessments or one assessment followed by death from any cause within 1 week~~

SECTION 3.4.4: Exploratory Outcome Measures

The exploratory outcome measures for this study are:

- ~~Objective response, DCR, DOR, TIR, and TTR as determined by the IRF according to RECIST v1.1~~
- ~~DCR, defined as the rate of patients with a CR or PR as best response or with stable disease maintained for ≥6 weeks as determined by the investigator according to RECIST v1.1~~
- ~~Objective response, PFS, DCR, DOR, TIR, and TTR as determined by the investigator according to modified RECIST~~
- PFS at 6-month~~s~~ and ~~at~~ 1-~~-~~year *landmark timepoints*
- OS rate at 3-~~-~~year *landmark timepoint*
- *Milestone survival*
- *OS and investigator-assessed PFS according to RECIST v1.1 in subgroups based on demographic and baseline characteristics*

SECTION 4.1.1: Inclusion Criteria

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

- [redacted]

SECTION 4.3.2.1: Atezolizumab

Dose modifications to atezolizumab are not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events are provided in Section 5.1.6.2 *and Appendix 15.*

SECTION 4.4.2: Cautionary Therapy for Atezolizumab-Treated Patients

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-related adverse events are described in Section 5.1.6.2 *and Appendix 15.*

SECTION 4.4.3: Prohibited Therapy

The following medications are prohibited while the patient is 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~~.

SECTION 4.5.4: Vital Signs

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

SECTION 4.5.5: Tumor and Response Evaluations

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 history of irradiated brain metastases at screening are not required to undergo imaging brain scans at subsequent tumor evaluations, unless scans are clinically indicated.* The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans)*….*

Patients who discontinue treatment for reasons other than radiographic disease progression per RECISTv1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by Sponsor, whichever occurs first.

Patients who start a new anti-cancer therapy in the absence of radiographic disease progression per RECIST v1.1 will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1(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.

Scans will be submitted ~~for central review~~ to an IRF.

SECTION 4.5.10: Patient-Reported Outcomes

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

SECTION 4.5.12.2: Assessments during Treatment

Tumor assessments should occur every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1 and every 9 weeks (±7 days) after completion of the Week 48 tumor assessment, regardless of treatment delays until radiographic disease progression per RECIST v1.1 or loss of clinical benefit for patients in Arm A who continue treatment 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 per RECIST v1.1 (e.g., toxicity,*

symptomatic deterioration) and patients who start non-protocol anti-cancer therapy in the absence of radiographic disease progressin per RECIST v1.1 will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by Sponsor, whichever occurs first.

SECTION 4.5.12.4: Follow-Up Assessments

Patients who discontinue study treatment for any reason other than *radiographic* progressive disease or loss of clinical benefit will complete the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L at each tumor assessment visit and will complete the SILC at home on a weekly basis, until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit as determined by the investigator for atezolizumab-treated patients who continue treatment after radiographic disease progression)*,* ~~(unless the patient~~ withdraw*al of*~~s~~ consent *,death, loss to follow-up,* or ~~the Sponsor terminates~~*termination of* the study *by the Sponsor, whichever occurs first*~~)~~.

~~Ongoing or new serious adverse events, adverse events of special interest, or adverse events thought to be related to study treatment will be followed up until the event has resolved to the baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that the study treatment or participation is not the cause of the adverse events.~~

Survival follow-up *information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from the study (this request must be documented in the source documents and signed by the investigator)*~~should continue until death, withdrawal of consent, the patient is lost to follow-up, or study termination by the Sponsor, whichever occurs first~~. 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.

SECTION 5.1: SAFETY PLAN

…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 for reporting instructions). These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and e-mailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form

using the fax number or e-mail address provided to investigators. ~~Investigators are instructed to report all serious adverse events and adverse events of special interest considered related to study treatment regardless of time after study~~. The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections *and in Appendix 15.*

SECTION 5.1.1: Risks Associated with Atezolizumab

Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo et al. 2010). Suggested workup and management guidelines procedures for suspected immune-related adverse events are provided in Section 5.1.6.2 and in ~~Section 6 (Guidance for the Investigator) of the Atezolizumab Investigator's Brochure~~ *Appendix 15.*

SECTION 5.1.5.1: Monitoring

~~Patients will be followed up for serious adverse events and adverse events of special interest for 90 days after their last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. For all other adverse events, patients will be followed up for 30 days after their last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. Investigators are instructed to report all serious adverse events and adverse events of special interest considered related to study treatment regardless of time after study.~~

~~Patients who have an ongoing study treatment- related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.~~

Patients will be followed for adverse events (including deaths, serious adverse events, and adverse events of special interest) during and after the adverse event reporting period as described in Sections 5.3.1, 5.3.5.7, 5.5, and 5.6.

SECTION 5.1.6.1: General Notes Regarding Dose Modification

~~Refer to the Atezolizumab Investigator's Brochure for more detailed information regarding dose modification.~~

SECTION 5.1.6.2: Atezolizumab Dose Modification and Management of Specific Adverse Events

Management of systemic immune activation is presented below. Refer to ~~the Atezolizumab Investigator's Brochure~~ *Appendix 15* for details on management of infusion-related reactions, gastrointestinal, dermatologic, endocrine, pulmonary toxicity,

hepatotoxicity, pancreatic toxicity, neurologic toxicity, or potential eye toxicity, and other immune-related adverse events.

SECTION 5.3.1: Adverse Event Reporting Period

After initiation of study drug, all serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of non—protocol-*specified* systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy after the last dose of study treatment, whichever occurs first. ~~Investigators are instructed to report all serious adverse events and adverse events of special interest considered to be related to study treatment, regardless of time after study (see Section 5.6.1).~~*Instructions for reporting adverse events that occur after the safety reporting period are provided in Section Section 5.6.*

SECTION 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 Completion/Early Discontinuation~~*Death Attributed to Progressive Disease* eCRF. All other deaths *occurring during the adverse event reporting period*~~in the study~~, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). The iDMC will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. ~~The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.~~ If the cause of death is unknown and cannot be ascertained at the time of reporting, **"Death due to Unknown Cause"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), the event should be replaced by the established cause of death. *The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

~~During survival follow-up, deaths attributed to progression of NSCLC should be recorded only on the Study Completion/Early Discontinuation eCRF~~. *Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.*

SECTION 5.3.5.8: Preexisting Medical Conditions

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

SECTION 5.3.5.10: Hospitalization or Prolonged Hospitalization

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

~~The following hospitalization scenarios are not considered to be adverse events:~~

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:

~~The following hospitalization scenario is not considered to be a serious adverse event but should be reported as an adverse event instead:~~

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

SECTION 5.4.1: Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted] M.D.
Mobile Telephone No.: [redacted]
~~Mobile Telephone No:~~ [redacted]

SECTION 5.4.2.2: Events That Occur after Study Drug Initiation

~~Investigators are instructed to report all serious adverse events and adverse events of special interest considered related to study treatment regardless of time after study.~~ 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.

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

~~SECTION 5.5.3: Post Study Adverse Events~~

~~Investigators are instructed to report all serious adverse events or adverse events of special interest that occur after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug for adverse events and 90 days after the last dose of study drug for serious adverse events and adverse events of special interest or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first), if the event is believed to be related to prior study drug treatment, regardless of time after study.~~

~~The investigator should report these events directly to Roche or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or email address provided to investigators.~~

SECTION 5.6: ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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

In addition, if the investigator becomes aware of a serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and 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.

SECTION 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Approximately 568 patients will be randomized in the global enrollment phase of this study. [redacted]

The primary analyses of Study GO29438 will include patients enrolled during the global enrollment phase~~; .~~ [redacted]

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

Safety analyses will be performed on data for all randomized patients who received any amount of study drug, with patients grouped according to whether any ~~full or partial dose~~*amount* of atezolizumab was received*, including cases when atezolizumab was received in error*.

SECTION 6.1: DETERMINATION OF SAMPLE SIZE

To control the overall type I error rate *using the group sequential Holm procedure (Ye et al. 2012)* ~~(Bretz et al. 2009)~~ for the one-sided test at 0.025 in the analyses of patients enrolled during the global enrollment phase, PFS in the ITT population will be tested at a one-sided α-level of 0.002 *and OS in the ITT population will be tested at a one-sided α-level of 0.023*. If *only* PFS is statistically significant, OS in the ITT population will be tested at a one-sided α-level of 0.025. Otherwise, OS in the ITT population will be tested at a one-sided α-level of 0.023. *If only OS is statistically significant, PFS in the ITT population will be tested at a one-sided α-level of 0.025 at the time of the final analysis of PFS. Otherwise, PFS in the ITT population will be tested at a one-sided α-level of 0.002 at the time of PFS final analysis.* The overview of the α control strategy is shown in Figure 3.

The sample size of this study is determined on the basis of the number of events required to demonstrate efficacy with regard to both PFS and OS (as defined in Section 6.4).

The estimates of the number of events required to demonstrate efficacy in the ITT population with regard to PFS *and OS* are based on the following assumptions:

- *1:1 randomization ratio*
- One-sided significance level of 0.002 *for PFS and 0.023 for OS*
- ~~92~~*96*.0% power to detect an HR of 0.65, corresponding to an improvement in median PFS from 6 months to 9.2 months
- No interim analysis for PFS
- ~~Dropout rate of 10% per 24 months~~
- ~~Exponential distribution for PFS~~

~~The estimates of the number of events required to demonstrate efficacy in the ITT population with regard to OS are based on the following assumptions:~~

- ~~One-sided significance level of 0.023~~
- 8~~2~~*1*% power to detect an HR of 0.75, corresponding to an improvement in median OS from 14 months to 18.7 months
- ~~Two~~ *One* interim OS analyses will be performed~~, one~~ at the time of the PFS final analysis with an information fraction of approximately ~~60~~*78*% (i.e., ~~60~~*78*% of the required OS events have occurred). To adjust for the multiplicity due to the interim analyses, the Lan-DeMets approximation to the O'Brien-Fleming boundary will be used.
- Dropout rate of 10% per 24 months *assumed for all treatment arms*
- *Event times exponentially distributed*
- ~~Exponential distribution for OS~~

With these assumptions, the PFS final analysis will be conducted after approximately ~~396~~ *458* PFS events have occurred in the ITT population, and ~~when the last patient is randomized~~ *at least* ~~9~~ *10 months after the last patient is enrolled* during the global enrollment phase, whichever occurs ~~last~~*later*. This is expected to occur approximately ~~25~~ *30* months after the first patient is randomized. This number of events corresponds to a minimum detectable difference in HR of approximately *0.764 for a one-sided α-level of 0.002. Based on the group sequential Holm procedure (Ye et al. 2012), if only OS is statistically significant, then PFS in the ITT population will be tested at a one-sided α-level of 0.025 at the time of PFS final analysis. In this case, the number of events corresponds to a minimum detectable difference of approximately 0.833 in HR.*

The interim OS analysis is planned to be performed at the time of the PFS final analysis. However, if there are significantly fewer than the expected 312 OS events at the time of the final PFS analysis, a nominal α of 0.01% (negligible impact on overall type I error rate) will be spent on the OS analysis at the time of the final PFS analysis and a second interim OS analysis will then be conducted after approximately 312 OS events have occurred (see Section 6.8.1).

Given the sample size of 568, this will result in approximately ~~414~~ *398* OS events in the ITT population for the final analysis of OS, which is expected at approximately 4~~5~~ *42* months after the first patient is randomized.

SECTION 6.4: EFFICACY ANALYSES

~~The primary efficacy analyses for PFS and OS will include randomized patients in the ITT population. ORR will be analyzed using all randomized patients. DOR, TIR, and TTR will be assessed in patients who have an objective response. TTD analyses in the PRO measures will be conducted on all patients with a non-missing baseline PRO assessment. Change from baseline analysis for PRO measures will be performed using~~

~~the patients who have both a non-missing baseline assessment and at least one non-missing post-baseline assessment.~~

SECTION 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. *The primary efficacy analyses for PFS and OS will be analyzed in the ITT population.*

~~For U.S. registration purposes, the co-primary efficacy endpoint of PFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits. Type I error control will be applied to this analyses of PFS.~~

The type I error control plan for PFS and OS is presented in Section 6.1. A group sequential design will be used for testing OS to account for the conduct of the interim analysis, which is expected to occur approximately 30 months after the first patient is enrolled in the study. Details about the timing of the OS interim analysis and stopping boundaries are provided in Section 6.8.1. Details about 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 the unblinding of the study.

~~To control the overall level of significance at a one-sided error of 0.025, comparisons with respect to PFS and OS between the treatment and control arm will be conducted as follows (see Figure 3):~~

~~PFS will be tested at a one-sided alpha level of 0.002. If the one-sided p-value corresponding to the stratified log-rank test is less than 0.002, the null hypothesis will be rejected, and it will be concluded that atezolizumab prolongs duration of PFS relative to the control arm.~~

- ~~If the null hypothesis of the PFS testing is rejected, the overall one-sided significance level for OS is 0.025. Otherwise, the overall one-sided significance level for OS is 0.023. Two interim analyses of OS will be conducted in the ITT population: the first interim analysis will be conducted at the time of the PFS final analysis, and the other when approximately 80% of the total OS events required for the final analysis have occurred using the Lan-DeMets approximation to the O'Brien-Fleming boundary. If the one-sided p-value corresponding to the stratified log-rank test is less than the alpha level at the corresponding analysis, the null hypothesis will be rejected, and it will be concluded that atezolizumab prolongs duration of OS relative to the control arm in ITT population.~~

The null and alternative hypotheses regarding PFS and OS can be phrased in terms of the survival functions S_{PFS_A} (t), S_{OS_A} (t) in *the atezolizumab-containing treatment arm (*Arm A*)* and S_{PFS_B} (t), S_{OS_B} (t) in *the control arm (*Arm B*)*, respectively:

$$H_0: S_{PFS_A}(t) = S_{PFS_B}(t) \text{ versus } H_1: S_{PFS_A}(t) > S_{PFS_B}(t)$$

$$H_0: S_{OS_A}(t) = S_{OS_B}(t) \text{ versus } H_1: S_{OS_A}(t) > S_{OS_B}(t)$$

Comparisons with respect to PFS and OS between the treatment and control arms will be tested based on a stratified log-rank test. *The stratification factors will be sex (male vs. female), ECOG performance status (0 vs. 1), type of chemotherary (carboplatin vs. cisplatin), and smoking status (never vs. current and/or former).* The stratification factors will be those used during randomization, as recorded in IxRS. Results from an unstratified analysis will also be presented. The HR ~~comparing the treatment effect between the treatment and control arms~~ will be estimated using a stratified Cox regression model~~, including 95% CIs~~. Kaplan-Meier methodology will be used to estimate median PFS and OS for each treatment arm~~, and Kaplan-Meier curves will be constructed to provide~~*and to construct survival curves for* visual descriptions of the difference between the treatment and control arms.

SECTION 6.4.2.1: Objective Response Rate

ORR is defined as the proportion of patients who had an objective response. The analysis population for ORR will be all randomized patients. *The confirmation of response in accordance with RECIST v.1.1 is not required, but ORR with confirmation may be evaluated as an exploratory endpoint.* An estimate of ORR and its 95% CI will be calculated using the Clopper Pearson method for each treatment arm. CIs for the difference in ORRs between the two treatment arms will be determined using the normal approximation to the binomial distribution. *The ORR will be compared between the two arms using the stratified Cochran-Mantel-Haenszel test, stratified by the same factors used in the primary PFS and OS analysis (see Section 6.4.1).*

~~SECTION 6.4.2.3: Time to Response~~

~~TTR will be assessed in patients who had an objective response as determined by the investigator using RECIST v1.1. TTR is defined as the time between the date of randomization and the date of first occurrence of a CR or PR (whichever status is recorded first). TTR is based on a non-randomized subset of patients (specifically, patients who achieved an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes. The methodologies outlined for the analysis of PFS will be used for the analyses of TTR.~~

~~SECTION 6.4.2.4: Time in Response~~

~~The two treatment arms will be compared with respect to TIR. Non-responders will be considered as having an event and TIR will be defined as date of randomization plus~~

~~1 day; and for responders, TIR will be same as DOR. The methodologies outlined for the analysis of PFS will be used for the analyses of TIR.~~

~~SECTION 6.4.2.5: Progression Free Survival as Assessed by the Independent Review Facility~~

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

SECTION 6.4.2.4: Patient-Reported Outcomes

~~TTD using EORTC is defined as the time from baseline to the first time the patient's score shows a ≥10 point increase above baseline in any of the following EORTC transformed symptom subscale scores (whichever comes first): cough, dyspnea (single item), dyspnea (multi-item subscale), chest pain, or arm/shoulder pain. The linear transformation gives each individual symptom subscale a possible score of 0 to 100. In order for the symptom to be considered "deteriorated," a score increase of ≥10 points above baseline must be held for at least two consecutive assessments or an initial score increase of ≥ 10 points is followed by death within 3 weeks from the last assessment. A ≥10 point change in the symptoms subscale score is perceived by patients as clinically significant (Osoba et al. 1998). Data for patients will be censored at the last time when they completed an assessment if they have not deteriorated. If no post baseline assessment is performed, data for patients will be censored at the randomization date plus 1 day. TTD using the EORTC scale will be analyzed using the same methods as for PFS.~~

~~PROs of HRQoL, lung cancer-related symptoms, and health status will be measured using the EORTC QLQ-C30 and EORTC QLQ-LC13. Summary statistics (mean, SD, median, 25th and 75th percentiles, and range) and the mean change from baseline of linear-transformed scores will be reported for all the items and subscales of the EORTC QLQ-C30 questionnaire and the QLQ-LC13 according to the EORTC scoring manual guidelines and the SILC scale symptom severity score. Completion and compliance rates will be summarized at each timepoint by treatment arm. Only patients with a non-missing baseline assessment and at least one non-missing post-baseline assessment will be included in the analyses.~~

The change from baseline per SILC scale will be analyzed for each of the lung cancer symptom scores (chest pain, cough, dyspnea). The analysis will be performed for patients in the ITT population with a non-missing baseline and at least a post-baseline PRO assessment (i.e., PRO evaluable population).

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

TTD in lung-related symptoms is defined as the time from baseline to the time the patient's score on the EORTC QLQ C30 or LC13 shows a ≥10-point increase above baseline in each of the following EORTC-transformed scores for cough, dyspnea (single item), dyspnea (multi-item subscale) and chest pain. A ≥10-point change in score is perceived by patients to be clinically significant (Osoba et al. 1998). If no baseline or post-baseline assessment is performed, data for patients will be censored at the date of randomization plus 1 day. TTD in symptoms will be analyzed in the ITT population through use of the same methods described for the PFS and OS analyses (see Section 6.4.1). Additional details regarding the analysis for the EORTC measures will be described in the SAP.

SECTION 6.4.3: Handling of Missing Data

For PFS, data for 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* ~~In the analysis of PFS for U.S. registration purposes, data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits (see Section 6.4.1).~~

SECTION 6.5: SAFETY ANALYSES

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

~~Drug~~ *Study drug* exposure*, including treatment duration, number of doses, and dose intensity,* will be summarized *for each treatment arm using descriptive statistics*~~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. *The proportion of patients experiencing at least one adverse event will be reported by toxicity term and treatment arm.*

~~SECTION 6.7.1: DCR by Investigator Assessment per RECIST v1.1~~

~~DCR is defined as the rate of patients with CR or PR as best response or stable disease maintained for ≥ 6 weeks per RECIST v1.1.~~

~~The methodologies outlined for the ORR analysis will be used for the DCR analysis based on investigator assessment.~~

SECTION 6.7.1.1: Progression-Free Survival Rate at Landmark Timepoints

The PFS rate*, defined as the probability that a patient will be alive without disease progression after randomization* (e.g., at 6 months and at 1 year)*,* will be estimated using Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated using Greenwood's formula. The 95% CIs for the difference in PFS rates between the treatment arms will be estimated using the normal approximation method*, and standard errors will be computed through use of the Greenwood method.*

SECTION 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 *tumor* assessments scheduled immediately prior to the date of the PFS event *according to RECIST v1.1*, the patient will be counted as having progressed on the date of the first of these missing assessments.

~~SECTION 6.7.2: Objective Response Rate, Disease Control Rate, Duration of Response, and Time to Response by Independent Review Facility Assessment per RECIST v1.1~~

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

SECTION 6.7.2.5: Non–Protocol-Specified Anti-Cancer Therapy

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

Further details regarding these sensitivity analyses will be described in the SAP.

~~SECTION 6.7.3: Objective Response Rate, Disease Control Rate, Duration of Response, Time in Response, Progression Free Survival, and Time to Response per Modified RECIST~~

~~Analyses using modified RECIST criteria (see Appendix 5) for ORR, DCR, DOR, TIR, PFS, and TTR as determined by the investigator will also be conducted (for atezolizumab-treated patients). Comparisons between the treatment arms will be made.~~

~~The methods outlined for the primary and secondary efficacy endpoint analyses will be used for these analyses.~~

SECTION 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. Results from these exploratory analyses will not be included in the Clinical Study Report.* ~~Additional analyses of 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 will be conducted as appropriate.~~

SECTION 6.7.4: EQ-5D-5L Health Status Data

EQ-5D-5L health status data will be used for obtaining utility measures for economic modeling. These analyses will not be included in the Clinical Study Report.

SECTION 6.7.5.: Exploratory Patient-Reported Outcome Analyses

Compliance rates for each questionnaire will be summarized in the ITT population as detailed in the SAP.

Summary statistics (mean, SD, median, 25th and 75th percentiles, and range) and the mean change from baseline at each timepoint will be reported for each score of the PRO questionnaires.

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.

SECTION 6.8.1: Planned Interim Analyses

~~Two~~ The interim efficacy ~~analyses~~ analysis of OS ~~a~~ will be conducted by the Sponsor at the time of the final PFS analysis. ~~Two interim efficacy analyses of OS are planned and will be performed by the Sponsor. The first interim OS analysis will be conducted at the time of the final PFS analysis. It is expected that there will be approximately 248 OS events in the ITT population, but the exact timing of this analysis will depend on the actual number and timing of PFS events.~~

The ~~second~~ interim OS analysis will be conducted when approximately *312*~~332~~ OS events in the ITT population have been observed. This is expected to occur approximately ~~33~~ *30* months after the first patient is randomized, but the exact timing of this analysis will depend on the actual number and timing of OS events. *If there are significantly fewer than the expected 312 OS events at the time of the final PFS analysis, a nominal two-sided α of 0.01% (negligible impact on overall type I error rate)*

will be spent on the OS analysis at the time of the final PFS analysis and a second interim OS analysis will then be conducted after approximately 312 OS events have occurred.

The final OS analysis will be conducted when approximately ~~414~~ *398* OS events in the ITT population have been observed. This is expected to occur approximately ~~45~~ *42* months after the first patient is randomized, but the exact timing of this analysis will depend on the actual number and timing of OS events.

SECTION 6.9: [redacted]

Approximately 568 patients will be randomized in the global enrollment phase of this study. [redacted]

SECTION 9.2: PROTOCOL DEVIATIONS

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

SECTION 9.5: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

~~http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf~~

TABLE 10: Administration of First and Subsequent Infusions of Atezolizumab

Table 10 has been updated to align with current model document language.

TABLE 20: Analysis Timing and Stopping Boundary of Overall Survival

Table 20 has been revised to reflect the changes to the protocol.

Figure 3: Overview of the Alpha Control Strategy

Figure 3 has been updated to reflect changes to the protocol.

APPENDIX 1: Schedule of Assessments

The schedule of activities has been revised to reflect the changes to the protocol.

APPENDIX 15: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Appendix 15 has been added.

REFERENCES

References have been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (MPDL3280A, ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH CARBOPLATIN OR CISPLATIN+PEMETREXED COMPARED WITH CARBOPLATIN OR CISPLATIN+PEMETREXED IN PATIENTS WHO ARE CHEMOTHERAPY-NAIVE AND HAVE STAGE IV NON-SQUAMOUS NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO29438
VERSION NUMBER:	5
EUDRACT NUMBER:	2015-003605-42
IND NUMBER:	117296
TEST PRODUCT:	Atezolizumab (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. Contact details will be provided to the investigator prior to study start.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (MPDL3280A, ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH CARBOPLATIN OR CISPLATIN + PEMETREXED COMPARED WITH CARBOPLATIN OR CISPLATIN + PEMETREXED IN PATIENTS WHO ARE CHEMOTHERAPY-NAIVE AND HAVE STAGE IV NON-SQUAMOUS NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO29438
VERSION NUMBER:	5
EUDRACT NUMBER:	2015-003605-42
IND NUMBER:	117296
TEST PRODUCT:	Atezolizumab (RO5541267)
PHASE:	III
INDICATION:	Non-squamous non–small cell lung cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of atezolizumab in combination with carboplatin or cisplatin + pemetrexed compared with carboplatin or cisplatin + pemetrexed in patients who are chemotherapy-naive and have Stage IV non-squamous non–small cell lung cancer (NSCLC). Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

The co-primary objectives of this study are:

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)
- To evaluate the efficacy of atezolizumab as measured by overall survival (OS)

The secondary efficacy objectives for this study are:

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed objective response rate (ORR) according to RECIST v1.1
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed duration of response (DOR) according to RECIST v1.1
- To evaluate the OS rate at 1 and 2 years
- To determine the impact of atezolizumab as measured by *the change from baseline* in patient-reported lung cancer symptoms of cough, dyspnea (single-item and multi-item subscales), chest pain, or arm/shoulder pain, using the European Organization for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire–Core 30 (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13)

- To determine the impact of atezolizumab as measured by *the change from baseline* in patient-reported lung cancer symptoms (chest pain, dyspnea, and cough) scores using the Symptoms in Lung Cancer (SILC) scale symptom severity scores

Safety Objectives

The safety objectives for this study are:

- To evaluate the safety and tolerability of atezolizumab when given in combination with carboplatin or cisplatin + pemetrexed or as maintenance therapy with pemetrexed alone
- To evaluate the incidence and titers of anti-therapeutic antibody against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

Pharmacokinetic Objectives

The PK objectives for this study are:

- To characterize the pharmacokinetics of atezolizumab when given in combination with carboplatin or cisplatin + pemetrexed or pemetrexed alone
- To characterize the pharmacokinetics of carboplatin when given in combination with atezolizumab and pemetrexed
- To characterize the pharmacokinetics of cisplatin when given in combination with atezolizumab + pemetrexed
- To characterize the pharmacokinetics of pemetrexed when given in combination with atezolizumab + carboplatin or cisplatin

Exploratory Objectives

The exploratory objectives for this study are:

- *To evaluate the PFS rate at 6-month and 1-year landmark timepoints*
- To evaluate the OS rate at 3 years in each treatment arm
- *To evaluate the efficacy of atezolizumab as measured by OS and investigator-assessed PFS according to RECIST v1.1 in subgroups based on demographic and baseline characteristics*
- *To evaluate the efficacy of atezolizumab as measured by milestone survival*
- To evaluate the relationship between biomarkers in tumors and blood (including but not limited to programmed death–ligand 1 (PD-L1), programmed death–1 (PD-1), somatic mutations and others), as defined by immunohistochemistry (IHC), quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR), next-generation sequencing, and/or other methods and measures of efficacy
- 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 and compare patient's health status as assessed by the EuroQoL 5 Dimensions 5-Level questionnaire to generate utility scores for use in economic models for reimbursement
- To determine the impact of atezolizumab in each of the treatment comparisons as measured by change from baseline in patient-reported outcomes (PROs) of health-related quality of life, lung cancer–related symptoms, and health status 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 (IMpower 132) designed to evaluate the safety and efficacy of atezolizumab in combination with cisplatin or

carboplatin + pemetrexed compared with treatment with cisplatin or carboplatin + pemetrexed in patients who are chemotherapy-naive and have Stage IV non-squamous NSCLC.

Eligible patients will be stratified by sex (male vs. female), smoking status (never vs. current and/or former), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1) and chemotherapy regimen (carboplatin vs. cisplatin) and randomized by a 1:1 ratio to receive one of the following treatment regimens:

- Induction phase (four or six 21-day cycles):

  Arm A: atezolizumab + carboplatin or cisplatin + pemetrexed

  Arm B: carboplatin or cisplatin + pemetrexed

- Maintenance phase (21-day cycles):

  Arm A: atezolizumab + pemetrexed

  Arm B: pemetrexed

Treatment with chemotherapy (both in Arm A and B) should be discontinued in all patients who exhibit evidence of progressive disease by RECIST 1.1. During induction or maintenance treatment, patients randomized to Arm A may continue treatment with atezolizumab beyond progressive disease by RECIST v1.1, provided they are experiencing clinical benefit as assessed by the investigator.

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 the completion of the Week 48 tumor assessment, tumor assessment will be required every 9 weeks. Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab-treated only 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 (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.

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.*

Number of Patients

Approximately 568 patients will be enrolled across all sites during the global enrollment phase of the study. [redacted]

Target Population

Inclusion Criteria

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

- Signed Informed Consent Form
- Male or female, 18 years of age or older
- ECOG performance status of 0 or 1
- Histologically or cytologically confirmed, 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)

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

- No prior treatment for Stage IV non-squamous NSCLC

  Patients with a sensitizing mutation in the epidermal growth factor receptor (*EGFR*) gene are excluded given that erlotinib, gefitinib, or another *EGFR* tyrosine kinase inhibitor is the appropriate initial treatment of *EGFR*-mutant NSCLC.

  Patients with an anaplastic lymphoma kinase (*ALK*) fusion oncogene are excluded given that crizotinib or other *ALK* inhibitors is the appropriate initial 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 at a local or 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 dose of chemotherapy and/or radiotherapy.
- 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.
- Patients should submit a pre-treatment tumor tissue sample (if available). If tumor tissue is not available (e.g., depleted for prior diagnostic testing), patients are still eligible.

  If tumor tissue is available, a representative formalin-fixed paraffin-embedded (FFPE) tumor specimen in paraffin block or unstained, freshly cut, serial sections (preferably at least 10) from an FFPE tumor specimen, are preferred. If 10 sections are not available, fewer can be submitted.

  If FFPE specimens described above are not available, any type of specimens (including fine-needle aspiration, cell pellet specimens [e.g., from pleural effusion], and lavage samples) are also acceptable.

    This specimen should be accompanied by the associated pathology report.

    Any available tumor tissue sample should be submitted before or within 4 weeks after enrollment.
- 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.

Calculated creatinine clearance (CRCL) $\geq$45 mL/min or, if using cisplatin, calculated CRCL must be $\geq$60 mL/min

- [redacted]
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab or 6 months after the last dose of cisplatin.

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

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the chemotherapy treatment period and for at least 6 months after the last dose of chemotherapy.

  With pregnant female partners, men must remain abstinent or use a condom during the chemotherapy treatment period and for at least 6 months after the last dose of chemotherapy.

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

Exclusion Criteria

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

Cancer-Specific Exclusions

- Patients with a sensitizing mutation in the *EGFR* gene or an *ALK* fusion oncogene
- Active or untreated CNS metastases as determined by CT or magnetic resonance imaging evaluation during screening and prior radiographic assessments
- Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for $\geq$2 weeks prior to randomization

- Leptomeningeal disease
- Uncontrolled tumor-related pain

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

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

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

  Patients who are receiving denosumab prior to randomization must be willing and eligible to discontinue its use and replace it with a bisphosphonate instead while in the study.
- Malignancies other than NSCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous-cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
- 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 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 I diabetes mellitus who are receiving a stable dose of insulin regimen are eligible for this study.

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

  Rash must cover less than 10% of body surface area

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

  No acute exacerbations of underlying condition within the last 12 months (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 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 hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

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

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

- Active tuberculosis
- Severe infections within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received therapeutic oral or 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 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 receiving 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 render the patient at high risk from treatment complications
- Illness or condition that may interfere with a patient's capacity to understand, follow, and/or comply with study procedures

Exclusion Criteria Related to Medications

- Prior treatment with *EGFR* inhibitors or *ALK* inhibitors
- Any approved anti-cancer therapy, including hormonal therapy within 21 days prior to initiation of study treatment.
- 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 antigen 4 (CTLA-4) treatment may be enrolled, provided the following requirements are met:

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

No history of severe immune-mediated adverse effects from anti-CTLA-4 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 3 and 4)

- Treatment with systemic immunostimulatory agents (including but not limited to interferons, interleukin [IL]-2) within 4 weeks or 5 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 agents) within 2 weeks prior to randomization

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

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

Exclusion Criteria Related to Chemotherapy

- History of allergic reactions to cisplatin, carboplatin, or other platinum-containing compounds
- Patients with hearing impairment (cisplatin)
- Grade ≥2 peripheral neuropathy as defined by NCI CTCAE v4.0 (cisplatin)
- CRCL <60 mL/min for cisplatin or <45 mL/min for carboplatin

End of Study and Length of Study

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

- *The required number of deaths for the final analysis of OS has been observed among patients enrolled during the global enrollment phase*
- [redacted]
- *The last patient has been enrolled in the study (i.e., global enrollment phase* [redacted]

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

Investigational Medicinal Products

The investigational medicinal products for this study are atezolizumab and pemetrexed. Depending on local classification, in this study, cisplatin and carboplatin may either be considered a non-investigational medicinal product or an investigational medicinal product.

Test Product (Investigational Drug)

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.

Comparator

Institutions should follow their standard administration procedures for pemetrexed. The premedication doses administered should be in compliance with the prescribing information. All patients eligible for pemetrexed therapy should avoid taking non-steroidal anti-inflammatory drugs with long elimination half-lives for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration.

Non-Investigational Medicinal Products

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

Carboplatin should be administered 30 minutes after completion of pemetrexed administration by IV infusion over 30–60 minutes to achieve an initial target area under the concentration–time curve of 6 mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines.

Statistical Methods

Primary and Secondary Efficacy Analyses

The primary efficacy analyses for PFS and OS will include randomized patients in the ITT population. ORR will be analyzed using all randomized patients. DOR will be assessed in patients who have an objective response. PRO measures will be conducted on all patients with a non-missing baseline PRO assessment. Change from baseline analysis for PRO measures will be performed using the patients who have both a non-missing baseline assessment and at least one non-missing post-baseline assessment.

Determination of Sample Size

Determination of sample size is based on patients enrolled in the global enrollment phase. This study will randomize approximately 568 patients during the global enrollment phase. [redacted]

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 and 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.

One interim efficacy analysis of OS is planned and will be performed by the Sponsor. The first interim OS analysis will be conducted at the time of the final PFS analysis. It is expected that there will be approximately *312* OS events in the ITT population but the exact timing of this analysis will depend on the actual number and timing of PFS events. *If there are significantly fewer than the expected 312 OS events at the time of the final PFS analysis, a nominal two-sided α of 0.01% (negligible impact on overall type I error rate) will be spent on the OS analysis at the time of the final PFS analysis and a second interim OS analysis will then be conducted after approximately 312 OS events have occurred.*

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALK	anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
ATA	anti-therapeutic antibody
AUC	area under the concentration–time curve
BSC	best supportive care
C_{max}	maximum observed serum concentration
C_{min}	minimum observed serum concentration
CR	complete response
CRC	colorectal cancer
CRCL	creatinine clearance
CT	computed tomography
ctDNA	circulating tumor DNA
C_{trough}	trough concentration
CTLA-4	cytotoxic T-lymphocyte associated antigen 4
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
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
ePRO	electronic PRO
EQ-5D-5L	EuroQoL 5 Dimensions 5-Level Version
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GFR	glomerular filtration rate
HBcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
HRQoL	health-related quality of life
IC	tumor-infiltrating immune cell

Abbreviation	Definition
ICH	International Conference for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
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/Web response system
KRAS	GTPase Krase
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
Pac + Cb + Bev	paclitaxel + carboplatin + bevacizumab
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
Pem + Cb	pemetrexed + carboplatin
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
q3w	every 3 weeks
QLQ-C30	Quality-of-Life Questionnaire–Core 30
QLQ-LC13	Quality-of-Life Questionnaire Lung Cancer Module
qRT-PCR	quantitative reverse transcriptase–polymerase chain reaction
RCC	renal cell carcinoma
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan

Abbreviation	Definition
SILC	Symptoms in Lung Cancer
TC	tumor cell
TKI	tyrosine kinase inhibitor
TNF	tumor necrosis factor
TTD	time to deterioration
UBC	urothelial bladder cancer
ULN	upper limit of normal

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

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

Genotype-directed therapy has the potential to dramatically improve the balance of benefit and toxicity for selected patients with NSCLC characterized by alterations of driver oncogenes, including sensitizing *EGFR* mutations and *ALK* rearrangements. However, these mutations are more prevalent in adenocarcinoma NSCLC and are very rare in squamous NSCLC. Randomized Phase III studies of gefitinib (IPASS), erlotinib (EURTAC), and afatinib (LUX-Lung 3) showed significant improvement of progression-free survival (PFS) and objective response rate (ORR) compared with platinum doublet chemotherapy (Fukuoka et al. 2011; Rosell et al. 2012; Yang et al. 2012; respectively). Similarly, the ALK inhibitor crizotinib has demonstrated efficacy in patients with NSCLC that is 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 [USPI]). 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 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 who were allocated to chemotherapy had a significantly longer median survival than did those who were managed with BSC (8 vs. 5.7 months; hazard ratio [HR]=0.77, 95% CI: 0.66, 0.89).

The benefit conferred by platinum-based chemotherapy regimens appears to have reached a plateau in ORR (approximately 15%–22%) and median survival (7–10 months). More recently, the addition of bevacizumab to carboplatin and paclitaxel resulted in an increase in response rate from 15% to 35% and an increase in median overall survival (OS) from 10 to 12 months (see Table 1).

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

First-Line Therapy Regimen	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	6.5	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	
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	

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

First-Line Therapy Regimen	ORR (%)	Median PFS (months)	Median OS (months)	OS HR (95% CI)
Phase III studies [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	

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

[a] Schiller JH, Harrington D, Belani CP, et al. Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non–small-cell lung cancer. N Engl J Med 2002;346:92–8.

[b] Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non–small cell lung cancer. N Engl J Med 2006;355:2542–50.

[c] Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non–small cell lung cancer. J Clin Oncol 2008;26:3543–51.

[d] Socinski MA, Bondarenki I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a Phase III trial. J Clin Oncol 2012;30:2055–62.

[e] Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised Phase III trial. Lancet 2009;373:1525–31.

Despite the limited survival benefit conferred by cytotoxic chemotherapy, platinum-based regimens remain the standard first-line option for most patients with locally advanced and metastatic NSCLC that was not harboring an activating *EGFR* mutation or *ALK* gene rearrangement. In particular, for newly diagnosed advanced stage non-squamous NSCLC, the 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.

1.1.3 Platinum-Based Regimen for First-Line NSCLC

Several meta-analyses have compared the use of cisplatin and carboplatin as treatments for NSCLC. In general, although the ORR was higher in patients treated with cisplatin than in those treated with carboplatin, the 1-year and OS rates were comparable. When given in combination with a third-generation chemotherapy, cisplatin may result in longer survival than carboplatin (overall response of 30% vs. 24%, respectively; Hotta et al. 2004; Ardizzoni et al. 2007), but overall benefit was quite marginal, and subgroup analyses including additional, more recent studies indicate that there may be no difference between the two agents (Jiang et al. 2007; Azzoli et al. 2009).

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

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

1.1.4 Pemetrexed

Pemetrexed disodium (ALIMTA®, pemetrexed) is a novel pyrrolo[2,3 d]pyrimidine–based folic acid analogue. In vitro studies, pemetrexed inhibited multiple folate-dependent enzymes (thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl-transferase) crucial in the de novo biosynthesis of thymidine and purine nucleotides (Shih et al. 1997).

1.1.4.1 Pemetrexed plus Platinum Compounds in First-Line NSCLC

Two Phase II studies demonstrated that the combination of pemetrexed and carboplatin is tolerable and that its activity in first-line treatment of advanced-stage NSCLC is

comparable with other standard platinum doublets commonly used in clinical practice (Kelly et al. 2001; Scagliotti et al. 2002; Fossella et al. 2003; Reck et al. 2010). The toxicity profile of the pemetrexed/carboplatin combination appears to be more favorable than that seen with other standard regimens in first-line NSCLC.

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

In addition, a supportive study named PRONOUNCE was designed to assess the efficacy and safety of pemetrexed+carboplatin (Pem+Cb) followed by pemetrexed maintenance versus paclitaxel+carboplatin+bevacizumab followed by bevacizumab maintenance (Pac+Cb+Bev) in patients with advanced non-squamous NSCLC. The median PFS was 4.44 months for Pem+Cb versus 5.49 months for Pac+Cb+Bev (HR=1.06; 95% CI: 0.84, 1.35; p=0.610). The median OS for Pem+Cb was 10.5 months versus 11.7 months for Pac+Cb+Bev (HR=1.07; 95% CI: 0.83, 1.36; p=0.615). One- and 2-year survival rates were not significantly different between the arms and were 43.7% and 18.0% for Pem+Cb and 48.8% and 17.6% for Pac+Cb+Bev. Response rate and disease control rate (DCR) were 23.6% and 59.9% for Pem+Cb and 27.4% and 57.0% for Pac+Cb+Bev (p=0.414 and 0.575, respectively).

1.1.4.2 Pemetrexed Maintenance Therapy in NSCLC

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

0.95; p = 0.012). In the non-squamous population, the median OS was 15.5 months for pemetrexed-treated patients and 10.3 months for patients on placebo (unadjusted HR, 0.70; 95% CI: 0.56 to 0.88; p = 0.002).

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

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. 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 PFS and ORR compared with platinum-doublet chemotherapy (Fukuoka et al. 2011; Rosell et al. 2012; Yang et al. 2012). Similarly, the *ALK* inhibitors crizotinib and ceritinib have demonstrated efficacy in patients with NSCLC positive for *ALK* rearrangement as defined by fluorescence in situ hybridization (Crino et al. 2011; Camidge et al. 2012; Shaw et al. 2012; Shaw and Engelman 2014; XALKORI® 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.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (MPDL3280A) is a humanized immunoglobulin 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 programmed death–ligand 1 (PD-L1) and inhibits its interaction with its receptors, programmed death–1 (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 of patients with* locally advanced or metastatic urothelial *cancer after prior therapy*.

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). Safety and efficacy data are summarized below from the following studies:

- Study PCD4989g (GO27831): A Phase Ia, multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion every 3 weeks (q3w) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies

- Study GO28753 (hereinafter POPLAR): A randomized, Phase II, open-label study assessing the clinical benefit of atezolizumab as a single agent versus docetaxel in PD-L1 unselected 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 of the safety and pharmacology of atezolizumab (anti–PD-L1 antibody) administered with bevacizumab and/or with chemotherapy in patients with advanced solid tumors
- *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.*

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) and the POPLAR study.

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 ≥10% of all patients) included fatigue, decreased appetite, nausea, pyrexia, constipation, and cough (see Table 2).

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

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

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

Grade 3–4 adverse events (on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 [NCI CTCAE v4.0]) were reported in 239 patients (42.8%), of which 66 (11.8%) were considered related. Grade 3 and 4 adverse events considered related by the investigator included dyspnea, pneumonitis, increased ALT, increased AST, increased gamma-glutamyl transferase, 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-Related Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-related 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-related adverse events that were observed in patients treated with atezolizumab. Guidelines for the management of immune-related adverse events are described in Section 5.1.6.2.

1.3.2.2 Single-Agent Clinical Safety in Patients with NSCLC in the POPLAR Study

As of the 8 May 2015 data cutoff date, the Phase II POPLAR study included data from 142 patients treated with atezolizumab as a fixed dose of 1200 mg IV q3w and 135 patients treated with docetaxel 75 mg/m^2 IV q3w. The frequency of patients in the POPLAR study who reported any adverse event regardless of attribution was 96.3% for the atezolizumab arm and 95.8% for the docetaxel arm. A higher number of Grade $\geq$ 3 adverse events were observed in the docetaxel arm (56.3% vs. 44.4%), explained primarily by the difference in adverse events due to bone marrow suppression. Adverse events reported in at least 10% of patients in either treatment arm are listed in Table 3.

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

MedDRA Preferred Term	Atezolizumab n = 142 (%)	Docetaxel n = 135 (%)
Fatigue	55 (38.7)	54 (40.0)
Decreased appetite	49 (34.5)	28 (20.7)
Nausea	31 (21.8)	45 (33.3)
Cough	38 (26.8)	33 (24.4)
Dyspnoea	38 (26.8)	27 (20.0)
Diarrhea	24 (16.9)	38 (28.1)
Constipation	29 (20.4)	32 (23.7)
Alopecia	3 (2.1)	52 (38.5)
Anemia	23 (16.2)	26 (19.3)
Pyrexia	24 (16.9)	16 (11.9)
Asthenia	14 (9.9)	22 (16.3)
Vomiting	18 (12.7)	18 (13.3)
Arthralgia	22 (15.5)	12 (8.9)
Rash	15 (10.6)	16 (11.9)
Insomnia	19 (13.4)	11 (8.1)
Back pain	16 (11.3)	11 (8.1)
Musculoskeletal pain	19 (13.4)	7 (5.2)
Myalgia	8 (5.6)	18 (13.3)
Neutropenia	2 (1.4)	17 (12.6)
Pneumonia	15 (10.6)	4 (3.0)
Neuropathy, peripheral	2 (1.4)	16 (11.9)

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

1.3.2.3 Clinical Safety in Combination 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 (CRC). As of 10 February 2015, 144 patients had been enrolled in this study: 39 in Arm A (atezolizumab + bevacizumab), 36 in Arm B (atezolizumab + bevacizumab and FOLFOX [oxaliplatin, leucovorin, and 5-fluorouracil]), 14 in Arm C (atezolizumab + carboplatin and paclitaxel), 24 in Arm D (atezolizumab + carboplatin and pemetrexed), 20 in Arm E (atezolizumab + carboplatin and nab-paclitaxel), and 11 in Arm F (atezolizumab + nab paclitaxel). The treatment combinations have been generally well tolerated. No DLTs have been reported during

the dose-escalation stage in any study arm. Patients are being enrolled in safety and biopsy expansion cohorts in Arms A and B as well as in additional arms testing atezolizumab in combination with commonly used NSCLC chemotherapy doublets.

A total of 141 of 144 patients (97.9%) reported at least one adverse event while receiving study drug. The majority of these events were Grade 2 and 3 in severity. The five most commonly reported adverse events across the study arms (≥10% in 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. See Table 4 for all adverse events reported in each treatment arm of Study GP28328.

Table 4 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-related AEs	12 (30.8)	28 (77.8)	8 (57.1)	11 (45.8)	11 (55.0)	2 (16.7)	72 (49.7)

AE = adverse event.

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

All patients who were enrolled in Arms C and D experienced an adverse event; 95% of patients who were enrolled in Arm E experienced an adverse event, and 83.3% of patients enrolled in Arm F experienced an adverse event. The adverse events commonly reported in 2 or more patients in Arms C, D, and E included anemia, decreased appetite, hypomagnesemia, nausea, neutropenia, constipation, vomiting, fatigue, rash, cough, and diarrhea. Adverse events commonly reported in 2 or more patients in Arm F included dermatitis, upper respiratory infection, alopecia, peripheral sensory neuropathy, fever, constipation, neutrophil count decreased, anemia, diarrhea, headache, nausea, and fatigue.

1.3.3 Clinical Activity

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

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

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

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

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

Table 5 displays the investigator-assessed confirmed ORR, confirmed 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 (IC) and tumor cells (TC) for PD-L1 expression on baseline tumor tissue from NSCLC patients have been performed.

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

Table 5 Patients with NSCLC in Study PCD4989g: Investigator-Assessed Confirmed Objective Response Rate by Tumor PD-L1 Expression, Duration of Response, and 6-Month Progression-Free Survival Rates (per RECIST Version 1.1)

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

DOR = duration of response; IC = tumor-infiltrating immune cell; IHC = immunohistochemistry; NSCLC = non–small cell lung cancer; ORR = objective response rate; PFS = progression-free survival; PR = partial response; PD = progressive disease; PD-L1 = programmed death–ligand 1; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; TC = tumor cell.

Notes: This table is based on a data cutoff of 2 Dec 2014 of NSCLC patients. ORR includes confirmed responses. "+" denotes a censored value.

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

The primary OS analysis in the POPLAR study was conducted when 173 deaths had occurred (clinical cutoff, 8 May 2015). Demographic characteristics were comparable between treatment arms in the intent-to-treat (ITT) population. The median age was 62 years (range: 42–82 years for the atezolizumab arm, range: 36–84 years for the docetaxel arm), and the majority of patients had one prior therapy (64.6% for

atezolizumab and 67.1% for docetaxel), non-squamous histology (66.0% for atezolizumab and 66.4% for docetaxel), and Eastern Cooperative Oncology Group (ECOG) performance status of 1 (67.6% for atezolizumab and 68.3% for docetaxel). More females were enrolled in the docetaxel arm (46.9% vs. 35.4%).

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

Table 6 Efficacy Results in the POPLAR Study: 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)	14.3	7.2
95% CI	11.6, NE	5.6, 12.5

NE = not estimable.

In summary, the data from the POPLAR study show that atezolizumab provides survival benefit in previously treated patients with NSCLC.

1.3.3.3 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 who were enrolled into 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 into 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 response rate in all three arms combined was 63% (26 of 41 patients).

Within each cohort, the ORR was 50% (95% CI: 16%, 84%) in Arm C (4 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. Careful attention was paid to the use of steroid premedication with pemetrexed in Arm A of this study because of the potential for steroids to hinder atezolizumab activity. Specifically, efforts to reduce prophylactic steroid use were successful without resulting in any significant increase in the incidence of rash, nausea, or other related toxicities (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 and the mean volume of distribution under steady-state conditions 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 in the 10-, 15-, and 20-mg/kg dose cohorts 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 or efficacy has been observed.

1.3.5 Rationale for Atezolizumab Dosage

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

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

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

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

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

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

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

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

downregulation of immune responses, including inhibition of T-cell activation and cytokine production (Butte et al. 2007; Yang et al. 2011).

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

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 GO29438 initiation, Study PCD4989g, a Phase Ia dose-escalation and expansion study of patients treated with atezolizumab as a single agent had the following clinical activity: 345 evaluable patients were dosed by 21 October 2013 (data cutoff date as of 21 April 2014) with a minimum of 6 months of follow-up; 62 patients experienced objective responses per RECIST v1.1 with an ORR of 18.0% (95% CI: 14.1%, 22.3%). Objective responses were observed across a broad range of malignancies, including NSCLC, RCC, melanoma, and UBC.

In addition, as explained above, the POPLAR study key efficacy results for the ITT population and the PD-L1−selected subgroup categories indicate that an OS benefit in the atezolizumab arm was observed, with a stratified HR of 0.78 (95% CI: 0.59, 1.03) even though PFS and ORR for the atezolizumab arm were similar to those for the docetaxel arm.

1.4.1 Rationale for Testing Atezolizumab in Combination with Carboplatin or Cisplatin and Pemetrexed

Platinum-based regimens remain the standard first-line option for patients with locally advanced or metastatic NSCLC that is 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% to 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 NSCLC patients will enable future tests of this hypothesis.

The combination of platinum-based doublet chemotherapy and atezolizumab in NSCLC was evaluated in the Phase Ib study GP28328 as detailed in Section 1.3.3.3. On the

basis of results observed in GP28328, Study GO29438 is designed to evaluate whether the anti-tumor effect seen in atezolizumab-treated patients would translate into statistically significant and clinically relevant improvement in PFS and OS when used in combination with carboplatin or cisplatin+pemetrexed compared with carboplatin or cisplatin+pemetrexed in patients with non-squamous NSCLC. This study will allow for the evaluation of the efficacy of atezolizumab in the ITT population.

This study 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 are excluded given that the appropriate and current standard-of-care treatments of these patients is with an *EGFR* tyrosine kinase or *ALK* inhibitor.

In order to account for the possibility of pseudoprogression and 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 and 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 NSCLC patients, in addition to platinum-based chemotherapy. 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

Unless stated otherwise, the following objectives will be assessed in patients who are chemotherapy-naive and have stage IV non-squamous NSCLC (the ITT population)

treated with atezolizumab + carboplatin or cisplatin + pemetrexed (Arm A) in comparison with carboplatin or cisplatin + pemetrexed (Arm B).

2.1 EFFICACY OBJECTIVES

2.1.1 Co-Primary Efficacy Objectives

The co-primary objectives of this study are:

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed PFS according to RECIST v1.1
- To evaluate the efficacy of atezolizumab as measured by OS

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives for this study are:

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed ORR according to RECIST v1.1
- To evaluate the efficacy of atezolizumab as measured by investigator-assessed DOR according to RECIST v1.1
- To evaluate the OS rate at 1 and 2 years
- 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 Organization for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire–Core 30 (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13)
- To determine the impact of atezolizumab as measured by *the change from baseline* in patient-reported lung cancer symptoms (chest pain, dyspnea, and cough) scores using the Symptoms in Lung Cancer (SILC) scale symptom severity scores

2.2 SAFETY OBJECTIVES

The safety objectives for this study are:

- To evaluate the safety and tolerability of atezolizumab when given in combination with carboplatin or cisplatin + pemetrexed or as maintenance therapy with pemetrexed alone
- 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:

- To characterize the pharmacokinetics of atezolizumab when given in combination with carboplatin or cisplatin + pemetrexed or pemetrexed alone

- To characterize the pharmacokinetics of carboplatin when given in combination with atezolizumab and pemetrexed
- To characterize the pharmacokinetics of cisplatin when given in combination with atezolizumab + pemetrexed
- To characterize the pharmacokinetics of pemetrexed when given in combination with atezolizumab + carboplatin or cisplatin

2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are:

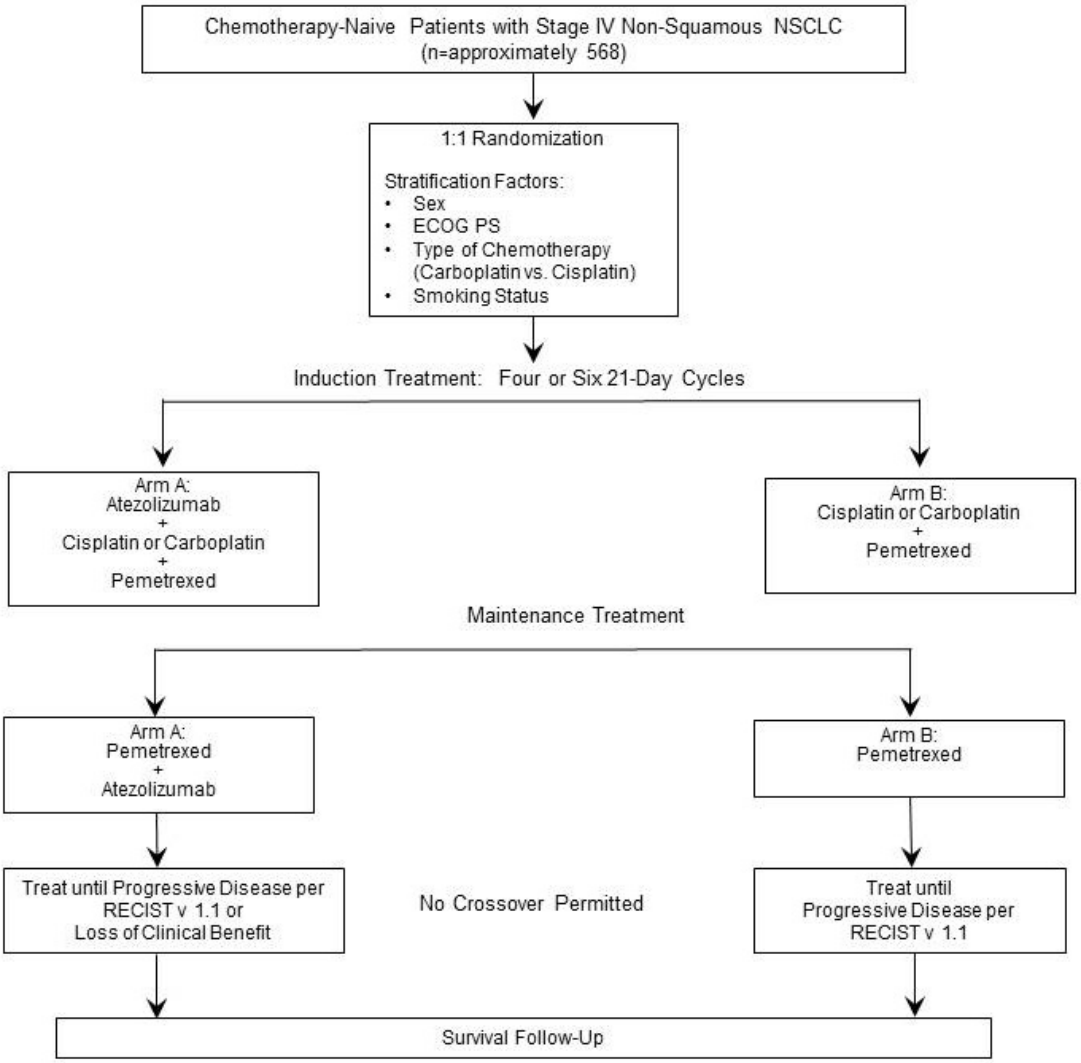
- *To evaluate the PFS rate at 6-month and 1-year landmark timepoints*
- To evaluate the OS rate at 3 years in each treatment arm
- *To evaluate the efficacy of atezolizumab as measured by OS and investigator-assessed PFS according to RECIST v1.1 in subgroups based on demographic and baseline characteristics*
- *To evaluate the efficacy of atezolizumab as measured by milestone survival*
- To evaluate the relationship between biomarkers in tumors and blood (including, but not limited to, PD-L1, PD-1, somatic mutations and others), as defined by immunohistochemistry (IHC), quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR), next-generation sequencing (NGS), and/or other methods and measures of efficacy
- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status, mechanisms of resistance, and/or response to study treatment
- To evaluate and compare patient's health status as assessed by the EuroQoL 5 Dimensions 5-Level (EQ-5D-5L) questionnaire to generate utility scores for use in economic models for reimbursement
- To determine the impact of atezolizumab in each of the treatment comparisons described in Section 2.1.1 as measured by change from baseline 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 QLQ-LC13

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a randomized, Phase III, multicenter, open-label study (IMpower 132) designed to evaluate the safety and efficacy of atezolizumab in combination with cisplatin or carboplatin + pemetrexed compared with treatment with cisplatin or carboplatin + pemetrexed in patients who are chemotherapy-naive and have Stage IV non-squamous NSCLC. Figure 1 illustrates the study design. Schedules of assessments are provided in Appendix 1 and Appendix 2.

Figure 1 Study Schema



ECOG PS=Eastern Cooperative Oncology Group performance status; NSCLC=non–small cell lung cancer; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1.

Eligible patients will be stratified by sex (male vs. female), smoking status (never vs. current and/or former), ECOG performance status (0 vs. 1) and chemotherapy regimen (carboplatin vs. cisplatin) and randomized by a 1:1 ratio to receive one of the following treatment regimens as shown in Table 7.

Table 7 Study GO29438 Treatment Arms

Treatment Arm	Induction (Four or Six 21-Day Cycles)	Maintenance (21-Day Cycles)
A	Atezolizumab + carboplatin or cisplatin + pemetrexed	Atezolizumab + pemetrexed
B	Carboplatin or cisplatin + pemetrexed	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 the following occurs (whichever occurs first): 1) administration of four or six cycles, 2) unacceptable toxicity, or 3) documented disease progression.

Following the induction phase, patients who have not experienced disease progression or unacceptable toxicity will continue treatment with maintenance therapy as shown in Table 7. Patients randomized to either Arm A or B will continue treatment with pemetrexed maintenance until progressive disease, unacceptable toxicity, or death. During induction or maintenance treatment, patients randomized to Arm A may continue treatment with atezolizumab beyond progressive disease by RECIST v1.1, provided they are experiencing clinical benefit as assessed by the investigator as described below:

For Treatment Arm A

During treatment (induction or maintenance), patients who show evidence of clinical benefit will be permitted to continue atezolizumab after RECIST v1.1 for progressive disease are met if they meet all of the following criteria:

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

Treatment with chemotherapy (both in Arm A and B) should be discontinued in all patients who exhibit evidence of progressive disease by 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 the completion of the Week 48 tumor assessment, tumor assessment will be required every 9 weeks. Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab-treated only 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 (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.

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.*

This study will initially enroll approximately 568 patients across all sites in a global enrollment phase. [redacted].

3.1.1 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will be used to evaluate safety *data when* a minimum of 12 patients receiving cisplatin-based chemotherapy have been enrolled into each treatment arm with a minimum follow-up of approximately 60 days*, and then* approximately every 6 months *thereafter until the study is unblinded for primary efficacy analyses or the study is terminated by the Sponsor.*

The Sponsor will remain blinded to the efficacy results until the final PFS analysis. All summaries and analyses by treatment arm for the iDMC review will be prepared by an external independent Data Coordinating Center (iDCC). *The safety data will include disposition, demographic data, adverse event data (e.g. serious adverse events and adverse events of special interest), study conduct data, and relevant laboratory data. Efficacy data (excluding data on deaths) will not be included in the iDMC safety data reviews.* Following the *safety* data 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.

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 (IRBs) and Ethics Committees (ECs).

3.2 END OF STUDY AND LENGTH OF STUDY

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

- *The required number of deaths for the final analysis of OS has been observed among patients enrolled during the global enrollment phase (see Section 6.8.1)*
- [redacted] *(see Section 6.9)*
- *The last patient has been enrolled in the study (i.e., global enrollment phase* [redacted]

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

3.3 RATIONALE FOR STUDY DESIGN

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

Despite recent improvements in treatment, the prognosis for patients with advanced NSCLC remains dismal, with a median OS of approximately 12.3 months (Sandler et al. 2006). Patients who receive second-line treatment for their disease have an even more limited prognosis, with a median survival duration of approximately 8–9 months (Stinchcombe et al. 2008). Approved therapies are associated with significant toxicities (e.g., neuropathy, febrile neutropenia, myelosuppression, and alopecia) that negatively affect 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 in several tumor types (including NSCLC) correlates with response to therapy (Topalian et al. 2012).

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 patients with squamous and non-squamous disease, OS was 10.1 versus 8.6 months (HR=0.80, 95% CI: 0.49, 1.30) and 15.5 versus 10.9 months (HR=0.69, 95% CI: 0.47, 1.01), respectively, in the atezolizumab arm compared with the docetaxel arm (Fehrenbacher et al. 2016).

On the basis of promising efficacy activity of atezolizumab as a single agent (POPLAR, Study PCD4989g) and in combination with platinum-doublet therapy (Study GP28328) and the safety findings from Study GP28328 indicating no additive toxicity of atezolizumab in combination with platinum-based chemotherapy or bevacizumab, this study will evaluate atezolizumab in combination with platinum-based chemotherapy. 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

A common standard of care in first-line treatment for advanced stage non-squamous NSCLC is a platinum doublet with either cisplatin or carboplatin and pemetrexed. In this study, all patients in the experimental arm will receive the platinum doublet of carboplatin or cisplatin with pemetrexed with atezolizumab followed by maintenance pemetrexed+atezolizumab. The control group will receive the combination of carboplatin or cisplatin+pemetrexed followed by pemetrexed maintenance. This control group is recognized as a standard of care for the first-line treatment of non-squamous NSCLC based on the results of the two previous Phase III studies as stated above and is the most commonly used first-line regimen in the United States and Europe (see Section 1.1).

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, 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 co-primary endpoints, 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 co-primary endpoints prior to study start, including predefined methods for handling missing data and censoring rules. Final efficacy analyses will only be performed at the prespecified analysis timepoints in the protocol.

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

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 POPLAR study in patients with advanced NSCLC, an OS benefit in the atezolizumab arm compared with the docetaxel arm was observed, with a stratified HR of 0.73 (95% CI: 0.53, 0.99) (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 therapies and/or palliative care (Temel et al. 2010), the OS analysis may be confounded (Miller et al. 2012). Therefore, investigator-assessed PFS is being retained as a co-primary endpoint, and crossover from the control arm to the experimental arm 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; in addition, its determination is not generally confounded by subsequent therapies. Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the benefit-risk of the new treatment compared with available therapies (Guidance for Industry 2007; European Medicines Agency 2012). To ensure the validity of investigator-assessed PFS as a co-primary endpoint, a number of measures have been implemented: a substantial, clinically meaningful target magnitude of benefit (target HR of 0.65 in the ITT 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 or 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 and/or 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 and tumor-immune infiltration, this study will allow patients randomized to the atezolizumab treatment arms to remain on atezolizumab after apparent radiographic progression, provided the benefit-risk ratio is judged to be favorable. Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status (see Section 3.1).

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 effects on HRQoL (Hyde and Hyde 1974; Hopwood and Stephens 1995; Sarna et al. 2004). This is especially true for studies that use PFS as a primary endpoint, where it is important to better understand in what regard the delay in disease progression is meaningful to patients.

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

In addition, the SILC scale will be used to assess the effect and impact of atezolizumab *as measured by the change from baseline in patient-reported* specific lung cancer symptoms (chest pain, dyspnea, and cough) in patients with Stage IV, non-squamous NSCLC in the first-line setting.

The EQ-5D-5L (see Appendix 9) is included in the study to generate utility scores for use in economic models for reimbursement. Results from the EQ-5D-5L are not planned to be used for market authorization.

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

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 therapy (Topalian et al. 2012). This correlation was also observed with atezolizumab in Study PCD4989g (Herbst et al. 2014; Horn et al. 2015), and the FIR (Spiegel et al. 2015), BIRCH (Study GO28754) (Besse et al. 2015), and POPLAR (Fehrenbacher et al. 2016) studies. In this study, although tumor tissues are not required for enrollment, baseline archival and/or fresh tumor specimens from patients will be obtained if available and may be tested (retrospectively) for PD-L1 expression by a central laboratory.

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

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

3.4.1.1 Co-Primary Efficacy Outcome Measures

The primary efficacy outcome measures for this study are:

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the randomization date plus 1 day.
- OS, defined as the time from randomization to death from any cause

3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are:

- Objective response, defined as PR or CR as determined by the investigator according to RECIST v1.1
- DOR, defined as the time interval from first occurrence of a documented objective response to the time of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever comes first
- OS at 1- and 2-year *landmark timepoints*
- 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
- *Change from baseline* in patient-reported lung cancer symptoms (cough, dyspnea, or chest pain) with use of the SILC scale symptom score

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are:

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

3.4.3 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are the following:

- Maximum observed serum atezolizumab concentration (C_{max}) after infusion (Arm A)
- 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 (Arm A)
- Plasma concentrations for carboplatin or cisplatin (Arm A)
- Plasma concentrations for pemetrexed (Arm A)

See Appendix 2 for specific sample collection times.

3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are:

- PFS at 6-month and 1-year *landmark timepoints*
- OS rate at 3-year *landmark timepoint*
- *Milestone survival*

- *OS and investigator-assessed PFS according to RECIST v1.1 in subgroups based on demographic and baseline characteristics*
- Status of PD-L1–, immune- and NSCLC-related and other exploratory biomarkers in archival and/or fresh 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
- Utility scores of the EQ-5D-5L
- Change from baseline in PROs of HRQoL, lung cancer–related symptoms, and health status as assessed by the EORTC QLQ-C30 and QLQ-LC13

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients may be eligible if they are chemotherapy-naive and have Stage IV, non-squamous NSCLC. Approximately 568 patients will be enrolled during the global enrollment phase of the study. [redacted]

4.1.1 Inclusion Criteria

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

- Signed Informed Consent Form
- Male or female, 18 years of age or older
- ECOG performance status of 0 or 1 (see Appendix 10)
- Histologically or cytologically confirmed, Stage IV non-squamous NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 7th edition; Detterbeck et al. 2009; see Appendix 3)

  Patients with tumors of mixed non-small cell 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 are excluded given that erlotinib, gefitinib, or another *EGFR* TKI is the appropriate initial treatment of *EGFR*-mutant NSCLC.

  Patients with an *ALK* fusion oncogene are excluded given that crizotinib or other *ALK* inhibitors is the appropriate initial 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 at a local or 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 dose of chemotherapy and/or radiotherapy
- 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.
- Patients should submit a pre-treatment tumor tissue sample (if available). If tumor tissue is not available (e.g., depleted for prior diagnostic testing), patients are still eligible.

  If tumor tissue is available, a representative formalin-fixed paraffin-embedded (FFPE) tumor specimen in paraffin block or unstained, freshly cut, serial sections (preferably at least 10) from an FFPE tumor specimen are preferred. If 10 sections are not available, fewer can be submitted.

  If FFPE specimens described above are not available, any type of specimens (including fine-needle aspiration, cell pellet specimens [e.g., from pleural effusion], and lavage samples) are also acceptable.

  This specimen should be accompanied by the associated pathology report. See Section 4.5.7.1 for further details.

  Any available tumor tissue sample should be submitted before or within 4 weeks after enrollment.
- 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 receiving 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.

Calculated creatinine clearance (CRCL) $\geq$45 mL/min or, if using cisplatin, calculated CRCL must be $\geq$60 mL/min

- [redacted]
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<$1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab or 6 months after the last dose of cisplatin.

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

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

  With partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<$1% per year during the chemotherapy treatment period and for at least 6 months after the last dose of chemotherapy.

With pregnant partners, men must remain abstinent or use a condom during the chemotherapy treatment period and for at least 6 months after the last dose of chemotherapy.

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

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

- Patients with a sensitizing mutation in the *EGFR* gene or an *ALK* fusion oncogene
- Active or untreated CNS metastases as determined by CT or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments
- Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥2 weeks prior to randomization
- Leptomeningeal disease
- Uncontrolled tumor-related pain

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

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

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

  Patients who are receiving denosumab prior to randomization must be willing and eligible to discontinue its use and replace it with a bisphosphonate instead while in the study.
- Malignancies other than NSCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS >90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous-cell skin cancer, localized

prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)

- 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 granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 12 for a comprehensive list of autoimmune diseases)

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

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

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

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

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

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

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

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

- Positive test for HIV

    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 hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

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

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

  Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to randomization, unstable arrhythmias, or unstable angina

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction $<$50% must be receiving 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 may interfere with a patient's capacity to understand, follow, and/or comply with study procedures

4.1.2.3 Exclusion Criteria Related to Medications

- Prior treatment with *EGFR* inhibitors or *ALK* inhibitors
- Any approved anti-cancer therapy, including hormonal therapy within 21 days prior to initiation of study treatment.
- 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 antigen 4 (CTLA-4) treatment may be enrolled, provided the following requirements are met:

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

  No history of severe immune-related adverse effects from anti-CTLA-4 (NCI CTCAE Grade 3 and 4)

- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons, interleukin 2) within 4 weeks or 5 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 are allowed.

4.1.2.4 Exclusion Criteria Related to Chemotherapy

- History of allergic reactions to cisplatin, carboplatin, or other platinum-containing compounds
- Patients with hearing impairment (cisplatin)
- Grade ≥2 peripheral neuropathy as defined by NCI CTCAE v4.0 (cisplatin)
- CRCL <60 mL/min for cisplatin or <45 mL/min for carboplatin

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study.

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

Randomization to one of the two treatment arms
(carboplatin/cisplatin+pemetrexed+atezolizumab or carboplatin/cisplatin+pemetrexed)

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

- Sex (male vs. female)
- Smoking status (never vs. current or former)
- ECOG performance status (0 vs. 1)
- Chemotherapy (cisplatin vs. carboplatin)

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 business days after randomization.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab

The atezolizumab drug product is provided as a sterile liquid in 20-mL glass vials. 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 or Cisplatin+Pemetrexed

The comparator arm includes a platinum-based regimen (carboplatin or cisplatin based on investigator's choice)+pemetrexed. This study will randomize approximately 568 patients in the global enrollment phase.

[redacted]

Each study drug will be used in the commercially available formulation (with the exception of atezolizumab) and will be provided by the Sponsor if it is considered an investigational medical oroduct (IMP) by local regulations (see Section 4.3.3).

For information on the formulation, packaging, and handling of cisplatin, carboplatin, and pemetrexed, see the local prescribing information for each drug.

4.3.2 Dosage, Administration, and Compliance

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

Arm A: Atezolizumab → [carboplatin or cisplatin + pemetrexed]

Arm B: [carboplatin or cisplatin + pemetrexed]

During the induction phase, a chemotherapy cycle counts toward the prespecified number of induction chemotherapy cycles (4 or 6) 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 14.

Patients who experience no further clinical benefit (for patients enrolled into Arm A, see Section 3.1 for definition) or disease progression (for patients enrolled into 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 will begin maintenance therapy (atezolizumab + pemetrexed in Arm A or pemetrexed in Arm B).

During treatment (induction or maintenance), Arm A patients 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. However, treatment with chemotherapy should be discontinued.

Patients should receive anti-emetics and IV hydration for platinum-pemetrexed treatments according to the local standard of care and manufacturer's instruction. However, due to their immunomodulatory effects, premedication with steroids should be limited when clinically feasible. In addition, in the event of pemetrexed-related skin rash, topical steroid use is recommended as front-line treatment whenever is clinically feasible. Table 8 lists the premedication for pemetrexed. Table 9 lists the suggested infusion times for treatment administration for pemetrexed + platinum during the induction and maintenance phases.

Table 8 Premedication for Pemetrexed

Premedication	Dose and Route	Timing
Folic acid	350–1000 μg PO	Once daily beginning at least 5–7 days before Cycle 1, Day 1 and continuing until 3 weeks after discontinuation of pemetrexed
Vitamin B_{12}	1000 μg IM	q9w beginning Cycle 1, Day 1 and continuing until 3 weeks after discontinuation of pemetrexed
Dexamethasone (suggested)	4 mg PO	Twice daily the day before, the day of, and the day after pemetrexed administration

IM = intramuscular; PO = oral; q9w = every 9 weeks.

Table 9 Treatment Regimen for Pemetrexed + Platinum-Based Chemotherapy

Study Drug	Dose and Route	Induction Period (Four or Six Cycles)	Maintenance Period (Until PD)
Pemetrexed	500 mg/m² IV	Over approximately10 minutes on Day 1 q3w	Over approximately 10 minutes on Day 1 q3w
Carboplatin	AUC 6 IV	Over approximately 30–60 minutes on Day 1 q3W	Not applicable
		OR	
Cisplatin	75 mg/m²	Over 1–2 hours on Day 1 q3w	Not applicable

AUC = area under the concentration–time curve; IV = intravenous; PD = progressive disease; q3w = every 3 weeks.

Guidelines for dose modification and treatment interruption or discontinuation for carboplatin or cisplatin and pemetrexed are provided in Section 5.1.6.1, Section 5.1.8, 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 and 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 minutes before starting infusion. • Infuse atezolizumab (1200 mg in a 250 mL 0.9% NaCl IV bag) over 60 (± 15) minutes. • If clinically indicated, record patient's vital signs (*pulse* rate, respiratory rate, blood pressure, and temperature) during the infusion at 15, 30, 45, and 60 minutes (±5-minute windows are allowed for all timepoints). • If clinically indicated, record patient's vital signs (*pulse* rate, respiratory rate, blood pressure, and temperature) at 30 (±10) minutes after the infusion. • Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If patient experienced infusion-related reaction during any previous infusion, premedication with antihistamines may be administered for Cycles ≥2 at the discretion of the treating physician. • Record patient's vital signs (*pulse* rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • If the patient tolerated the first infusion well without infusion-associated adverse events, the second infusion may be delivered over 30 (±10) minutes. • 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) minutes. Record patient's vital signs (*pulse* rate, respiratory rate, blood pressure, and temperature) every 15 (±5) minutes during the infusion if clinically indicated or patient experienced symptoms during the previous infusion. Record patient's vital signs (*pulse* rate, respiratory rate, blood pressure, and temperature) 30 (±10) minutes after the infusion if clinically indicated or patient experienced symptoms during the previous infusion.

IV = intravenous; NaCl = sodium chloride.

Dose modifications to atezolizumab are not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events are provided in Section 5.1.6.2 *and Appendix 15.*

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

4.3.2.2 Pemetrexed + Carboplatin or Cisplatin

4.3.2.2.1 Pemetrexed

Institutions should follow their standard administration procedures for pemetrexed. The premedication doses administered should be in compliance with the prescribing information. All patients eligible for pemetrexed therapy should avoid taking non-steroidal anti-inflammatory drugs with long elimination half-lives for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration.

4.3.2.2.2 Cisplatin

IV infusion should be administered approximately 30 minutes after completion of the pemetrexed infusion at a dose of 75 mg/m² over 1–2 hours or per standard of care at the institution. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and after receiving cisplatin.

Refer to local clinical practice guidelines for further details.

4.3.2.2.3 Carboplatin

Carboplatin should be administered 30 minutes after completion of pemetrexed administration by IV infusion over 30–60 minutes to achieve an initial target area under the concentration–time curve (AUC) of 6 mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines.

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

Calvert Formula

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

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

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

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

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

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

If a patient's GFR is estimated based on serum creatinine measurements by the isotope dilution mass spectroscopy method, the U.S. Food and Drug Administration (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 150 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 at the following Web site for more details:

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

4.3.3 Investigational Medicinal Product Accountability

The investigational medicinal products for this study are atezolizumab and pemetrexed. Depending on local classification, in this study, cisplatin and carboplatin may either be considered a non−investigational medicinal product or an IMP.

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

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

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

4.3.4 Post-Study Access to Atezolizumab

The Sponsor will evaluate the appropriateness of continuing to provide atezolizumab to patients assigned to this treatment after evaluating the primary and secondary efficacy outcome measures and safety data gathered in the study and in accordance with the

Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

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

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

4.4 CONCOMITANT THERAPY

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

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
- Megestrol administered as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)
- Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency

In general, investigators should manage a patient's care with supportive therapies as clinically indicated per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H_2-receptor antagonist per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or

respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 11).

All medications must be recorded on the appropriate Concomitant Medications electronic Case Report Form (eCRF).

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

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

Systemic corticosteroids are recommended, with caution at the discretion of the treating physician, for the treatment of specific adverse events when associated with atezolizumab therapy. Guidelines for the management of immune-related adverse events are described in Section 5.1.6.2 *and Appendix 15.*

4.4.3 Prohibited Therapy

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

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

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

The concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, their use for patients in the study is allowed at the discretion of the investigator provided that there are no known interactions with any study treatment. As noted above, herbal therapies intended for the treatment of cancer are prohibited.

4.5 STUDY ASSESSMENTS

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

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

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

4.5.1 Informed Consent Forms and Screening Log

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

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

Patients who are treated with atezolizumab and who show apparent radiographic progression at a tumor response evaluation must sign consent to acknowledge deferring other treatment options before continuing treatment with atezolizumab beyond apparent radiographic progression.

4.5.2 Medical History and Demographic Data

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

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

central evaluation of the mutational status of these genes. Review tissue requirements for central evaluation in the central laboratory instruction manual.

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

4.5.3 Physical Examinations

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

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

4.5.4 Vital Signs

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

Vital signs will be measured and recorded *at screening and* 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 atezolizumab infusion (every 15 [±5] minutes) if clinically indicated • Within 30 (±10) minutes after atezolizumab infusion if clinically indicated
Arms A and B	Within 30 (±10) minutes after carboplatin or cisplatin infusion
	Subsequent Cycles
Treatment Arm	Timepoints
Arm A	• Within 60 minutes prior to atezolizumab infusion • During the atezolizumab infusion (every 15 [±5] minutes) if clinically indicated or symptoms occurred during prior infusion • Within 30 (±10) minutes after atezolizumab infusion if clinically indicated or symptoms occurred during prior infusion

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

4.5.5 Tumor and Response Evaluations

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

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

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

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

Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1, may be used rather than repeating tests. All known sites of disease must be documented at screening and re assessed at each subsequent tumor evaluation. *Patients with history of irradiated brain metastases at screening are not required to undergo imaging brain scans at subsequent tumor evaluations, unless scans are clinically indicated.* The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Response will be assessed by the investigator using RECIST v1.1 (see Appendix 4) and modified RECIST (see Appendix 5) for patients in Arm A and RECIST v1.1 in 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) thereafter, after the completion of the Week 48 tumor assessment, regardless of treatment delays, until radiographic disease progression per RECIST v1.1 (loss of clinical benefit for atezolizumab-treated patients who continue treatment beyond disease progression according to RECIST v1.1 only), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Patients who discontinue treatment for reasons other than radiographic disease progression per RECISTv1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1

(or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by Sponsor, whichever occurs first.

Patients who start a new anti-cancer therapy in the absence of radiographic disease progression per RECIST v1.1 will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1(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 are treated with atezolizumab who continue 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 at Day 1 of each cycle during treatment prior to administration of study treatment. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

  Childbearing potential is defined as not having undergone surgical sterilization, hysterectomy, 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, free T3, free T4)

  Total T3 (instead of free T3) will be tested only at sites where free T3 testing cannot be performed.

- HBV serology: HBsAg, antibodies against HBsAg (HBsAb or anti-HBs), and hepatitis B core antibody (HBcAb)

  If the patient has a negative serology for HBsAg and a positive serology for HBcAb, an HBV DNA test must be obtained prior to randomization and must be negative.

- HCV serology: HCV antibody (anti-HCV)

  If the patient tests positive for anti-HCV, an HCV RNA must be obtained prior to randomization and be negative.

- HIV testing

  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.

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

- ATA assays (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.

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

  At selected sites, a subset of 20 patients in Arm A will undergo additional PK assessments for carboplatin, cisplatin, and pemetrexed.

    Plasma carboplatin, cisplatin, and pemetrexed concentrations will be assayed using validated methods.

- Biomarker assays in blood samples

  Blood samples will be obtained for biomarker evaluation (including, but not limited to, biomarkers that are related to NSCLC or tumor immune biology) from all eligible patients according to the schedule in Appendix 2. Samples will be processed to obtain EDTA 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).

Residual PK and ATA samples will be retained for further method development, validation, and characterization. Samples will be stored for up to 5 years after the date of final completion of the Clinical Study Report.

- 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 or Freshly Collected Tumor Tissue Samples at Screening

A pre-treatment tumor tissue (archival or freshly obtained) sample (if available) should be submitted before or within 4 weeks after enrollment. This specimen must be accompanied by the associated pathology report. Although any available tumor tissue sample can be submitted, it is strongly encouraged that the sites submit representative tumor specimens in paraffin blocks (preferred) or 10 (or more) serial, freshly cut, unstained slides exploratory biomarker analysis (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).

The preferred sample types include resections, core needle, excisional, incisional, punch, or forceps biopsies. If specimens described above are not available, any type of specimens (including fine-needle aspiration, cell pellet specimens e.g., from pleural effusion, and lavage samples) are also acceptable.

Tumor tissue should be of good quality based on total and viable tumor content. Tumor tissue from bone metastases that is subject to decalcification is not advisable. If tumor tissue is not available, the patient is still eligible.

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

4.5.7.2 Optional Tumor Samples at the Time of Radiographic Progression

Patients in all treatment arms can undergo an optional tumor biopsy to obtain a tumor sample at the time of radiographic disease progression (preferably within 40 days of radiographic progression or prior to start of the next anti-cancer treatment, whichever is sooner) if they have provided consent for Optional Biopsy.

The preferred sample types include resections, core needle, excisional, incisional, punch, or forceps biopsies. If such specimens are not available, any type of specimens including fine-needle aspiration, cell pellet specimens (e.g., from pleural effusion and lavage samples) can also be submitted.

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

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

4.5.7.3 Tumor Samples at Other Timepoints

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

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

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

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

4.5.8 Anti-Therapeutic Antibody Testing

Treatment with atezolizumab may elicit an immune response. Patients with signs of any potential immune response to atezolizumab will be closely monitored. Validated

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

4.5.9 Electrocardiograms

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

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

4.5.10 Patient-Reported Outcomes

PRO data will be collected via the EORTC QLQ-C30, EORTC QLQ-LC13, SILC, and EQ-5D-5L to 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 instructions for completing the PRO questionnaires electronically will be provided by the investigator staff. The data will be transmitted via a prespecified transmission method (e.g., Web or wireless) automatically after entry to a centralized database at the ePRO vendor. The data can be accessed by appropriate study personnel securely via the internet.

The EORTC QLQ-C30 (see Appendix 7) is a validated and reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) that consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health and quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scale scores can be obtained for the multi-item scales.

The EORTC QLQ-C30 module takes approximately 15 minutes to complete. This questionnaire will be completed on the ePRO tablet at each scheduled study visit during study treatment and during survival follow-up at 3 months and 6 months following disease progression or loss of clinical benefit (for atezolizumab-treated patients who continue treatment after radiographic disease progression according to RECIST v1.1).

The EORTC QLQ-LC13 (see Appendix 8) module incorporates one multiple-item scale to assess dyspnea and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. The EORTC QLQ-LC13 module takes approximately 15 minutes to complete. This questionnaire will be completed on the ePRO tablet at each scheduled study visit during the study treatment period and during survival follow-up at 3 months and 6 months following disease or loss of clinical benefit (for atezolizumab-treated patients who continued treatment after disease progression according to RECIST v1.1).

The SILC scale (see Appendix 13) 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 continue treatment after disease progression according to RECIST v1.1).

The EQ-5D-5L is a generic, preference-based health utility measure with questions about mobility, self-care, usual activities, pain and discomfort, and anxiety and depression that is used to build a composite of the patient's health status (see Appendix 9). The EQ-5D-5L will be used in this study for economic modeling. This questionnaire will be completed on the ePRO tablet at each scheduled study visit during the study treatment period and during survival follow-up at 3 months and 6 months following disease progression or loss of clinical benefit (for atezolizumab-treated patients who continued treatment after disease progression according to RECIST v1.1).

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

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

4.5.11 Samples for Roche Clinical Repository

4.5.11.1 Overview of the Roche Clinical Repository

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

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

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

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's IRB or 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 or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

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

4.5.11.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the study is closed. A patient's withdrawal from Study GO29438 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 GO29438.

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 <u>Timing of Assessments</u>

4.5.12.1 Screening and Baseline Assessments

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

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

4.5.12.2 Assessments during Treatment

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

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

After completion of the induction phase, one of three cycles may be delayed by 1 week (28 days instead of 21 days for one cycle) to allow for vacations or 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 completion of the Week 48 tumor assessment, regardless of treatment delays until radiographic disease progression per RECIST v1.1 or loss of clinical benefit for patients in Arm A who continue treatment 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 per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) and patients who start non-protocol anti-cancer therapy in the absence of radiographic disease progressin per RECIST v1.1 will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by Sponsor, whichever occurs first.*

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

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

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

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

4.5.12.3 Assessments at Study Drug Discontinuation Visit

When a patient discontinues all study treatment, regardless of the reason for discontinuation, the patient will be asked to return to the clinic within 30 days after the treatment for a study drug discontinuation visit. The visit at which the decision is made to discontinue treatment (e.g., loss of clinical benefit is confirmed [atezolizumab-treated patients who continued treatment after disease progression according to RECIST v1.1] or disease progression occurs) may be used as the study drug discontinuation visit.

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

4.5.12.4 Follow-Up Assessments

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

For patients who discontinue study treatment for any reason other than radiographic progressive disease per 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 per RECIST v1.1 (or loss of clinical benefit for patients treated with atezolizumab who continued treatment 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 per RECIST v1.1 should continue tumor assessments according to the protocol schedule of response assessments until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Follow-up data collection will also include ePROs (the SILC will be completed monthly only for the first 6 months after disease progression or loss of clinical benefit (for atezolizumab-treated patients) using an ePRO device at the patient's home.

EORTC QLQ-C30, EORTC QLQ-LC13, and the EQ-5D-5L 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 to record 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 *radiographic* progressive disease or loss of clinical benefit will complete the EORTC QLQ-C30,

EORTC QLQ-LC13, and EQ-5D-5L at each tumor assessment visit and will complete the SILC at home on a weekly basis, until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit as determined by the investigator for atezolizumab-treated patients who continue treatment after radiographic disease progression), withdrawal of consent ,*death, loss to follow-up, termination of* the study *by the Sponsor, whichever occurs first*.

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

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

4.5.12.5 Assessments at Unplanned Visits

Assessments for unscheduled visits related to a patient's underlying NSCLC, study drug, or adverse event should be performed as clinically indicated and entered 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 up 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-related adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Intolerable toxicity related to other components of study treatment
- If one component of study treatment is discontinued permanently 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 per RECIST v1.1

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

  Evidence of clinical benefit as assessed by the investigator

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

  No decline in ECOG performance status

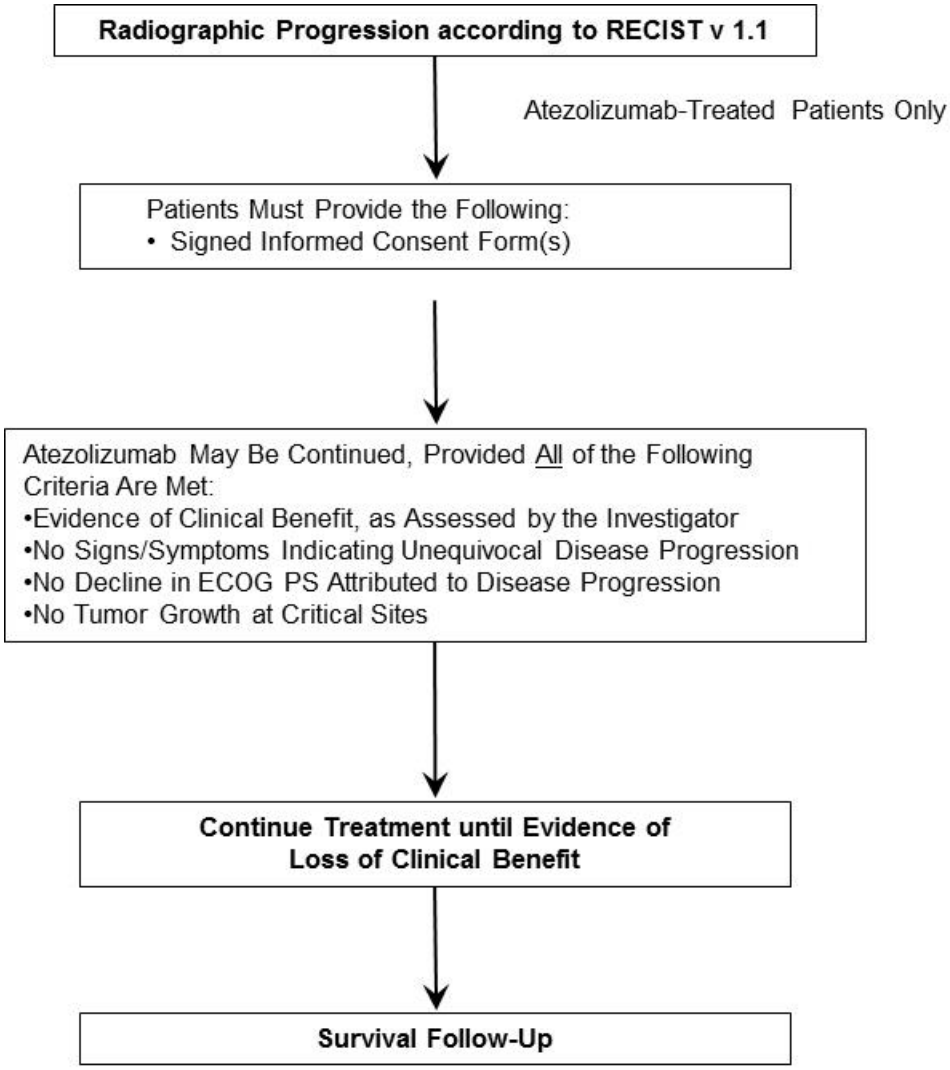
  Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing

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

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

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

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



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

4.6.3 Study and Site Discontinuation

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

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

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

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference 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

Atezolizumab is approved in the United States for the treatment of locally advanced or metastatic urothelial carcinoma. Human experience is currently limited and the entire safety profile is not known at this time. 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 or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. All other adverse events will be recorded during the study and for up to 30 days after the last dose of study treatment or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. *After the adverse event reporting period, all deaths should continue to be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment (see Section 5.6 for reporting instructions). These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and e-mailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or e-mail address provided to investigators.*

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections *and in Appendix 15*.

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-related 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-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo et al. 2010). Suggested workup and management guidelines procedures for suspected immune-related adverse events are provided in Section 5.1.6.2 and in *Appendix 15*.

5.1.2 Risks Associated with Pemetrexed Administration

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, see the prescribing information for pemetrexed.

5.1.3 Risks Associated with Carboplatin

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

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

5.1.4 Risks Associated with Cisplatin Chemotherapy

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

For more details regarding the safety profile of cisplatin, see the prescribing information for cisplatin.

5.1.5 General Plan to Manage Safety Concerns

5.1.5.1 Monitoring

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

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

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

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

Patients will be followed for adverse events (including deaths, serious adverse events, and adverse events of special interest) during and after the adverse event reporting period as described in Sections 5.3.1, 5.3.5.7, 5.5 and Section 5.6.

5.1.6 Dose Modification

5.1.6.1 General Notes Regarding Dose Modification

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

- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and treated as Grade 1 toxicity for dose-modification purposes.
- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment (i.e., atezolizumab, carboplatin, or cisplatin and/or pemetrexed if applicable) 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 or cisplatin and/or pemetrexed (if applicable), the treatment cycles will be restarted such that the atezolizumab (if applicable) infusions remain synchronized and aligned with the chemotherapy schedule.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one chemotherapy drug, the dose of the other chemotherapy drug does not require modification.
- The investigator may use discretion in modifying or accelerating the dose modification guidelines described below depending on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing patient compliance and access to supportive care.

5.1.6.2 Atezolizumab Dose Modification and Management of Specific Adverse Events

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment 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 up for safety and efficacy as specified in Section 5.2.1.

If, in the judgment of the investigator, the patient is likely to derive clinical benefit from atezolizumab after a hold beyond 105 days, study drug may be restarted with the approval of the Medical Monitor.

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) $\leq$10 mg/day. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

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

Management of systemic immune activation is presented below. Refer to *Appendix 15* for details on management of infusion-related reactions, gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, pancreatic toxicity, neurologic toxicity, or potential eye toxicity, and other immune-related adverse events.

Refer to Appendix 11 for precautions for anaphylaxis.

5.1.7 Systemic Immune Activation

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

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

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

5.1.8 Pemetrexed Dose Modification and Management of Specific Adverse Events

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

Treatment with pemetrexed should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after two dose reductions or if treatment is delayed for more than 63 days due to toxicities (see Table 13).

Hematologic Toxicity

At the start of each cycle, the ANC must be ≥1500/μLand the platelet count must be ≥100,000/μL. Treatment should be delayed for up to 63 days to allow sufficient time for recovery. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines (Smith et al. 2006; NCCN 2012). Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest (nadir) platelet and neutrophil values from the previous cycle (see Table 12).

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

Table 12 Pemetrexed Dose Modification for Hematologic Toxicities

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

[a] Nadir of prior cycle.

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

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

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

Non-Hematologic Toxicity

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

If a patient develops a non-hematologic toxicity (Table 13), pemetrexed should be withheld for up to 63 days until resolution to equal or less than the patient's baseline (or Grade $\leq$1 if patient did not have that toxicity at baseline). Treatment should be resumed according to the guidelines in Table 13. For a Grade 3 or 4 neurotoxicity, pemetrexed should be resumed at 50% of the previous dose upon improvement, or discontinued immediately (based on investigator's clinical judgment).

Table 13 Pemetrexed Dose Modification for Non-Hematologic Toxicities

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

Treatment Delays Caused by Insufficient Folic Acid or Vitamin B12 Supplementation

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

- The patient has taken folic acid for at least 5 days immediately preceding the first dose of pemetrexed, and
- The patient has received a vitamin B_{12} injection (which can be given on Cycle 1, Day 1)

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

For more details regarding pemetrexed dose modification, see the prescribing information for pemetrexed.

5.1.9 Platinum Chemotherapy Dose Modification and Management of Specific Adverse Events

5.1.9.1 Cisplatin

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

Hematologic Toxicity

At the start of each cycle, the ANC must be ≥ 1500/μL and the platelet count must be ≥ 100,000/μL. Treatment should be delayed for up to 63 days to allow sufficient time for recovery. Growth factors may be used in accordance with ASCO and NCCN guidelines (Smith et al. 2006; NCCN 2012). Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest platelet and neutrophil values from the previous cycle (see Table 14).

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

Table 14 Cisplatin Dose Modification for Hematologic Toxicities

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

[a] Nadir of prior cycle.

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

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

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

Non-Hematologic Toxicity

If a patient develops a non-hematologic toxicity (see Table 15) cisplatin should be withheld for up to 63 days until resolution to equal or less than the patient's baseline (or Grade ≤1 if patient did not have that toxicity at baseline). Treatment should be resumed according to the guidelines in Table 15.

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

Table 15 Cisplatin Dose Modification for Non-Hematologic Toxicities (Excluding Neurotoxicity)

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

[a] Despite the use of anti-emetics.

Nephrotoxicity

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

Neurotoxicity

In the event of neurotoxicity, the recommended dose adjustment for cisplatin is documented in Table 16. For a Grade 3 or 4 neurotoxicity, cisplatin should be resumed at 50% of the previous dose upon improvement or discontinued immediately (based on investigator's clinical judgment).

Table 16 Cisplatin Dose Modification for Associated Neurotoxicity

Toxicity	Cisplatin Dose
Grade 0–1 neurotoxicity	100% of previous dose
Grade 2 neurotoxicity	75% of previous dose
Grade 3 or 4 neurotoxicity	50% of previous dose or permanent discontinuation

If the patient develops ototoxicity, subsequent doses of cisplatin should not be given until an audiometric analysis indicates that auditory acuity is within normal limits (http://www.drugs.com/pro/platinol.html). Refer to Table 16 for dose modification.

5.1.9.2 Carboplatin

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

Additional guidance has been provided regarding recommended dose reductions, holds, and discontinuations of study treatment for toxicities and/or to comply with the prescribing information (see Section 4.3.2).

Hematologic Toxicity

At the start of each cycle, the ANC must be ≥1500/μL and the platelet count must be ≥100,000/μL. Treatment should be delayed for up to 63 days to allow sufficient time for recovery. Growth factors may be used in accordance with ASCO and NCCN guidelines (Smith et al. 2006; NCCN 2012). Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest platelet and neutrophil values from the previous cycle (see Table 17).

Table 17 Carboplatin Dose Modification for Hematologic Toxicities

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

[a] Nadir prior cycle.

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

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

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

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

Non-Hematologic Toxicity

For a non-hematologic toxicity (see Table 18), treatment should be delayed for up to 63 days until resolution to less than or equal to the patient's baseline value (or Grade $\leq$1 if patient did not have that toxicity at baseline). Dose reductions at the start of the subsequent cycle will be made on the basis of non-hematologic toxicities from the dose administered in the preceding cycle. Table 18 provides the relevant dose adjustments for non-hematologic toxicities.

Table 18 Carboplatin Dose Modification on the Basis of Non-Hematologic Toxicities in the Preceding Cycle

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

AUC = area under the concentration–time curve.

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

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

[c] Despite the use of anti-emetics.

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

5.1.10 Potential Overlapping Toxicities

To date, on the basis of safety data from Study GP28328, the risk of overlapping toxicities between atezolizumab, carboplatin or cisplatin, and pemetrexed 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 Section 5.1.6.2, Section 5.1.8, and Section 5.1.9 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 when the next dose

should have been given (see Section 5.1.6.2). Prompt symptomatic management is appropriate for mild immune-related adverse events. In severe cases, immune-mediated toxicities may be acutely managed with systemic corticosteroids or TNF-α inhibitors. These cases should be discussed with the Medical Monitor.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including all 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 result (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 and/or birth defect in a neonate or 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

  Colitis

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

  Hepatitis

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

  Systemic lupus erythematosus

Neurologic disorders: Guillain-Barré syndrome, myasthenia gravis, and meningoencephalitis

Nephritis

- Events suggestive of hypersensitivity, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome, systemic immune activation, and infusion-reaction syndromes
- Cases of potential drug-induced liver injury that include an elevated ALT or AST level in combination with either an elevated bilirubin level 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 exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

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

treatment, whichever occurs first. *Instructions for reporting adverse events that occur after the safety 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 19 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 19 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) rather than individual signs and symptoms should be recorded on the Adverse Event eCRF (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminase levels). 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 *Death Attributed to Progressive Disease* eCRF. All other deaths *occurring during the adverse event reporting period*, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). The iDMC will monitor the frequency of deaths from all causes.

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

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 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" *or "worsened headache"*).

5.3.5.9 Worsening of NSCLC

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

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

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

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

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

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

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

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

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

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

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

5.3.5.12 Patient-Reported Outcome Data

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events
- 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.
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 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 or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study treatment or initiation of new 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 with use of the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study, within 5 months after the last dose of atezolizumab, or within 6 months after the last dose of cisplatin. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form with use of the fax number or 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 or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Atezolizumab is not expected to be genotoxic. In addition, the anticipated concentrations of atezolizumab in seminal fluid as well as the potential risk to the developing conceptus is low after seminal transfer of atezolizumab to a female partner.

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the chemotherapy treatment period or within 6 months after the last dose of chemotherapy (i.e., carboplatin, cisplatin, or pemetrexed). 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. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

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

5.4.3.3 Abortions

Any 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).

5.4.3.4 Congenital Anomalies and Birth Defects

Any congenital anomaly or 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 up 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 up 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 up 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, regardless of cause, should be reported through use of the Long-Term Survival Follow-up eCRF.

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

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Atezolizumab Investigator's Brochure
- Prescribing information for each chemotherapy agent (cisplatin, carboplatin, and pemetrexed)

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

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a randomized, Phase III, global, multicenter, open-label study designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin or cisplatin+pemetrexed compared with treatment with carboplatin or

cisplatin + pemetrexed in patients who are chemotherapy-naive and have Stage IV non-squamous NSCLC.

Approximately 568 patients will be randomized in the global enrollment phase of this study. [redacted]

The primary analyses of Study GO29438 will include patients enrolled during the global enrollment phase. [redacted].

The *efficacy* analyses will be performed on all randomized patients (ITT) with patients grouped according to the treatment assigned at randomization, regardless of whether they received any assigned study drug.

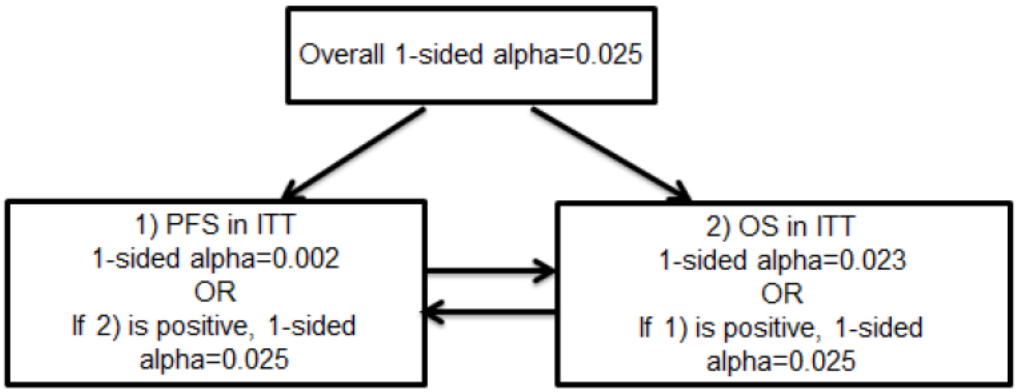
Safety analyses will be performed on data for all randomized patients who received any amount of study drug, with patients grouped according to whether any *amount* of atezolizumab was received*, including cases when atezolizumab was received in error*.

6.1 DETERMINATION OF SAMPLE SIZE

Determination of sample size is based on patients enrolled in the global enrollment phase. This study will randomize approximately 568 patients during the global enrollment phase. [redacted]

To control the overall type I error rate *using the group sequential Holm procedure (Ye et al. 2012)* for the one-sided test at 0.025 in the analyses of patients enrolled during the global enrollment phase, PFS in the ITT population will be tested at a one-sided α-level of 0.002 *and OS in the ITT population will be tested at a one-sided α-level of 0.023*. If *only* PFS is statistically significant, OS in the ITT population will be tested at a one-sided α-level of 0.025. Otherwise, OS in the ITT population will be tested at a one-sided α-level of 0.023. *If only OS is statistically significant, PFS in the ITT population will be tested at a one-sided α-level of 0.025 at the time of the final analysis of PFS. Otherwise, PFS in the ITT population will be tested at a one-sided α-level of 0.002 at the time of PFS final analysis.* The overview of the α control strategy is shown in Figure 3.

Figure 3 Overview of the Alpha Control Strategy



ITT = intent to treat; PFS = progression-free survival; OS = overall survival.

The sample size of this study is determined on the basis of the number of events required to demonstrate efficacy with regard to both PFS and OS (as defined in Section 6.4).

The estimates of the number of events required to demonstrate efficacy in the ITT population with regard to PFS *and OS* are based on the following assumptions:

- *1:1 randomization ratio*
- One-sided significance level of 0.002 *for PFS and 0.023 for OS*
- *96*.0 % power to detect an HR of 0.65, corresponding to an improvement in median PFS from 6 months to 9.2 months
- No interim analysis for PFS
- 8*1*% power to detect an HR of 0.75, corresponding to an improvement in median OS from 14 months to 18.7 months
- *One* interim OS analyses will be performed at the time of the PFS final analysis with an information fraction of approximately *78*% (i.e., *78*% of the required OS events have occurred). To adjust for the multiplicity due to the interim analyses, the Lan-DeMets approximation to the O'Brien-Fleming boundary will be used.
- Dropout rate of 10% per 24 months *assumed for all treatment arms*
- *Event times exponentially distributed*

With these assumptions, the PFS final analysis will be conducted after approximately *458* PFS events have occurred in the ITT population, and *at least 10 months after the last patient is enrolled* during the global enrollment phase, whichever occurs *later*. This is expected to occur approximately *30* months after the first patient is

randomized. This number of events corresponds to a minimum detectable difference in HR of approximately *0.764 for a one-sided α-level of 0.002. Based on the group sequential Holm procedure (Ye et al. 2012), if only OS is statistically significant, then PFS in the ITT population will be tested at a one-sided α-level of 0.025 at the time of PFS final analysis. In this case, the number of events corresponds to a minimum detectable difference of approximately 0.833 in HR.*

The interim OS analysis is planned to be performed at the time of the PFS final analysis. However, if there are significantly fewer than the expected 312 OS events at the time of the final PFS analysis, a nominal α of 0.01% (negligible impact on overall type I error rate) will be spent on the OS analysis at the time of the final PFS analysis and a second interim OS analysis will then be conducted after approximately 312 OS events have occurred (see Section 6.8.1).

Given the sample size of 568, this will result in approximately *398* OS events in the ITT population for the final analysis of OS, which is expected at approximately *42* months after the first patient is randomized.

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. Major protocol deviations, including major deviations of inclusion/exclusion criteria, will be reported and summarized by treatment arm.

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

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

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. *The primary efficacy analyses for PFS and OS will be analyzed in the ITT population.*

PFS is defined as the time between the date of randomization and the date of first documented disease progression or death, whichever occurs first. Patients who have not experienced disease progression or 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. Patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.

The type I error control plan for PFS and OS is presented in Section 6.1. A group sequential design will be used for testing OS to account for the conduct of the interim analysis, which is expected to occur approximately 30 months after the first patient is enrolled in the study. Details about the timing of the OS interim analysis and stopping boundaries are provided in Section 6.8.1. Details about 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 the unblinding of the study.

The null and alternative hypotheses regarding PFS and OS can be phrased in terms of the survival functions S_{PFS_A} (t), S_{OS_A} (t) in *the atezolizumab-containing treatment arm (*Arm A*)* and S_{PFS_B} (t), S_{OS_B} (t) in *the control arm (*Arm B*)*, respectively:

$$H_0: S_{PFS_A}(t) = S_{PFS_B}(t) \text{ versus } H_1: S_{PFS_A}(t) > S_{PFS_B}(t)$$

$$H_0: S_{OS_A}(t) = S_{OS_B}(t) \text{ versus } H_1: S_{OS_A}(t) > S_{OS_B}(t)$$

Comparisons with respect to PFS and OS between the treatment and control arms will be tested based on a stratified log-rank test. *The stratification factors will be sex (male vs. female), ECOG performance status (0 vs. 1), type of chemotherary (carboplatin vs. cisplatin), and smoking status (never vs. current and/or former).* The stratification factors will be those used during randomization, as recorded in IxRS. Results from an unstratified analysis will also be presented. The HR will be estimated using a stratified Cox regression model. Kaplan-Meier methodology will be used to estimate median PFS and OS for each treatment arm *and to construct survival curves for* visual descriptions of the difference between the treatment and control arms.

The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS and OS for each treatment arm (Brookmeyer and Crowley 1982).

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Objective Response Rate

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

ORR is defined as the proportion of patients who had an objective response. The analysis population for ORR will be all randomized patients. *The confirmation of response in accordance with RECIST v.1.1 is not required, but ORR with confirmation may be evaluated as an exploratory endpoint.* An estimate of ORR and its 95% CI will

be calculated using the Clopper Pearson method for each treatment arm. CIs for the difference in ORRs between the two treatment arms will be determined using the normal approximation to the binomial distribution. *The ORR will be compared between the two arms using the stratified Cochran-Mantel-Haenszel test, stratified by the same factors used in the primary PFS and OS analysis (see Section 6.4.1).*

6.4.2.2 Duration of Response

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

6.4.2.3 Overall Survival Rate at Landmark Timepoints

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

6.4.2.4 Patient-Reported Outcomes

The change from baseline per SILC scale will be analyzed for each of the lung cancer symptom scores (chest pain, cough, dyspnea). The analysis will be performed for patients in the ITT population with a non-missing baseline and at least a post-baseline PRO assessment (i.e., PRO evaluable population).

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

TTD in lung-related symptoms is defined as the time from baseline to the time the patient's score on the EORTC QLQ C30 or LC13 shows a ≥10-point increase above baseline in each of the following EORTC-transformed scores for cough, dyspnea (single item), dyspnea (multi-item subscale) and chest pain. A ≥10-point change in score is perceived by patients to be clinically significant (Osoba et al. 1998). If no baseline or post-baseline assessment is performed, data for patients will be censored at the date of randomization plus 1 day. TTD in symptoms will be analyzed in the ITT population through use of the same methods described for the PFS and OS analyses (see Section 6.4.1). Additional details regarding the analysis for the EORTC measures will be described in the SAP.

6.4.3 Handling of Missing Data

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

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

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

For TTD with use of the EORTC, 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, patients will be censored at the randomization date plus 1 day.

6.5 SAFETY ANALYSES

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

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

Verbatim description of adverse events will be mapped to MedDRA thesaurus terms and graded according to NCI CTCAE v4.0. All adverse events occurring during or after the first study drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grade $\geq$3), adverse events of special interest, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. *The proportion of patients experiencing at least one adverse event will be reported by toxicity term and treatment arm.*

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

Changes in vital signs will be summarized by treatment arm.

Deaths reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation will be summarized by treatment arm.

6.6 PHARMACOKINETIC ANALYSES

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

Plasma concentrations of carboplatin, cisplatin, and pemetrexed will be collected in this study as outlined in Appendix 2. The concentrations of carboplatin, cisplatin, and pemetrexed 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 rate*, defined as the probability that a patient will be alive without disease progression after randomization* (e.g., at 6 months and at 1 year)*,* will be estimated using Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated using Greenwood's formula. The 95% CIs for the difference in PFS rates between the treatment arms will be estimated using the normal approximation method*, and standard errors will be computed through use of the Greenwood 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 for the comparisons between treatment arms in which patients who receive non–protocol-specified anti-cancer therapy before a PFS event will be censored at the last tumor assessment date before receipt of non–protocol-specified anti-cancer therapy.

6.7.1.3 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, smoking status, and type of chemotherapy), the duration of PFS in these subgroups will be examined. Summaries of PFS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median PFS, will be produced separately for each level of the categorical variables for the comparisons between treatment arms.

6.7.1.4 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 *tumor* assessments scheduled immediately prior to the date of the PFS event *according to RECIST v1.1*, the patient will be counted as having progressed on the date of the first of these missing assessments.

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

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 for the comparisons between 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.

6.7.2.2 Subgroup Analysis

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

6.7.2.3 Overall Survival Rate at 3-Year Landmark

The OS rates at 3 years will be estimated using Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated using the standard error derived from Greenwood's formula. The 95% CI for the difference in OS rates between the two treatment arms will be estimated using the normal approximation method.

6.7.2.4 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 Statistical Analysis Plan (SAP).

6.7.2.5 *Non–Protocol-Specified Anti-Cancer Therapy*

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

Further details regarding these sensitivity analyses will be described 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. Results from these exploratory analyses will not be included in the Clinical Study Report.*

6.7.4 *EQ-5D-5L Health Status Data*

EQ-5D-5L health status data will be used for obtaining utility measures for economic modeling. These analyses will not be included in the Clinical Study Report.

6.7.5 *Exploratory Patient-Reported Outcome Analyses*

Compliance rates for each questionnaire will be summarized in the ITT population as detailed in the SAP.

Summary statistics (mean, SD, median, 25th and 75th percentiles, and range) and the mean change from baseline at each timepoint will be reported for each score of the PRO questionnaires.

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.

6.8 INTERIM ANALYSES

6.8.1 Planned Interim Analyses

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 and 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.

The interim efficacy analysis of OS will be conducted by the Sponsor at the time of the final PFS analysis.

The interim OS analysis will be conducted when approximately *312* OS events in the ITT population have been observed. This is expected to occur approximately *30* months after the first patient is randomized, but the exact timing of this analysis will depend on the actual number and timing of OS events. *If there are significantly fewer than the expected 312 OS events at the time of the final PFS analysis, a nominal two-sided α of 0.01% (negligible impact on overall type I error rate) will be spent on the OS analysis at the time of the final PFS analysis and a second interim OS analysis will then be conducted after approximately 312 OS events have occurred.*

The final OS analysis will be conducted when approximately *398* OS events in the ITT population have been observed. This is expected to occur approximately *42* months after the first patient is randomized, but the exact timing of this analysis will depend on the actual number and timing of OS events.

To control type I error for OS, the stopping boundaries for the OS interims and final analysis are to be computed with use of the Lan-DeMets approximation to the O'Brien-Fleming boundary as shown in Table 20.

Table 20 Analysis Timing and Stopping Boundary of Overall Survival

Analysis Timing	Planned Information Fraction	Stopping Boundary for Rejection of H_0 ITT Population	
		One-sided alpha=0.023	*One*-sided alpha=0.025
Interim analysis	*78*%	HR *<0.769* (p≤*0.0102*)	HR *<.773* (p≤*0.0114*)
Final analysis	100%	HR *<0.814* (p≤*0.0200*)	HR *<0.817* (p≤*0.0217*)

HR=hazard ratio; ITT=intent-to-treat; p=one-sided p-value.

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 primary endpoint of PFS and/or OS beyond what is specified in Section 6.8.1. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

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

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

6.9 [redacted]

Approximately 568 patients will be randomized in the global enrollment phase of this study. [redacted]

[redacted]

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patient-reported data will be collected electronically through use of electronic devices provided by an ePRO vendor. The electronic device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with the FDA regulations for electronic records (21 Code of Federal Regulations, Part 11). The data will be transmitted to a centralized database at the ePRO vendor. 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 is available in the Study Reference Manual. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.4 SOURCE DATA DOCUMENTATION

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

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

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 the FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

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 and meet criteria specified in Section 4.6.2. This separate consent is to be signed after initial radiographic disease progression has occurred and patients have discussed other available treatment options and the potential risks of continuing treatment.
- A signature page for patients that consent to an optional biopsy at the time of radiographic disease progression (see Section 4.5.7.2)

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 FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann-La Roche Ltd. Approximately 225 sites globally will participate in the study and approximately 568 patients will be randomized. [redacted]

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	All Treatment Cycles [a]		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1–4 or 6)	Maintenance Phase		
	Days –28 to –1	Every 21 Days (± 3 Days) [b]	Every 21 Days (± 3 Days)	≤ 30 Days after Last Dose of Study Treatment	Every 3 Months after Disease Progression or Loss of Clinical Benefit
Informed consent	x				
Tumor tissue specimen (blocks or 10 or more FFPE slides preferred, if available). [c] Fresh or archival tissue can be used.	x				
Demographic data	x				
Medical history and baseline conditions	x				
NSCLC cancer history	x				
Vital signs [d]	x	x	x	x	
Weight	x	x	x	x	
Height	x				
Complete physical examination	x				
Limited physical examination [e]		x	x	x	
ECOG performance status	x	x	x	x	
12-Lead ECG	x	x [f]	x [f]	x [f]	
Hematology [g]	x	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	All Treatment Cycles [a]		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1–4 or 6)	Maintenance Phase		
	Days –28 to –1	Every 21 Days (± 3 Days) [b]	Every 21 Days (± 3 Days)	≤ 30 Days after Last Dose of Study Treatment	Every 3 Months after Disease Progression 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	x	x	
ALK and/or *EGFR* assessment if status is unknown (may be done locally or centrally)	x				
HIV, HBV, HCV serology [l]	x				
Urinalysis [m]	x				
Determination of duration of induction treatment	x				
Induction treatment administration Arm A: atezolizumab + carboplatin or cisplatin + pemetrexed Arm B: carboplatin or cisplatin + pemetrexed		x [n]			
Maintenance treatment administration Arm A: atezolizumab + pemetrexed Arm B: pemetrexed			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

Appendix 1
Schedule of Assessments (cont.)

Procedure	Screening	All Treatment Cycles [a]		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1–4 or 6)	Maintenance Phase		
	Days –28 to –1	Every 21 Days (± 3 Days) [b]	Every 21 Days (± 3 Days)	≤ 30 Days after Last Dose of Study Treatment	Every 3 Months after Disease Progression or Loss of Clinical Benefit
Serum sample for PK sampling (atezolizumab-treated patients only) [r]		x	x	x	120 (± 30) days after last dose of atezolizumab
Carboplatin, cisplatin, and pemetrexed PK sampling (20 patients in Arm A) [r]		x			
Optional tumor biopsy [s]		Optional at time of radiographic progression			
Blood samples for biomarkers [r]	x	x	x	x	120 (± 30) days after last dose of atezolizumab
Optional blood for DNA extraction (RCR only) [r, t]		x			
Informed consent to continue treatment beyond radiographic progression (atezolizumab-treated patients)		At time of radiographic progression			
Optional tumor biopsy at other timepoints (RCR only)		Any time during study treatment or during survival follow-up			
Adverse events	x	x	x	x [u]	x [u]
Concomitant medications	x [v]	x	x	x	
Patient-reported outcomes (EORTC QLQ-C30, EORTC QLQ-LC13, SILC, and EQ-5D-5L) [v]		x [w]	x [w]		x [w]
Survival and anti-cancer therapy follow-up		x	x		x [x]

Appendix 1
Schedule of Assessments (cont.)

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

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

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

[c] Any available tumor tissue sample can be submitted before or within 4 weeks after enrollment. It is strongly encouraged that the sites submit representative tumor specimens preferably in paraffin blocks or as 10 (or more) serial, freshly cut, unstained slides for biomarker analysis. 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.

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

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

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

[k] Thyroid function testing (TSH, free T3, free T4) collected at Cycle 1, Day 1 and every fourth cycle thereafter. Note: Total T3 will be tested only at sites where free T3 testing cannot be performed.

[l] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical study. HBV DNA must be collected prior to randomization in patients who have negative serology for hepatitis B surface antigen and positive serology for HBcAb.

[m] Urinalysis by dipstick (specific gravity, pH, glucose, protein, ketones, and blood) should be obtained at screening and when clinically indicated throughout the study.

Appendix 1
Schedule of Assessments (cont.)

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

[o] CT scans (with oral/IV contrast unless contraindicated) or MRI scans of the chest and abdomen. A CT 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 12 months following Cycle 1, Day 1, and then every 9 weeks (± 7 days) thereafter after completion of the Week 48 tumor assessment, regardless of treatment delays, until radiographic disease progression (loss of clinical benefit for patients assigned to atezolizumab who 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. See Section 4.5.5 for details.

[q] If a patient discontinues study treatment for any reason other than *radiographic* disease progression *per RECIST v1.1 (e.g., toxicity, symptomatic deterioration)*, tumor assessments will continue at the same frequency as would have been followed if the patient had remained on study treatment until radiographic disease progression (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 patient starts another anti-cancer therapy after study treatment discontinuation, unless consent is withdrawn.

[r] See Appendix 2 for detailed schedule.

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

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

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

[v] From 7 days before screening.

Appendix 1
Schedule of Assessments (cont.)

[w] EORTC QLQ-C30, EORTC QLQ-LC13, and the EQ-5D-5L questionnaires will be completed by the patients on the ePRO tablet at each scheduled study visit prior to administration of study drug and prior to any other study assessment(s). SILC will be completed using 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- 5L questionnaires will be completed at 3 and 6 months following disease progression. The SILC will be completed monthly during survival follow-up for 6 months following disease progression or loss of clinical benefit (for atezolizumab-treated patients who continue after disease progression according to RECIST v1.1). Patients who discontinue study treatment for any reason other than *radiographic* progressive disease or loss of clinical benefit will complete the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L at each tumor assessment visit and will complete the SILC at home on a weekly basis, until radiographic disease progression per RECIST v1.1 (or for atezolizumab-treated patients who continue treatment after radiographic disease progression) or loss of clinical benefit 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.

[x] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits *approximately every 3 months until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up (this request must be documented in the source documents and signed by the investigator). If the patient withdraws from the study, s*tudy 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 (Atezolizumab + Carboplatin or Cisplatin + Pemetrexed)	Arm B (Carboplatin or Cisplatin + Pemetrexed)
Screening	N/A	Biomarkers [a]	Biomarkers [a]
Cycle 1, Day 1	Pre-dose (same day as treatment administration)	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Biomarkers [b] • Carboplatin or cisplatin pharmacokinetics [c] • Pemetrexed pharmacokinetics [c]	Biomarkers [b]
	30 (±10) minutes after end of atezolizumab infusion	• Atezolizumab pharmacokinetics	NA
	5–10 minutes before the end of carboplatin or cisplatin infusion [b]	• Carboplatin or cisplatin pharmacokinetics [c]	NA
	1 hour after end of carboplatin or cisplatin infusion [b]	• Carboplatin or cisplatin pharmacokinetics [c]	NA
	5–10 minutes before the end of pemetrexed infusion [b]	• Pemetrexed pharmacokinetics [c]	NA
	1 hour after end of pemetrexed infusion [b]	• Pemetrexed pharmacokinetics [c]	NA
Cycle 2, Day 1	Pre-dose (same day as treatment administration)	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Biomarkers [b]	• Biomarkers [b]
Cycle 3, Day 1	Pre-dose (same day as treatment administration)	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Biomarkers [b] • Carboplatin or cisplatin pharmacokinetics [c] • Pemetrexed pharmacokinetics [c]	• Biomarkers [b]

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

Study Visit	Time	Arm A (Atezolizumab + Carboplatin or Cisplatin + Pemetrexed)	Arm B (Carboplatin or Cisplatin + Pemetrexed)
	5–10 minutes before the end of carboplatin or cisplatin infusion [b]	Carboplatin or cisplatin pharmacokinetics [c]	NA
	1 hour after end of carboplatin or cisplatin infusion [b]	Carboplatin or cisplatin pharmacokinetics [c]	NA
	5–10 minutes before the end of pemetrexed infusion [b]	Pemetrexed pharmacokinetics [c]	NA
	1 hour after end of pemetrexed infusion [b]	Pemetrexed pharmacokinetics [c]	NA
Cycles 4, 8, and 16, Day 1	Pre-dose (same day as treatment administration)	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Biomarkers [b]	• Biomarkers [b]
After Cycle 16, every eighth cycle, Day 1 (±3 days)	Pre-dose (same day as treatment administration)	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Biomarkers [b]	• Biomarkers [b]
At time of fresh biopsy (on-treatment or at progression, including during follow-up)	At visit	• Biomarkers [b]	• Biomarkers [b]
Treatment discontinuation visit	At visit	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Biomarkers [b]	• Biomarkers [b]
120 (±30 days) after last dose of atezolizumab	At visit	• Atezolizumab ATA • Atezolizumab pharmacokinetics • Biomarkers [b]	• Biomarkers [b]

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

Study Visit	Time	Arm A (Atezolizumab + Carboplatin or Cisplatin + Pemetrexed)	Arm B (Carboplatin or Cisplatin + Pemetrexed)
At any time during the study (RCR consent required)	At visit	Optional RCR blood (DNA extraction) [d]	Optional RCR blood (DNA extraction) [d]

ATA = anti-therapeutic antibody; NA = not applicable; PK = pharmacokinetic; RCR = Roche Clinical Repository.

Note: Serum PK samples for atezolizumab; plasma PK samples for carboplatin or cisplatin and pemetrexed.

[a] Whole blood for biomarkers.

[b] Plasma and serum for biomarkers.

[c] At selected centers, 20 patients in Arm A will undergo the additional PK assessments for carboplatin or cisplatin and pemetrexed where applicable.

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

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

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

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

ANATOMIC STAGE • PROGNOSTIC GROUPS

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

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

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

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1[3] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[4]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

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

a. Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resolution imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

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

b. Non-Measurable Tumor Lesions

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

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

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

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

c. Special Considerations Regarding Lesion Measurability

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

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

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

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

a. Measurement of Lesions

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

b. Method of Assessment

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

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

Clinical Lesions. Clinical lesions will be considered measurable only when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules).

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

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan on the basis of the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

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

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

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

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

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

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

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

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

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

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

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

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

RESPONSE CRITERIA

a. Evaluation of Target Lesions

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

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

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

- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

b. Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the

baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

<u>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.</u>

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.

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

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

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

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

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

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

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

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

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a

convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm; the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be “unable to assess” except where there is clear progression. Overall response would be “unable to assess” if either the target response or the non-target response is “unable to assess,” except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

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

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

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

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

c. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective

progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

If a patient undergoes an excisional biopsy or other appropriate approach (e.g., multiple passes with large core needle) of a new lesion or an existing solitary progressive lesion that following serial sectioning and pathological examination reveals no evidence of malignancy (e.g., inflammatory cells, fibrosis, etc.), then the new lesion or solitary progressive lesion will not constitute disease progression.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 5
Modified Response Evaluation Criteria in Solid Tumors

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions. Therefore, modified response criteria have been developed that account for the possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment.

Modified Response Evaluation Criteria in Solid Tumors (RECIST) is derived from RECIST, Version 1.1 (v1.1) conventions[1] and immune-related response criteria[2] (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.

[1] 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.

[2] Wolchok et al. Clin Can Res 2009;15:7412–20; Nishino et al. J Immunother Can 2014;2:17; Nishino et al. Clin Can Res 2013;19:3936–43.

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

A.1 MEASURABLE LESIONS

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

A.2 NON-MEASURABLE LESIONS

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

A.3 SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions

Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

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

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment

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

B. TUMOR RESPONSE EVALUATION

B.1 DEFINITIONS OF TARGET/NON-TARGET LESIONS

Target Lesions

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

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

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor.

Appendix 5
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 CR (i.e., a CR is attained only with the complete disappearance of all tumor lesions, including non-target lesions) and will not be used to assess progressive disease.

New Lesions

During the study, all new lesions identified and recorded after baseline must be assessed at all tumor assessment timepoints. New lesions will also be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST, (e.g., non–lymph node lesions must be $\geq$ 10 mm; see note for new lymph node lesions below). Up to a maximum of five new lesions total (and a maximum of two lesions per organ), all with measurements at all timepoints, can be included in the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the tumor response evaluation.

New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint will be measured from that point on and contribute to the sum of longest diameters (SLD), if the maximum number of 5 measurable new lesions being followed has not been reached.

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

B.2 CALCULATION OF SUM OF THE DIAMETERS

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

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

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

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

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

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

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

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

B.3 RESPONSE CRITERIA

Timepoint Response

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

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

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

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the diameters while on study.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and selected new measurable lesions, taking as reference the smallest sum on study (nadir SLD; this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Impact of New Lesions on Modified RECIST

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall modified RECIST tumor response.

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is considered not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would only happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed but

those gave a sum of 80 mm, the patient will be assigned PD status, regardless of the contribution of the missing lesion.

Table 1 Modified RECIST Timepoint Response Definitions

% Change in Sum of the Diameters [a]	Non-Target Lesion Response Assessment	Overall Modified RECIST Timepoint Response
−100% from baseline [b]	CR	CR
−100% from baseline [b]	Non-CR or not all evaluated	PR
≤ −30% from baseline	Any	PR
> −30% to <+20%	Any	SD
Not all evaluated	Any	NE
≥ +20%from nadir SLD	Any	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; SLD = sum of the longest diameter.

[a] Percent change in sum of the diameters (including measurable new lesions when present).

[b] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm in order to meet the definition of CR.

Appendix 6
Anti–PD-L1 Immunohistochemistry

OVERVIEW

The Ventana anti–PD-L1 (SP142) rabbit monoclonal primary antibody immunohistochemistry (IHC) assay will be used to determine programmed death–ligand 1 (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 GO29438, 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 NSCLC patients with locally advanced or metastatic disease who might benefit from treatment with atezolizumab.

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

DEVICE DESCRIPTION

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

SCORING SYSTEM

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

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

Appendix 7
EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

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

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

Please go on to the next page

Appendix 7
EORTC QLQ-C30 (cont.)

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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Appendix 8
EORTC QLQ-LC13

ENGLISH

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :	Not at All	A Little	Quite a Bit	Very Much
31. How much did you cough?	1	2	3	4
32. Did you cough up blood?	1	2	3	4
33. Were you short of breath when you rested?	1	2	3	4
34. Were you short of breath when you walked?	1	2	3	4
35. Were you short of breath when you climbed stairs?	1	2	3	4
36. Have you had a sore mouth or tongue?	1	2	3	4
37. Have you had trouble swallowing?	1	2	3	4
38. Have you had tingling hands or feet?	1	2	3	4
39. Have you had hair loss?	1	2	3	4
40. Have you had pain in your chest?	1	2	3	4
41. Have you had pain in your arm or shoulder?	1	2	3	4
42. Have you had pain in other parts of your body?	1	2	3	4
If yes, where _____				
43. Did you take any medicine for pain?				
1 No **2 Yes**				
If yes, how much did it help?	1	2	3	4

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Appendix 9
EQ-5D-5L

Health Questionnaire

English version for the USA

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

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

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

ANXIETY / DEPRESSION

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

2

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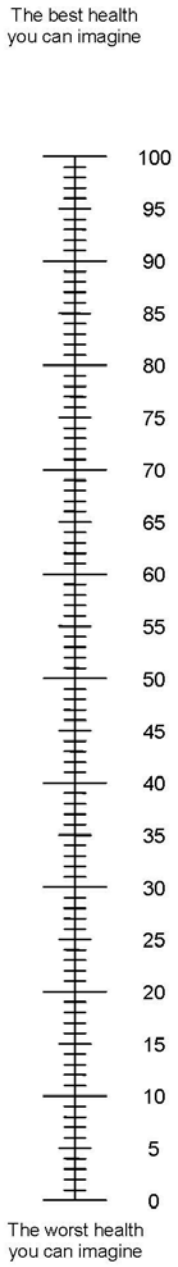
Appendix 9
EQ-5D-5L (cont.)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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Appendix 10
Eastern Cooperative Oncology Group Performance Status Scale

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

Appendix 11
Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

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

Appendix 12
Preexisting Autoimmune Diseases

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias for whom 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	Epidermolysis bullosa acquista	Ord's thyroiditis
Addison's disease	Gestational pemphigoid	Pemphigus
Ankylosing spondylitis	Giant cell arteritis	Pernicious anemia
Antiphospholipid antibody syndrome	Goodpasture's syndrome	Polyarteritis nodusa
Aplastic anemia	Graves' disease	Polyarthritis
Autoimmune hemolytic anemia	Guillain-Barré syndrome	Polyglandular autoimmune syndrome
Autoimmune hepatitis	Hashimoto's disease	Primary biliary cirrhosis
Autoimmune hypoparathyroidism	IgA nephropathy	Psoriasis
Autoimmune hypophysitis	Inflammatory bowel disease	Reiter's syndrome
Autoimmune myocarditis	Interstitial cystitis	Rheumatoid arthritis
Autoimmune oophoritis	Kawasaki's disease	Sarcoidosis
Autoimmune orchitis	Lambert-Eaton myasthenia syndrome	Scleroderma
Autoimmune thrombocytopenic purpura	Lupus erythematosus	Sjögren's syndrome
Behcet's disease	Lyme disease - chronic	Stiff-Person syndrome
Bullous pemphigold	Meniere's syndrome	Takayasu's arteritis
Chronic fatigue syndrome	Mooren's ulcer	Ulcerative colitis
Chronic inflammatory demyelinating polyneuropathy	Morphea	Vitiligo
	Multiple sclerosis	Vogt-Kovanagi-Harada disease
Chung-Strauss syndrome	Myasthenia gravis	Wegener's granulomatosis
Crohn's disease	Neuromyotonia	
Dermatomyositis	Opsoclonus myoclonus syndrome	
Diabetes mellitus type 1	Optic neuritis	
Dysautonomia		

Appendix 13
Symptoms in Lung Cancer

Symptoms in Lung Cancer (SILC)

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

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

☐$_0$ No pain at all

☐$_1$ Mild pain

☐$_2$ Moderate pain

☐$_3$ Severe pain

☐$_4$ Very severe pain

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

☐$_0$ Never

☐$_1$ Rarely

☐$_2$ Sometimes

☐$_3$ Often

☐$_4$ Always

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

☐$_0$ No coughing at all

☐$_1$ Mild coughing

☐$_2$ Moderate coughing

☐$_3$ Severe coughing

☐$_4$ Very severe coughing

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

☐$_0$ Never

☐$_1$ Rarely

☐$_2$ Sometimes

☐$_3$ Often

☐$_4$ Always

Appendix 13
Symptoms in Lung Cancer (cont.)

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

Appendix 13
Symptoms in Lung Cancer (cont.)

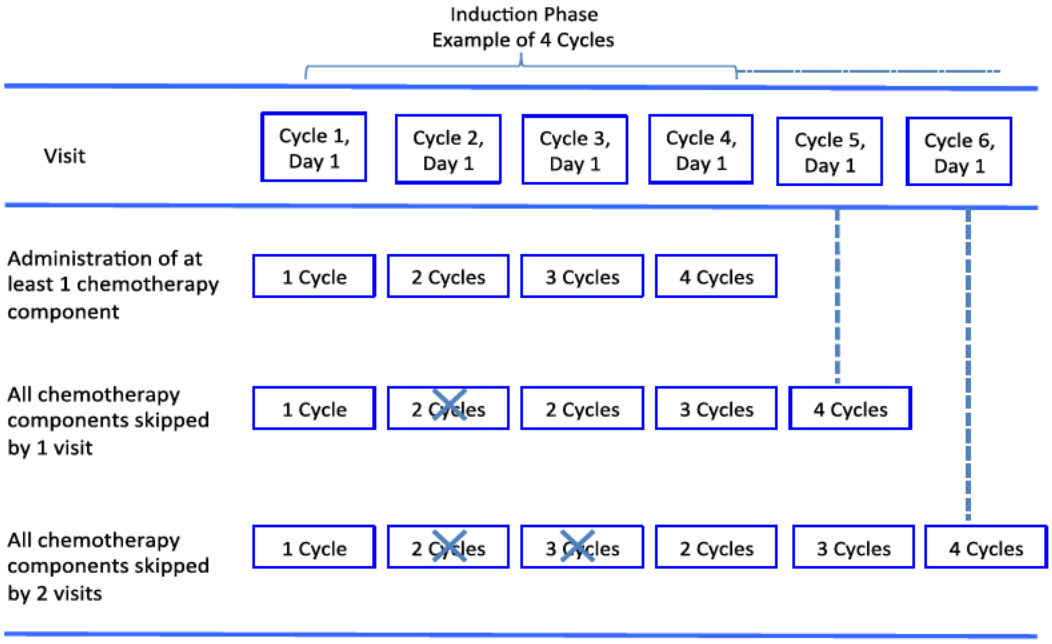
Item #	Question
9	Over the past week, how often did you feel short of breath when walking up a flight of stairs or hill? ☐$_0$ Never ☐$_1$ Rarely ☐$_2$ Sometimes ☐$_3$ Often ☐$_4$ Always

Appendix 14
Additional Guidance on Chemotherapy Administration

For the purposes of this protocol, the Sponsor defines a chemotherapy cycle as the administration of at least one chemotherapy component (i.e., carboplatin, cisplatin, or pemetrexed). 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 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 all chemotherapy is withheld for more than 63 days from the last chemotherapy dose, 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 three non-consecutive cycles before chemotherapy should be permanently discontinued.

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

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

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

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

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

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

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment.

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

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

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

BAL =bronchoscopic alveolar lavage.

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

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

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

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

HEPATIC EVENTS

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

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

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

Table 2 Management Guidelines for Hepatic Events

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

LFT =liver function tests.

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

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

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

Table 2 Management Guidelines for Hepatic Events (cont.)

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

LFT =liver function tests.

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

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

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

GASTROINTESTINAL EVENTS

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

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

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

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

GI =gastrointestinal.

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

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

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

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

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

GI =gastrointestinal.

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

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

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

ENDOCRINE EVENTS

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

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

and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events

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

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

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

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

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

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

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

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

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

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

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

Table 4 Management Guidelines for Endocrine Events (cont.)

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

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

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

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

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

OCULAR EVENTS

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

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 5 Management Guidelines for Ocular Events

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

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

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

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

IMMUNE-RELATED MYOCARDITIS

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

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

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

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 6 Management Guidelines for Immune-Related Myocarditis

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

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

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

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

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

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

INFUSION-RELATED REACTIONS

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

Guidelines for medical management of IRRs during Cycle 1 are provided in Table 7. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 7 Management Guidelines for Infusion-Related Reactions

Event	*Management*
IRR, Grade 1	• *Reduce infusion rate to half the rate being given at the time of event onset.* • *After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate.* • *If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.*
IRR, Grade 2	• *Interrupt atezolizumab infusion.* • *Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen).* • *After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset.* • *For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs.*
IRR, Grade 3 or 4	• *Stop infusion.* • *Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen).* • *Permanently discontinue atezolizumab and contact Medical Monitor.* [a]

IRR =infusion-related reaction.

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

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	*Management*
Amylase and/or lipase elevation, Grade 2	• *Continue atezolizumab.* • *Monitor amylase and lipase weekly.* • *For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.*
Amylase and/or lipase elevation, Grade 3 or 4	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to GI specialist.* • *Monitor amylase and lipase every other day.* • *If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.* [c]

GI =gastrointestinal.

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

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

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

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	*Management*
Immune-related pancreatitis, Grade 2 or 3	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to GI specialist.* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Immune-related pancreatitis, Grade 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Refer patient to GI specialist.* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

GI =gastrointestinal.

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

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

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

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	*Management*
Dermatologic event, Grade 1	• *Continue atezolizumab.* • *Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).*
Dermatologic event, Grade 2	• *Continue atezolizumab.* • *Consider patient referral to dermatologist.* • *Initiate treatment with topical corticosteroids.* • *Consider treatment with higher-potency topical corticosteroids if event does not improve.*
Dermatologic event, Grade 3	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to dermatologist.* • *Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Dermatologic event, Grade 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c]

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

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

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

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	*Management*
Immune-related neuropathy, Grade 1	• *Continue atezolizumab.* • *Investigate etiology.*
Immune-related neuropathy, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Investigate etiology.* • *Initiate treatment as per institutional guidelines.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Immune-related neuropathy, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Initiate treatment as per institutional guidelines.*
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Refer patient to neurologist.* • *Initiate treatment as per institutional guidelines.* • *Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.*

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

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

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

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-RELATED MENINGOENCEPHALITIS

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

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for Immune-Related Meningoencephalitis

Event	*Management*
Immune-related meningoencephalitis, all grades	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [a] • *Refer patient to neurologist.* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

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