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**

NCT Number: **NCT02657434**

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STATISTICAL ANALYSIS PLAN

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

STUDY DRUG: Atezolizumab

VERSION NUMBER: 3

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SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted], Ph.D.

DATE FINAL: 7 May 2018

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STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL		
[redacted]	Company Signatory	07-May-2018 20:35:09

TABLE OF CONTENTS

[redacted]

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

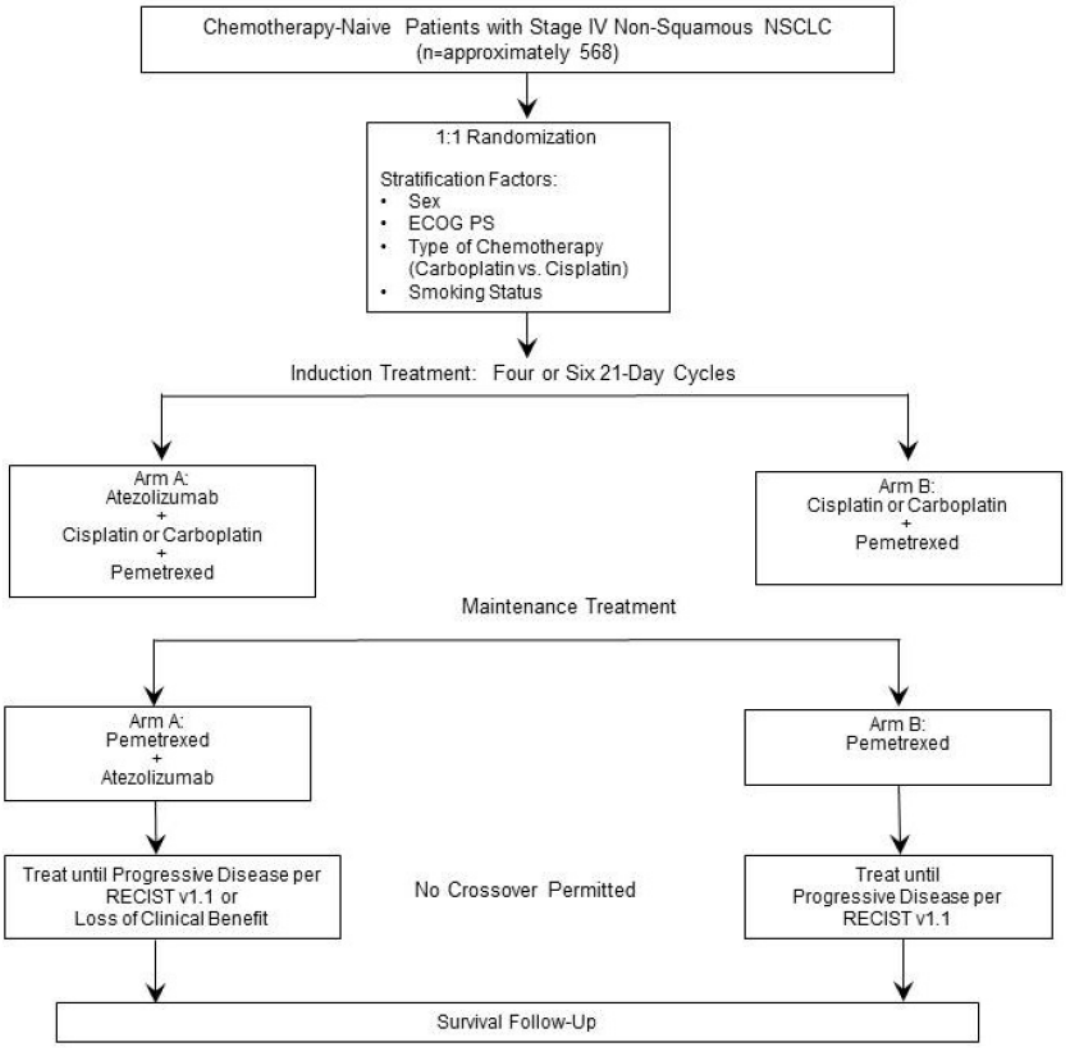
1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study GO29438 (IMpower132), a Phase III, open-label, randomized study of atezolizumab (anti–programmed death–ligand 1 [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 (NSCLC). The background for the study can be found in the study protocol.

2. STUDY DESIGN

This is a randomized, Phase III, multicenter, open-label study designed to evaluate the 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.

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 were 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 treatment regimens shown in Table 1.

Table 1 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

Patients randomized to Arm A receive 1200 mg of atezolizumab. Atezolizumab infusions are administered per the instructions outlined in the protocol.

Institutions should follow their standard administration procedures for pemetrexed. The premedication doses administered should be in compliance with the prescribing information.

Cisplatin by intravenous (IV) infusion should be administered approximately 30 minutes after completion of the pemetrexed infusion at a dose of 75 mg/m^2 over 1–2 hours or per standard of care at the institution.

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.

The number of cycles of induction treatment (four or six) is at the discretion of the investigator and will be determined and documented prior to randomization. Induction treatment is 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 continue treatment with maintenance therapy as shown in Table 1. Patients randomized to either Arm A or B 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 Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), provided they are experiencing clinical benefit as assessed by the investigator.

Treatment with chemotherapy (both in Arm A and B) is discontinued for all patients who exhibit evidence of progressive disease by RECIST v1.1.

Patients 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 are required every 9 weeks. Patients 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) 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.

An independent Data Monitoring Committee (iDMC) monitors safety data.

This study had planned to enroll approximately 568 patients across all sites in the global enrollment phase. [redacted]

2.1 PROTOCOL SYNOPSIS

The protocol synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 OUTCOME MEASURES

2.2.1 Co-Primary Efficacy Outcome Measures

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

- Progression free survival (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
- Overall survival (OS), defined as the time from randomization to death from any cause

2.2.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are:

- Objective response, defined as partial response (PR) or complete response (CR) as determined by the investigator according to RECIST v1.1
- Duration of response (DOR), defined as the time interval from first occurrence of a documented objective response to the time of disease progression as determined

by the investigator using RECIST v1.1 or death from any cause, whichever comes first

- OS rates at 1-year and 2-year landmark timepoints
- Time to deterioration (TTD) in patient-reported lung cancer symptoms, defined as time from randomization to deterioration (10-point change) on each of the European Organization for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire–Core 30 (QLQ-C30) and supplemental lung cancer module (QLQ-LC13) symptom subscales
- Change from baseline in patient-reported lung cancer symptoms with use of the Symptoms in Lung Cancer (SILC) scale symptom score

2.2.3 Exploratory Efficacy Outcome Measures

The exploratory efficacy outcome measures for this study are:

- PFS rates at 6-month 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
- 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 EuroQoL 5 Dimensions 5-Level Version (EQ-5D-5L) for use in medical economic modeling
- 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

2.2.4 Pharmacokinetic Outcome Measures

The pharmacokinetic (PK) outcome measures for this study are:

- 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 ($\pm$30) days after the last dose of atezolizumab (Arm A)
- Plasma concentrations for carboplatin or cisplatin (Arm A)
- Plasma concentrations for pemetrexed (Arm A)

2.2.5 Safety Outcome Measures

The safety outcome measures for this study are:

- Incidence, nature, and severity of adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0)
- Changes in vital signs, physical findings, and clinical laboratory test results during and following study treatment administration
- Incidence of anti-drug antibody (ADA) response to atezolizumab and potential correlation with PK, safety, and efficacy parameters

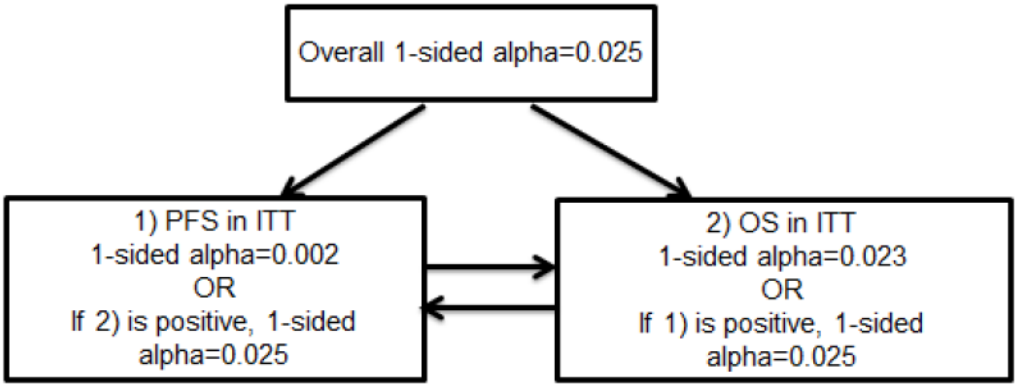
2.3 DETERMINATION OF SAMPLE SIZE

2.3.1 Determination of Sample Size in the Global Enrollment Phase

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. 2013) for the one-sided test at 0.025 in the analyses of patients enrolled during the global enrollment phase, PFS in the ITT (intent-to-treat) 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 the initially assigned 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 primary analysis of PFS. Otherwise, PFS in the ITT population will be tested at the initially assigned one-sided α-level of 0.002 at the time of PFS primary analysis. The overview of the α control strategy is shown in Figure 2.

Figure 2 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.

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

- 1:1 randomization ratio
- One-sided significance level of 0.002 for PFS and 0.023 for OS
- Log-rank test
- 96.0% power to detect a hazard ratio (HR) of 0.65, corresponding to an improvement in median PFS from 6 months to 9.2 months
- No interim analysis for PFS
- 81% 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 primary 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

2.3.2 [redacted]

[redacted]

[redacted]

2.4 ANALYSES TIMING

There are no interim analyses planned for the co-primary endpoint of PFS in this study. The PFS primary analysis will be conducted when 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. 2013), 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 primary analysis. In this case, the number of events corresponds to a minimum detectable difference of approximately 0.833 in HR as shown in Table 2.

The interim efficacy analysis of OS will be conducted by the Sponsor at the time of the primary PFS analysis. It is estimated that approximately 312 OS events in the ITT population will have been observed at this timepoint and it is expected to occur approximately 30 months after the first patient is randomized.

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 Pocock boundary as shown in Table 3. The stopping boundary for the OS interim will be adjusted according to the observed number of OS events at the time of primary PFS analysis.

Table 2 Analysis Timing and Stopping Boundaries of Progression-Free Survival

	Stopping Boundary for Rejection of H_0 ITT Population	
Analysis Timing	One-Sided alpha=0.002	One-Sided alpha=0.025
Final analysis	HR<0.764	HR<0.833

HR=hazard ratio; ITT=intent-to-treat

Table 3 Analysis Timing and Stopping Boundaries of Overall Survival

	Planned Information Fraction	Stopping Boundary for Rejection of H_0 ITT Population	
Analysis Timing		One-sided alpha=0.023	One-sided alpha=0.025
Interim analysis	78%	HR < 0.792 (p ≤ 0.0196)	HR < 0.795 (p ≤ 0.0213)
Final analysis	100%	HR<0.794 (p ≤ 0.0108)	HR < 0.797 (p ≤ 0.0119)

HR=hazard ratio; ITT=intent-to-treat.

Note: p=one-sided p-value.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Eligible patients will be randomized in a 1:1 ratio to receive either carboplatin/cisplatin+pemetrexed+atezolizumab or carboplatin/cisplatin+pemetrexed with the use of a stratified permuted-block randomization. The randomization will be stratified for the following factors:

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

Under Versions 1 and 2 of Protocol GO29438, PD-L1 expression by immunohistochemistry (IHC) (tumor cell [TC] 2/3 and any tumor-infiltrating immune cell [IC] vs. TC0/1 and IC2/3 vs. TC0/1 and IC0/1) was used as one of the stratification

factors instead of chemotherapy. Distribution of stratification factors between treatment arms will be assessed to evaluate potential imbalances.

3.2 DATA MONITORING

An iDMC has been used to evaluate safety during the study on a regular basis. All summaries and analyses by treatment arm for the iDMC review are prepared by an external independent Data Coordinating Center. Members of the iDMC are external to the Sponsor and follow a separate iDMC Charter that outlines their roles and responsibilities, as well as a detailed monitoring plan. Refer to the iDMC Charter for further detail.

4. STATISTICAL METHODS FOR PATIENTS ENROLLED IN THE GLOBAL ENROLLMENT PHASE

The analyses described in this SAP will supersede those specified in Protocol GO29438 for the purposes of a regulatory filing. The analyses throughout Section 4 are based only on those patients who are enrolled in the global enrollment phase, [redacted]

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

The ITT population is defined as all randomized patients, whether or not the patients received the assigned treatment. [redacted] The ITT patients will be analyzed according to the treatment assigned at randomization by the interactive voice/Web response system (IxRS).

4.1.2 Pharmacokinetic-Evaluable Population

PK analyses will be based on PK observations from all patients who received atezolizumab, carboplatin, cisplatin or pemetrexed treatment and who provided at least one evaluable PK sample. [redacted].

4.1.3 Safety Population

The safety population is defined as patients who received any amount of study treatment. [redacted] Patients who received any amount of atezolizumab will be analyzed as part of the Arm A even if atezolizumab was given in error. Patients who were randomized to the study but did not receive any study drug will not be included in the safety population.

4.2 ANALYSIS OF STUDY CONDUCT

Enrollment, major protocol deviations (including major deviations of inclusion and/or exclusion criteria), and reasons for discontinuation from the study will be summarized

by treatment arm for the ITT population. Study treatment administration and reasons for discontinuation from study treatment will be summarized by treatment arm for the safety population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic characteristics, such as age and race/ethnicity, and baseline disease characteristics, such as histology subtype, current disease status, and stratification factors (sex, smoking status, ECOG performance status, chemotherapy), will be summarized by treatment arm for the ITT population.

Baseline values are the last available data obtained prior to the patient receiving the first dose of any study treatments on Cycle 1, Day 1 visits unless otherwise noted. Descriptive statistics (mean, median, SD, range) will be presented for continuous variables, and frequencies and percentages will be presented for categorical variables.

4.4 EFFICACY ANALYSIS

All efficacy endpoints will be analyzed on the ITT population. The stratification factors will be those used for randomization and will be obtained from the IxRS (sex, smoking status, ECOG performance status, and chemotherapy type). [redacted] if at least one stratum (i.e., a combination of stratification factor levels across sex, smoking status, ECOG performance status, and chemotherapy type per IxRS) has fewer than 10 events (PFS or OS events), the stratification factor (one of 4 stratification factors: sex, smoking status, ECOG performance status, and chemotherapy type per IxRS) which contains the level with the smallest number of patients will be removed from the stratified analyses. The removal of the stratification factor will continue until there is no stratum with fewer than 10 events (PFS or OS events). The final set of stratification factors used in stratified analyses will be applied to all endpoints where stratified analyses are planned.

4.4.1 Co-Primary Efficacy Endpoints

4.4.1.1 Progression-Free Survival

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

Treatment comparisons will be based on the stratified log-rank test in the ITT population. The null and alternative hypotheses can be phrased in terms of the survival functions $S_{PFS\_A}(t)$ and $S_{PFS\_B}(t)$ in Arm A and Arm B, respectively:

$$H_0: S_{PFS\_A}(t) = S_{PFS\_B}(t) \text{ versus } H_1: S_{PFS\_A}(t) > S_{PFS\_B}(t)$$

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

The HR, $\lambda_{PFS\_A}/\lambda_{PFS\_B}$, where λ_{PFS_A} and λ_{PFS_B} represent the hazard of PFS in Arm A and Arm B, respectively, will be estimated with a stratified Cox regression model and the same stratification variables used for the stratified log-rank test.

Results from an unstratified analysis will also be provided.

4.4.1.2 Overall Survival

OS is defined as the time from randomization to 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.

OS will be analyzed with the same methodologies as PFS. Treatment comparisons will be based on the stratified log-rank test in the ITT population. The null and alternative hypotheses can be phrased in terms of the survival functions $S_{OS\_A}(t)$ and $S_{OS\_B}(t)$ in Arm A and Arm B, respectively:

$$H_0: S_{OS\_A}(t)=S_{OS\_B}(t) \text{ versus } H_1: S_{OS\_A}(t)>S_{OS\_B}(t)$$

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 Objective Response Rate

Objective response rate (ORR) is defined as the proportion of patients who had an objective response (confirmation not required). An objective response is defined as either CR or PR, as determined by the investigator with use of RECIST v1.1. Patients not meeting these criteria, including patients without any post-baseline tumor assessments, will be considered non-responders.

The analysis population for ORR will be the ITT population. An estimate of ORR and its 95% CI will be calculated with the Clopper-Pearson method for each treatment arm. The 95% CIs for the difference in ORRs between the two treatment arms will be computed 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 analyses (see Section 4.4.1). Confirmation of response according to RECIST v1.1 is not required, but for the exploratory purposes, ORR with confirmation may be reported.

4.4.2.2 Duration of Response

DOR is defined for patients with an objective response as the time from the first documented objective response to documented disease progression as determined by the investigator with use of RECIST v1.1 or death from any cause, whichever occurs first.

Data for patients who are alive and who have not experienced disease progression at the time of the analysis will be censored at the date of the last tumor assessment. If no tumor assessments were performed after the date of the first occurrence of the objective response (CR or PR), DOR will be censored at the date of the first occurrence of the objective response. Because the determination of DOR is based on a non-randomized subset of patients, formal hypothesis testing will not be performed. DOR will be estimated using KM methodology. Comparisons between treatment arms will be made using the stratified and unstratified log-rank test for descriptive purposes only.

Confirmation of response in accordance with RECIST v1.1 will not be required, but for exploratory purposes, DOR for patients with confirmed response may be reported.

4.4.2.3 Overall Survival Rates at 1- and 2-Year Landmark Timepoints

The OS rates at the 1-and 2-year landmark time points are defined as the probabilities that patients are alive 1-and 2-years after randomization, respectively. The OS rate at the 1-and 2-year landmark timepoints after randomization within the ITT population will be estimated for each treatment arm using KM methodology, along with 95% CI calculated with the standard error derived from the Greenwood formula. The 95% CI for the difference in OS rates between the two treatment arms will be estimated with the normal approximation method, with standard errors computed using the Greenwood method.

4.4.2.4 Patient-Reported Outcomes

The EORTC QLQ-C30 and EORTC QLQ-LC13 will be scored according to the EORTC scoring manual (Fayers et al. 2001). All EORTC scales and single-item measures will be linearly transformed so that each score has a range of 0-100. A high score for a functional/global health status scale represents a high or healthy level of functioning/HRQoL; however a high score for a symptom scale or item represents a high level of symptomatology or problems. A ≥10-point change in the symptoms subscale score is perceived by patients as clinically significant (Osoba et al. 1998).

The SILC questionnaire comprises three individual symptoms (dyspnea, cough, chest pain) and will be scored at the individual symptom level, thus will have a dyspnea score, chest pain score, and cough score. Each individual symptom score will be calculated as the average of responses for the symptom items [e.g. Chest Pain Score=mean (item 1; item 2)]. An increase in score is suggestive of a worsening in symptomology (i.e. frequency or severity). A score change of ≥0.3 points for the dyspnea and cough symptom scores is considered to be clinically significant; whereas a score change of ≥0.5 points for the chest pain score is considered to be clinically significant.

The ITT population will be used for TTD analysis. Patients whose symptoms have not deteriorated before the last PRO assessment is completed will be censored at the date of last PRO assessment. Patients with no baseline assessment or post-baseline assessments will be censored at the date of randomization plus 1 day.

TTD according to the EORTC QLQ-C30 and EORTC QLQ-LC13 measures will be evaluated in each of the following linearly transformed symptom scores: cough, dyspnea (single item), dyspnea (multi-item subscale), chest pain, or arm/shoulder pain. 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. The methodologies outlined for the analysis of PFS will be used for the analyses of TTD of the prespecified symptoms of the EORTC QLQ-C30 and EORTC QLQ-LC13 measure. The estimated Kaplan-Meier plots will be provided for each symptom separately.

Summary statistics (mean, SD, median, range) of the change from baseline per SILC scales may be provided. The analysis will be performed for patients in the PRO-evaluable population, which is defined as all randomized patients with a non-missing baseline assessment and at least one non-missing post-baseline assessment until treatment discontinuation. Graphs of the mean changes and standard errors over time from the baseline assessment for the scales will be provided for each treatment arm. The analysis of SILC change from baseline will be performed at all on-treatment timepoints, as well as at the time of disease progression per RECIST v1.1 (PRO assessment completed within 7 days of date of radiographic disease progression), at the last dose of treatment received before treatment discontinuation for any cause, and at the survival follow-up visits through 6 months. Repeated measures mixed-effect model will be used for comparing the scale scores (SILC) between treatment arms. The model will include a term for intercept, a term for linear time trend, a term for treatment group, and a term of treatment-by-time interaction. Repeated measured over time will be accounted for by unstructured covariance structure.

In addition, to interpret the evolution over time in lung-cancer disease symptoms, the analyses described in Section 4.4.3.5 may be documented in the PRO-evaluable population.

Analyses including the SILC questionnaire may not be included within the CSR.

4.4.3 Exploratory Efficacy Endpoints

4.4.3.1 Exploratory Analyses of Progression-Free Survival

4.4.3.1.1 PFS at 6-Months and 1-Year Landmark Timepoints

PFS rates at 6 months and 1 year will be estimated and analyzed using the same method as described in Section 4.4.2.3.

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

The impact of non–protocol-specified anti-cancer therapy (NPT) on PFS as determined by the investigator will be assessed depending on the number of patients who receive NPT before a PFS event. If >5% of patients received NPT before a PFS event in any treatment arm, a sensitivity analysis will be performed for the comparisons between two

treatment arms in which data from patients who received NPT before a PFS event will be censored at the last tumor assessment date before receipt of NPT.

The methods outlined for the primary efficacy endpoints will be used for these analyses.

4.4.3.1.3 Subgroup Analyses

The consistency of PFS results in subgroups will be examined in the populations where PFS benefit has been demonstrated. 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 and displayed in a forest plot (Lewis and Clarke 2001).

4.4.3.1.4 Impact of Missing Scheduled Tumor Assessments

The impact of missing scheduled tumor assessments on PFS will be assessed depending on the number of patients who missed assessments scheduled immediately prior to the date of disease progression per RECIST v1.1 or the data cutoff. If $>5\%$ of patients missed two or more assessments scheduled immediately prior to the date of disease progression per RECIST v1.1 or the data cutoff in any treatment arm, the following two sensitivity analyses will be performed:

- 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 assessments scheduled immediately prior to the date of the PFS event, the patient will be counted as having disease progression on the date of the first of these missing assessments.

Statistical methodologies analogous to those used in the primary analysis of PFS as specified in Section 4.4.1 will be used for this sensitivity analysis.

4.4.3.2 Exploratory Analyses of Overall Survival

4.4.3.2.1 Overall Survival at 3-Year Landmark Timepoint

OS rate at 3 years will be estimated and analyzed using the same method as described in Section 4.4.2.3.

4.4.3.2.2 Impact of Loss to Follow-Up

The impact of loss to follow-up on OS will be assessed depending on the number of patients who are lost to follow-up. If $>5\%$ of patients are lost to follow-up for OS in either treatment arm, a sensitivity analysis will be performed for the comparisons between two treatment arms 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.

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

4.4.3.2.3 Subgroup Analyses

The consistency of OS results in subgroups will be examined in the populations where OS benefit has been demonstrated. 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), and 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 and displayed in a forest plot (Lewis and Clarke 2001).

4.4.3.2.4 Milestone Overall Survival Analysis

To assess the potential effect of long-term survival and delayed clinical effects, a milestone OS analysis may be conducted (Chen 2015). The milestone timepoints may be chosen such that the patients included in the analysis will achieve a certain patient-event ratio. The milestone OS analysis will be conducted only when the milestone duration has elapsed from the time the last patient entered the study, using the same methods as those specified for the primary OS analysis.

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

The impact of NPT on OS will be assessed depending on the number of patients who receive NPT. If $>$ 10% of patients received an NPT in the control arm, the following analyses may be performed to compare treatment arms:

- The discount method uses a “discounted” survival time after switching for patients who switch treatments based on a user-specified assumption for the effect on OS. OS will be discounted in accordance with a range of possible effects on OS of the subsequent NPT after treatment switching occurred (e.g., 10%, 20%, 30%).
- Rank-preserving structural failure time provides an estimate of the OS time for the control group had NPT not occurred (Robins and Tsiatis 1991). It estimates OS measured from the time of NPT by applying an estimate of the benefit of the NPT. The total overall survival time (sum of time to NPT and the estimated survival time after NPT started) will then be analyzed using the same methodology as for the primary analysis of OS.
- The inverse probability of censoring weighting method censors patients at start of NPT and uses the control arm patients to create weights that represent how NPT-treated-like a non-NPT-treated patient is (Robins and Finkelstein 2000). These time-varying weights are included in the OS analysis to correct the effect of NPT by giving increased weight to non-censored patients with similar characteristics to censored patients.

4.4.3.3 Biomarker Analysis

Exploratory biomarker analyses may be performed in an effort to understand the association of these markers with efficacy (PFS, OS, and/or ORR, etc.). The biomarkers include but are not limited to blood-based tumor mutational burden (bTMB) using the cut-offs of ≥10 and ≥16 separately (given data availability), and PD-L1 IHC using a cut-off of PD-L1 expression (e.g.at least 1% of tumor and/or tumor-infiltrating immune cells for TC1/2/3 or IC1/2/3 population with SP142 assay) (given data availability). Additional analyses of predictive, prognostic, and pharmacodynamic exploratory biomarkers (such as additional PD-L1 IHC assays or PD-L1 expression cut-offs) in archival and/or fresh tumor tissue and blood and their association with disease status, mechanisms of resistance, and/or response to study treatment may be conducted as appropriate. These exploratory analyses may not be included in the Clinical Study Report (CSR).

4.4.3.4 Utility Scores of the EuroQoL 5 Dimensions 5-Level Version

For the EQ-5D-5L health state profiles, descriptive statistics summarizing the proportions of patients who reported having "no," "slight," "moderate," "severe," or "extreme/unable" problems at each time point will be reported. Patients without post-baseline assessments will be excluded from this analysis. A single summary index from the EQ-5D-5L health states will be used in this study for economic modeling. These results will not be reported in the CSR.

4.4.3.5 Patient-Reported Outcomes of Health-Related Quality of Life

Additional PROs of health-related quality of life (Global Health Status), function (Physical and Role Function), commonly reported treatment-related symptoms (e.g., nausea/vomiting, diarrhea, and peripheral neuropathy), and disease-related symptoms (e.g., chest pain, cough, dyspnea) will be assessed according to the EORTC QLQ-C30, EORTC QLQ-LC13, and SILC scoring manual guidelines. Missing PRO scores will not be imputed. The following analyses may not be included in the Clinical Study Report.

In the ITT population, summary statistics (mean, SD, median, 25th and 75th percentiles, and range) and the proportion of patients per response category will be reported for all the items and subscales of the EORTC QLQ-C30 questionnaire and the EORTC QLQ-LC13 according to the EORTC scoring manual guidelines and the SILC symptom score by visit (baseline, end of treatment, disease progression, survival follow-up) and by treatment arm.

In the ITT population, completion and compliance rates will be summarized by number and proportion of patients among those expected to complete each questionnaire at each time point by treatment arm. If collected, reasons for non-completion will be summarized at each time point by treatment arm.

In addition, to interpret the evolution over time in lung-cancer disease symptoms, treatment-related symptoms, HRQoL, and function, the following analyses may be

documented in the PRO-evaluable population, which is defined as all randomized patients with a non-missing baseline assessment and at least one non-missing post-baseline assessment until treatment discontinuation.

- The mean change in scores from baseline at each timepoint, including end of treatment and disease progression. Repeated measures mixed-effect model will be used for comparing the scale scores (EORTC QLQ-C30, EORTC QLQ-LC13) between treatment arms. The model will include a term for intercept, a term for linear time trend, a term for treatment group, and a term of treatment-by-time interaction. Repeated measured over time will be accounted for by unstructured covariance structure.
- The number and proportion of patients with a clinically meaningful change will be summarized by treatment arm for each of the scale scores (EORTC QLQ-C30, EORTC QLQ-LC13, and SILC). The 95% CI around the proportion will be calculated using the Clopper-Pearson method for each treatment arm. The difference in proportions between the two treatment arms will be presented with a two-sided 95% CI based on a normal approximation to the binomial distribution.

PRO data obtained from measures completed during the survival follow-up phase (EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L, and SILC) will be summarized descriptively.

4.4.4 Sensitivity Analysis

4.4.4.1 Delayed Clinical Effect

If a delayed separation of the KM curves is observed at the beginning of the curves and the delay is $\geq$ 3 months, the following analyses could be conducted to assess a potential delayed clinical effect for the treatment group.

Restricted Mean Survival Time

The restricted mean survival time (RMST) will be computed for OS using the area under the curve from baseline to several timepoints. RMST will be computed for each treatment arm and the difference with its 95% CI will be displayed.

Weighted Log-Rank Analysis

Where the delayed clinical effect is $>$ 10% of the median survival time of the control group, an analysis of OS may be performed using the weighted log-rank test (Fleming and Harrington 1991) that weights more heavily on late events to account for the delayed clinical effect (Fine 2007).

4.4.4.2 Progression-Free Survival by Independent Review Facility

PFS as assessed by the IRF is defined as the time from randomization to the first documented disease progression as determined by the IRF using RECIST v1.1 or death from any cause, whichever occurs first. PFS as assessed by the IRF will be examined as sensitivity analysis using the same methods that will be used for PFS as assessed by the investigator.

4.5 PHARMACOKINETIC ANALYSES

PK analyses will be performed for the PK-evaluable population. 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. In addition, the concentrations of carboplatin, cisplatin, and pemetrexed will be summarized with these descriptive statistics.

Additional PK analyses will be conducted as appropriate, on the basis of the availability of data. These additional PK analyses will not be included in the CSR.

4.6 SAFETY ANALYSES

Unless specified otherwise, safety analyses described in this section will be conducted for the safety population, with patients grouped according to whether they received any atezolizumab treatment (i.e., patients who received any dose of atezolizumab will be included in the atezolizumab arm for the safety analyses).

4.6.1 Exposure of Study Medication

Study drug exposure statuses, which include treatment duration, number of cycles, and dose intensity, will be summarized for each treatment arm with descriptive statistics.

4.6.2 Adverse Events

Verbatim description of adverse events will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded by the investigator according to NCI CTCAE v4.0. Treatment-emergent adverse events will be summarized by mapped term, appropriate thesaurus level, NCI CTCAE grade, and treatment arm. In addition, serious adverse events, severe adverse events (Grade $\geq$ 3), adverse events of special interest, immune-mediated adverse events, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum grade.

For reporting purposes, “treatment emergent” is defined as adverse events occurring on or after the first dose of study drug is administered until the clinical cutoff date.

All listings of adverse events will also include all adverse events with onset on or after the first study drug treatment until the data cutoff date.

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

4.6.3 Laboratory Data

Laboratory data will be summarized by treatment arm. Values outside the normal ranges will be summarized by treatment arm. In addition, selected laboratory data will be summarized by treatment arm and NCI CTCAE grade.

4.6.4 Vital Signs

Changes in selected vital signs will be summarized by treatment arm and by change over time, which includes change from baseline. Baseline is defined as the measurement obtained on Cycle 1, Day 1 before the first dose of study drug is administered.

ECOG performance status will also be summarized over time.

4.6.5 Anti-Drug Antibody Against Atezolizumab

Incidence of ADA against atezolizumab will be summarized. The analyses of pharmacokinetics, key efficacy, and safety by ADA status will be conducted to explore the potential impact of immunogenicity.

4.7 MISSING DATA

See Sections 4.4 and 4.6 for methods for handling missing data for the primary and secondary endpoints.

5. [redacted]

[redacted]

[redacted]

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Appendix 1
Protocol Synopsis for Study GO29438

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]

Appendix 1
Protocol Synopsis for Study GO29438 (cont.)

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

  Lymphocyte count ≥500/μL

  Platelet count ≥100,000/μL without transfusion

  Hemoglobin ≥9.0 g/dL

  Patients may be transfused to meet this criterion.

  INR or aPTT ≤1.5×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 ≤2.5×ULN, with the following exceptions:

  Patients with documented liver metastases: AST and/or ALT ≤5×ULN

  Patients with documented liver or bone metastases: alkaline phosphatase ≤5×ULN.

  Serum bilirubin ≤1.25×ULN

  Patients with known Gilbert disease who have serum bilirubin level ≤3× ULN may be enrolled.

  Calculated creatinine clearance (CRCL) ≥45 mL/min or, if using cisplatin, calculated CRCL must be ≥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 (≥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 ≥ 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 ($\leq$ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study.

Appendix 1
Protocol Synopsis for Study GO29438 (cont.)

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.

Appendix 1
Protocol Synopsis for Study GO29438 (cont.)

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.*

Appendix 2
Schedule of Assessments for Study GO29438

Procedure	Screening	All Treatment Cycles a		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1–4 or 6)	Maintenance Phase	≤ 30 Days after Last Dose of Study Treatment	Every 3 Months after Disease Progression or Loss of Clinical Benefit
	Days –28 to –1	Every 21 Days (± 3 Days) [b]	Every 21 Days (± 3 Days)		
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	

Procedure	Screening	All Treatment Cycles a		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1–4 or 6)	Maintenance Phase	≤ 30 Days after Last Dose of Study Treatment	Every 3 Months after Disease Progression or Loss of Clinical Benefit
	Days –28 to –1	Every 21 Days (± 3 Days) [b]	Every 21 Days (± 3 Days)		
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 ADA assessment (atezolizumab-treated patients only) [r]		x	x	x	120 (± 30) days after last dose of atezolizumab
Serum sample for PK sampling (atezolizumab-treated patients only) [r]		x	x	x	120 (± 30) days after last dose of atezolizumab

Procedure	Screening	All Treatment Cycles [a]		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1–4 or 6)	Maintenance Phase	≤ 30 Days after Last Dose of Study Treatment	Every 3 Months after Disease Progression or Loss of Clinical Benefit
	Days –28 to –1	Every 21 Days (± 3 Days) [b]	Every 21 Days (± 3 Days)		
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]

ADA = anti-drug 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.

[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.

[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,* study staff may use a public information source (e.g., county records), when permissible, to obtain information about survival status only