Official Title: A Phase III, Multicenter, Randomized, Open-Label, Controlled Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Atezolizumab Given in Combination With Cabozantinib Versus Docetaxel Monotherapy in Patients With Metastatic Non-Small Cell Lung Cancer Previously Treated With an Anti-PD-L1/PD-1 Antibody and Platinum-Containing Chemotherapy

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STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL, CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF ATEZOLIZUMAB GIVEN IN COMBINATION WITH CABOZANTINIB VERSUS DOCETAXEL MONOTHERAPY IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER PREVIOUSLY TREATED WITH AN ANTI-PD-L1/PD-1 ANTIBODY AND PLATINUM-CONTAINING CHEMOTHERAPY**

PROTOCOL NUMBER: GO41892

STUDY DRUG: Atezolizumab (RO5541267) and Cabozantinib (XL184)

VERSION NUMBER: 1

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EUDRACT NUMBER: 2020-000100-11

SPONSOR: F. Hoffmann-La Roche Ltd

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

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STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
07-Feb-2022 19:20:03	Company Signatory	[redacted]

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1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study GO41892 (CONTACT-01), a Phase III, multicenter, randomized, open-label, controlled study evaluating the efficacy and safety of atezolizumab (MPDL3280A, anti-programmed death-ligand 1 [PD-L1] antibody), in combination with cabozantinib (inhibitor of multiple receptor tyrosine kinase [RTKs], including vascular endothelial growth factor receptor 2 [VEGFR2], mesenchymal-epithelial transition [MET], rearranged during transfection [RET], and Tyro3-Axl-Mer [TAM] family kinases) compared with docetaxel monotherapy in patients with metastatic non-small cell lung cancer (NSCLC) previously treated with an anti-PD-L1/programmed death 1 (PD-1) antibody and platinum-containing chemotherapy. The background for the study can be found in the study protocol.

2. STUDY DESIGN

This is a Phase III, multicenter, randomized, open-label study designed to evaluate the efficacy, safety, and pharmacokinetics of atezolizumab given in combination with cabozantinib compared with docetaxel in approximately 350 patients with metastatic NSCLC, with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation, who have progressed following treatment with anti-PD-L1/PD-1 antibody and platinum-containing chemotherapy.

Eligible patients were stratified by tumor histology (non-squamous vs. squamous), and prior NSCLC treatment regimen(s) at the following four levels:

1. Concurrent platinum-containing chemotherapy and anti-PD-L1/PD-1 antibody combination
2. Platinum-containing chemotherapy first, disease progression occurs, followed by anti-PD-L1/PD-1 antibody
3. Anti-PD-L1/PD-1 antibody monotherapy first, disease progression occurs, followed by platinum-containing chemotherapy without anti-PD-L1/PD-1 antibody
4. Anti-PD-L1/PD-1 antibody monotherapy first, disease progression occurs, followed by continued anti-PD-L1/PD-1 antibody in combination with platinum-containing chemotherapy added on

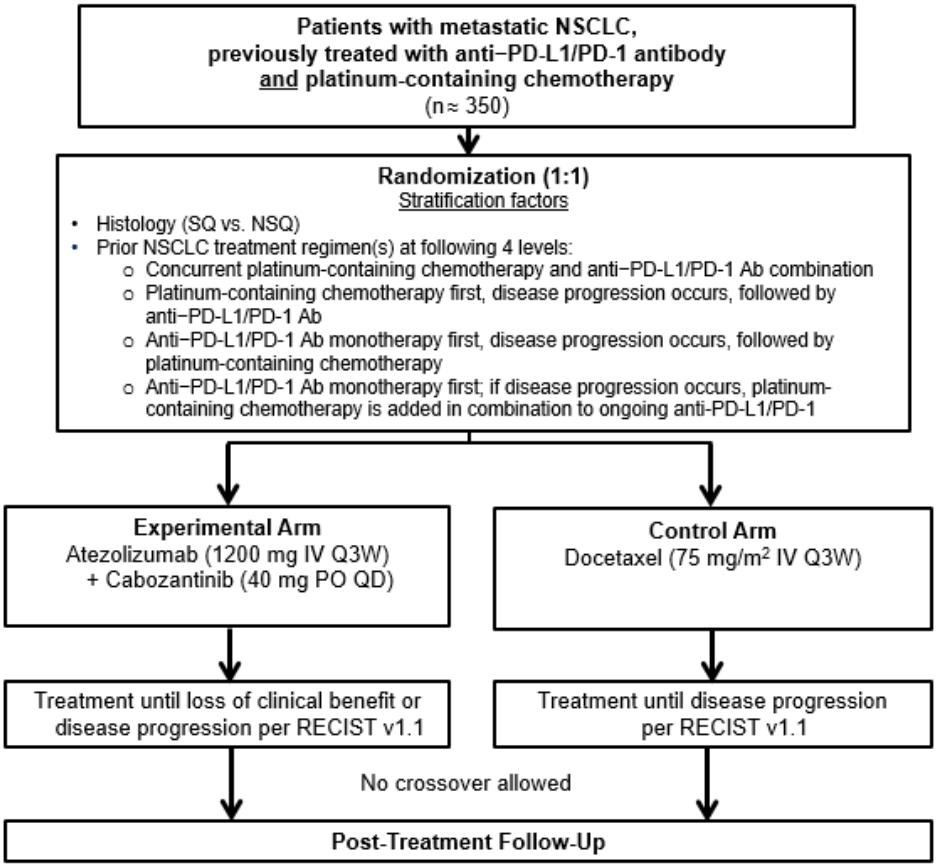
Eligible patients will be randomized in a 1:1 ratio to receive either atezolizumab plus cabozantinib (the experimental arm) or docetaxel monotherapy (the control arm).

In the experimental arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by intravenous (IV) infusion every 3 weeks (Q3W) on Day 1 of each 21-day cycle, followed by 40 mg cabozantinib (2×20-mg tablets), administered orally once a day (QD) on Days 1-21 of each cycle.

In the control arm, patients will receive docetaxel at a starting dose of 75 mg/m^2 Q3W, administered by IV infusion according to the locally approved label.

Treatment in the control arm will continue until unacceptable toxicity or disease progression as assessed by the investigator per Response Evaluation Criteria for Solid Tumors, Version 1.1 (RECIST v1.1). Treatment in the experimental arm will continue until unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). During the study treatment, patients randomized to the experimental arm who meet the criteria for disease progression per RECIST v1.1 and show evidence for clinical benefit may continue study treatment (atezolizumab and/or cabozantinib) at the investigator's discretion provided that the patients meet all of the criteria specified in study protocol Section 3.1 and provide written consent. Figure 1 illustrates the study design of which details can be found in the study protocol.

Figure 1 Study Schema



Ab = antibody; IV=intravenous; NSCLC = non-small cell lung cancer; NSQ = non-squamous; PD-L1/PD-1= progressive disease-ligand 1; PO = by mouth; QD = once a day; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SQ = squamous.

Patients will undergo tumor assessments at baseline and every 6 weeks (±7 days) for 48 weeks following Day 1 of Cycle 1 regardless of treatment delays (see study protocol Section 4.5.5 and Appendix 1). After the completion of the Week 48 tumor assessment, tumor assessments will be required every 9 weeks (±7 days) regardless of treatment delays until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Patients in the experimental arm who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments at the frequency described above until study treatment is discontinued. Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. In the absence of radiographic

disease progression per RECIST v1.1, tumor assessments should continue regardless of whether a patient starts a new anti-cancer therapy.

In order not to confound the overall survival (OS) endpoint, crossover will not be allowed from the control arm (docetaxel monotherapy) to the experimental arm (atezolizumab plus cabozantinib).

The primary efficacy endpoint is OS. See Section 2.2 for details on primary endpoint, secondary endpoints, and other endpoints such as safety, pharmacokinetics (PK), and exploratory outcome measures.

The primary analysis of all OS analyses will be performed on intent-to-treat (ITT) population (i.e., all randomized patients), with patients grouped according to the treatment assigned at randomization, regardless of whether they received any assigned study drug (See Section 4.1 for details on analysis populations).

There is one interim analysis planned for OS in this study. See Section 2.4 for detailed analysis timing.

An external independent Data Monitoring Committee (iDMC) will be set up to evaluate safety data on an ongoing basis and to review the interim analysis for OS.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Activities in Appendix 2 and Appendix 3.

2.2 OBJECTIVES AND ENDPOINTS

2.2.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus cabozantinib compared with docetaxel monotherapy on the basis of the following endpoint:

- OS, defined as the time between the date of randomization and date of death from any cause in the ITT population

2.2.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus cabozantinib compared with docetaxel monotherapy on the basis of the following endpoints:

- Progression-free survival (PFS), defined as the time from randomization to the first occurrence of the disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first, in the ITT population

- Confirmed objective response, defined as the proportion of patients with either a complete response (CR) or a partial response (PR), as determined by the investigator according to RECIST v1.1 on two consecutive occasions ≥4 weeks apart, in the ITT population with measurable disease at baseline
- Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first, in the ITT population with confirmed objective response
- Time to confirmed deterioration (TTCD) in patient-reported physical functioning (PF) and global health status/quality of life (GHS/QoL) as measured by the corresponding scale scores from the European Organization for Research and Treatment of Cancer Quality of Life–Core 30 (EORTC QLQ-C30) questionnaire in the ITT population
- PFS rates at 6 months and 1 year, defined as the proportion of patients alive and without progression as assessed by the investigator according to RECIST v1.1 at 6 months and 1 year after randomization estimated using Kaplan-Meier (KM) methodology in the ITT population
- OS rates at 1 and 2 years, defined as the proportion of patients alive at 1 and 2 years after randomization estimated using KM methodology in the ITT population

2.2.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of atezolizumab plus cabozantinib compared with docetaxel monotherapy on the basis of the following endpoint:

- Change from baseline and the proportion of patients who report deterioration, improvement or no change in their symptoms and function including quality of life (QoL) as measured by EORTC Quality of Life–Lung Cancer 13-Item Questionnaire (EORTC QLQ-LC13) and EORTC QLQ-C30

2.2.4 Pharmacokinetic Objective

The PK objective for this study is to characterize the PK profile of atezolizumab plus cabozantinib on the basis of the following endpoints:

- Serum concentration of atezolizumab at specific timepoints
- Plasma concentrations of cabozantinib at specific timepoints

2.2.5 Safety Objectives

The safety objective for this study is to evaluate the safety of atezolizumab plus cabozantinib compared with docetaxel monotherapy on the basis of the following endpoint:

- Incidence and severity of adverse events (AEs) with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)

The exploratory safety objective for this study is to evaluate the safety of atezolizumab+cabozantinib compared with docetaxel monotherapy from the patient's perspective on the basis of the following endpoints:

- Presence, frequency of occurrence, severity and/or degree of interference with daily function of selected symptoms frequently reported with the intake of atezolizumab, cabozantinib, or docetaxel, as determined through the use of NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE)
- Change from baseline in selected symptoms frequently reported with the intake of atezolizumab, cabozantinib, or docetaxel, as assessed through use of the PRO-CTCAE
- Frequency of patients' response of the degree they are troubled with treatment symptoms, as assessed through use of the single item EORTC Item List 46 (EORTC-IL46)

2.2.6 Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab plus cabozantinib on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) to atezolizumab at baseline and incidence of ADAs to atezolizumab after treatment

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs to atezolizumab on the basis of the following endpoint:

- Relationship between atezolizumab ADA status and efficacy, safety, or PK endpoints

2.2.7 Exploratory Biomarker Objective

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers on the basis of the following endpoint:

- Relationship between biomarkers in peripheral blood mononuclear cells (PBMC), plasma, serum, and tumor tissue (including, but not limited to, PD-L1, PD-1, prevalence of immune subsets, circulating factors, gene expression, gene expression signatures of tumor and immune biology, somatic mutations, tumor mutation burden, and others) and efficacy, PK, immunogenicity, or other endpoints

2.2.8 Health Status Utility Objective

The health status utility objective for this study is to evaluate health status utility scores of patients treated with atezolizumab plus cabozantinib compared with docetaxel monotherapy on the basis of the following endpoints:

- Health utility scores from the EuroQol 5-Dimension Questionnaire (5-level version, EQ-5D-5L) index-based at each timepoint
- Change from baseline at each timepoint using the EQ-5D-5L visual analog scale (VAS) scores

2.3 DETERMINATION OF SAMPLE SIZE

The study is designed to test the hypothesis that atezolizumab in combination with cabozantinib prolongs the duration of OS compared to the control arm (docetaxel) in the ITT population. This study randomized approximately 350 patients and the primary comparison of OS will be tested at a two-sided alpha level of 0.05. No formal hypothesis testing will be conducted on other endpoints.

OS will be tested using the group sequential method at the interim and final OS analyses. Statistical significance at the interim and final analyses of OS will be tested as described in Section 2.4.1.

The sample size determination is based on the number of events required to demonstrate efficacy with regards to OS in the ITT population. The estimates of the number of events required is based on the following assumptions:

- 1:1 randomization ratio
- OS curve follows the exponential distribution
- Two-sided significance level of 0.05 for the comparison of OS
- 90% power to detect an HR of 0.64 in OS in the ITT population, corresponding to an improvement in median OS from 9 to 14.1 months in the ITT population
- One OS interim analysis is to be performed when approximately 83% of the total number of OS events required for the final analysis have occurred. Crossing boundaries are determined based on the Hwang-Shih-DeCani alpha spending function with the gamma parameter of –2.5 (Hwang et al. 1990)
- Accrual duration of approximately 16 months
- Dropout rate of 5% per 24 months for each treatment arm for OS

With these assumptions, approximately 350 patients (approximately 175 per arm) in total will be randomized into the study.

2.4 ANALYSIS TIMING

2.4.1 Interim and Final Analysis Timing for OS

There is one interim analysis planned for the endpoint of OS.

The timing of the primary efficacy analysis will be driven by the number of events required for the OS interim analysis, which will be conducted when approximately 182 OS events have occurred. Based on the assumptions in Section 2.3, the OS interim analysis is expected to occur approximately 23 months after the first patient is randomized.

The final OS analysis will be conducted when approximately 220 OS events has occurred, which is expected to occur 28 months after the first patient is enrolled. This number of final OS events corresponds to a minimum detectable difference corresponding to an HR of approximately 0.757. The expected analysis timing for the OS interim and final analyses is shown in Table 1.

Table 1 Analysis for Overall Survival

	Analysis Timing		ITT population		
Analysis	Months from FPI	Percent Information, %	No. of Events (Event Ratio, %)	Power, % [a]	Stopping Boundary HR (p-value[b])
OS interim analysis	23	83	182 (52)	80	HR≤0.726 (p≤0.0310)
OS final analysis	28	100	220 (63)	90	HR≤0.757 (p≤0.0396)

FPI=first patient in; HR=hazard ratio; ITT=intent-to-treat; OS=overall survival.

[a] Power is calculated using two-sided alpha of 0.05.

[b] Two-sided p-value.

The stopping boundaries for the interim and final OS analyses are calculated using the Hwang-Shih-DeCani alpha spending function with the gamma parameter of –2.5, assuming the specified observed number of events (182 and 220, respectively), and are shown in Table 1. The p-value will be used to claim crossing of the boundaries. For example, if approximately 182 events have occurred in the ITT population at the time of the OS interim analysis, statistical significance of the OS endpoint in the ITT population will be declared if p≤0.0310.

Due to logistic considerations in event ascertainment and operational planning and conduct, the actual analyses may include more or fewer events than the target information fractions. The actual critical values employed at the interim and final analyses of OS will depend upon the actual information fraction at the time of the analyses.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Randomization to the treatment and control arms will occur in a 1:1 ratio using a permuted-block randomization method. Randomization will be stratified by the following factors:

- Histology (nonsquamous vs. squamous)
- Prior NSCLC treatment regimen(s) at the following four levels:
    1. Concurrent platinum-containing chemotherapy and anti-PD-L1/PD-1 antibody combination
    2. Platinum-containing chemotherapy first, disease progression occurs, followed by anti-PD-L1/PD-1 antibody
    3. Anti-PD-L1/PD-1 antibody monotherapy first, disease progression occurs, followed by platinum-containing chemotherapy without anti-PD-L1/PD-1 antibody
    4. Anti-PD-L1/PD-1 antibody monotherapy first, disease progression occurs, followed by continued anti-PD-L1/PD-1 antibody in combination with platinum-containing chemotherapy added on

3.2 DATA MONITORING

An external iDMC will be used to evaluate safety data and review the interim analysis for OS. Unblinded safety data will be reviewed on a periodic basis, approximately every 6 months from the point of first patient in until the time the database is locked. Unblinded efficacy data will be reviewed as part of an interim analysis for OS. All summaries and analyses by treatment arm for the iDMC review will be prepared by an independent data coordinating center (iDCC).

Following the data review, the iDMC will provide a recommendation as to whether the study may continue, whether amendment(s) to the protocol should be implemented, or whether the study should be stopped. For the interim analysis of OS, the iDMC will review the analysis results provided by the iDCC and will recommend or not recommend to unblind the study to the Sponsor. 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 to outline their roles and responsibilities, as well as a detailed monitoring plan.

4. STATISTICAL METHODS

The analyses described in this SAP will supersede those specified in Protocol GO41892 for the purposes of a regulatory filing.

4.1 ANALYSIS POPULATIONS

4.1.1 Efficacy Analysis Population

The randomized population or ITT population is defined as all randomized patients, whether or not the patient received the assigned treatment.

The analyses of PFS and all OS analyses will be performed on the ITT population. Patients are grouped according to the treatment assigned at randomization, regardless of whether they received any assigned study drug.

Confirmed objective response rate (ORR) will be analyzed in the ITT population who have measurable disease as assessed by investigator at baseline.

DOR will be assessed in patients in the ITT population who have a confirmed objective response as determined by the investigator using RECIST v1.1.

Analyses of the EORTC QLQ-C30 and EORTC QLQ-LC13 data will be conducted in the ITT population.

PFS rate at the 6-month and 1-year landmark timepoints will be analyzed in the same population as defined for the PFS analysis.

OS rate at the 1- and 2-year landmark timepoints will be analyzed in the same population as defined for the OS analyses.

4.1.2 Pharmacokinetic-Evaluable Population

The pharmacokinetic-evaluable population is defined as all patients who received any dose of atezolizumab or cabozantinib and who have evaluable PK samples.

4.1.3 Safety Population

The safety population includes treated patients, defined as all randomized patients who receive any amount of study drug. Specifically, a patient will be included in the experimental arm in the safety analyses if the patient receives any amount of atezolizumab or cabozantinib, regardless of the initial treatment assignment at randomization.

Analyses of the PRO-CTCAE and the EORTC IL46 data will be conducted in the safety population.

4.1.4 Immunogenicity Population

The immunogenicity analysis population will consist of all patients with at least one ADA assessment for atezolizumab. Patients will be grouped according to the treatment received.

4.2 ANALYSIS OF STUDY CONDUCT

Study enrollment, major protocol deviations, including major deviations from inclusion/exclusion criteria, and reasons for study termination will be summarized overall and by treatment arm for the ITT population. Study treatment administration and reasons for discontinuation from study treatment will be summarized for the safety population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic characteristics, such as age, sex, race/ethnicity, baseline disease characteristics (e.g., Eastern Cooperative Oncology Group [ECOG] performance status, smoking status), and stratification factors (histology, prior NSCLC treatment regimens) will be summarized by treatment arms. Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

Unless otherwise noted, baseline measurements are the last available data obtained prior to the patient receiving the first dose of any component of study drug on Cycle 1, Day 1.

4.4 EFFICACY ANALYSIS

Patients will be grouped for efficacy analyses according to the treatment assigned at randomization, whether or not the assigned treatment was received.

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is OS.

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

The null (H_0) and alternative (H_1) hypotheses regarding OS in a population can be phrased in terms of population hazard ratio (HR) λ between the atezolizumab plus cabozantinib arm (Arm A) and the docetaxel arm (Arm B):

H_0: $\lambda=1$ versus H_1:$\lambda\neq1$

If the estimate of the HR, λ is <1 and the two-sided p-value corresponding to the stratified log-rank test is less than the specified α level, then the null hypothesis will be rejected, and it will be concluded that the combination of atezolizumab plus cabozantinib prolongs the duration of OS relative to the control treatment.

The HR and associated 95% confidence interval (CI) will be estimated using a stratified Cox regression model with the same stratification variables used for stratified log-rank test. Results from an unstratified analysis will also be provided.

For OS analyses in the ITT population, the stratification factors will be histology, and prior NSCLC treatment regimens, as listed in Section 3.1. The stratification factors will be the same as those recorded in the interactive voice/web response system.

The analyses based on stratification factors as recorded on the electronic Case Report Form (eCRF) may also be provided.

Treatment comparison will be conducted by comparing Arm A versus Arm B based on stratified log-rank test for primary endpoint of OS at the two-sided significance level as described in Section 2.4.1. Kaplan-Meier methodology will be used to estimate the median OS and to construct survival curves for each treatment arm for a visual description of the difference among arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS (Brookmeyer and Crowley 1982).

Follow-up for OS, defined as the time from randomization to death or last known date alive, will be summarized for all patients included in the analysis (whether patient is alive or has died). Follow-up will be summarized using the KM method with data for patients who died censored at the date of death.

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 PFS in the ITT population

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

PFS by the investigator will be analyzed using the same method as the primary analysis of OS, described in Section 4.4.1.

4.4.2.2 Objective Response Rate

ORR is defined as the proportion of patients with a CR or PR on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1. Patients not meeting these criteria, including patients without any post-baseline tumor assessment, will be considered non-responders. ORR will be analyzed in patients with measurable disease at baseline and compared between treatment arms using the stratified Cochran-Mantel-Haenszel test, stratified by the same factors used in the primary OS analysis (Section 4.4.1). 95% CIs for the difference in ORRs between the two treatment arms will be determined using the normal approximation to the binomial

distribution. An estimate of ORR and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm.

4.4.2.3 Duration of Response

DOR will be assessed in patients who achieved a confirmed objective response as determined by the investigator according to RECIST v1.1. DOR is defined as the time from the date of the first occurrence of a confirmed CR or PR (whichever status is recorded first) until the first date of progression disease as determined by the investigator according to RECIST v1.1 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 the last tumor assessment date. 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.

4.4.2.4 Time to Confirmed Deterioration in Patient-Reported Physical Functioning and Global Health Status/Quality of Life

TTCD analyses will be performed for patient-reported physical functioning (items 1 to 5) and GHS/QoL (items 29 and 30) as measured by the EORTC QLQ-C30. Raw scores from both scales will be linearly transformed so that each score will range from 0 to 100. High scores (i.e., closer to 100) represent high/healthy level of functioning and health-related quality of life.

TTCD is defined as the time from the date of randomization to the first confirmed clinically meaningful deterioration on each respective scale score. Confirmed clinically meaningful deterioration for physical functioning and GHS/QoL is defined as a clinically meaningful decrease from baseline in physical functioning or GHS/QoL score that must be held for at least two consecutive assessments or an initial clinically meaningful decrease from baseline followed by death from any cause within 21 days or until the next tumor assessment, whichever occurs first. A score change of $\geq$10 points on either the EORTC QLQ-C30 physical functioning or GHS/QoL scale scores is determined as being clinically meaningful (Osoba et al. 1998).

The TTCD analyses will be performed in the ITT population and will include all data collected through disease progression and survival follow up. The methodologies that are outlined for the analysis of OS (Section 4.4.1) will be used for the analyses. TTCD for physical functioning and GHS/QoL will be summarized using the KM method. Comparison of TTCD for physical functioning and GHS/QoL between treatment arms will be performed using the stratified log-rank test; the stratified HRs and 95% CIs will also be reported. If no baseline or post-baseline assessment is performed, patients will be censored at the randomization date. Patients without a confirmed deterioration at the time of analysis will be censored at the last time they were known to have not deteriorated. There will be no imputation for missing baseline or post-baseline data for TTCD analyses.

4.4.2.5 PFS Rate at the 6-Month and 1-Year Landmark Timepoints

The PFS rates at 6 months and 1 year assessed by investigator will be estimated for each treatment arm using KM methodology, along with 95% CIs calculated using the standard error derived from Greenwood's formula. The 95% CI for the difference in PFS rates between the two treatment arms will be estimated using the normal approximation method, with standard errors computed using the Greenwood method.

4.4.2.6 OS Rate at the 1- and 2-Year Landmark Timepoints

The OS rate at the 1 and 2 years will be estimated for each treatment arm using KM methodology, 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, with standard errors computed using the Greenwood method.

4.4.3 Exploratory Efficacy Endpoints: Patient-Reported Outcomes

4.4.3.1 Completion Rate

Completion rates will be summarized by the number and the proportion of patients who completed the patient-reported outcome (PRO) questionnaires among those expected to complete the questionnaires at each timepoint. Reasons for non-completion will also be summarized if available.

4.4.3.2 Visit Score Summary and Change from Baseline

Visit summary and change from baseline analyses will be performed for the EORTC QLQ-C30 and QLQ-LC13 scales. Summary statistics (number of patients, mean, standard deviation, median, minimum, maximum) of score(s) and score change(s) from baseline will be presented. The analyses will be performed at each visit, end of treatment tumor progression, or clinical progression and will be presented by each treatment arm.

4.4.3.3 Proportion of Patients who Improved, Worsened, or Remained Stable

The number and proportion of patients who improved, worsened, or remained stable versus baseline on the EORTC QLQ-C30 and EORTC QLQ-LC13 scale scores will be summarized. For symptom scales, a decrease of ≥10 points from baseline will be considered an improvement, an increase of ≥10 points from baseline will be considered worsening, and a change of any other magnitude will be considered stabilization. For the functional and GHS/QoL scales, an increase of ≥10 points from baseline will be considered an improvement, a decrease of ≥10 points from baseline will be considered worsening, and a change of any other magnitude will be considered stabilization. The analyses will be performed at each visit, end of treatment tumor progression, or clinical progression and will be presented by each treatment arm.

4.4.4 Sensitivity Analyses

4.4.4.1 Non-Protocol Specified Anti-Cancer Therapy

The impact of subsequent non-protocol specified anti-cancer therapy (NPT) on OS will be assessed depending on the number of patients who received NPT. If >10% of patients received a NPT in either treatment arm, the following analyses may be performed to compare treatment arms:

- The discounted method uses a 'discounted' survival time after switching for patients who switch treatments based on a user-specified assumption for the effect in OS. OS may be discounted according to a range of possible effects on OS of the subsequent NPT after treatment switching occurred (e.g., 10%, 20%, 30%, etc.).

4.4.4.2 Loss to Follow-up

The impact of loss to follow-up on OS will be assessed depending on the number of patients who are lost to follow-up. If >5% of patients are lost to follow-up for OS in either treatment arm, a sensitivity analysis may be performed for the comparisons between two treatment arms in which patients who are lost to follow-up will be considered as having died at the last date they were known to be alive.

4.4.5 Subgroup Analyses

The consistency of OS results in subgroups will be examined. The subgroups are defined by the following:

- Demographics (e.g., age, sex, race/ethnicity)
- Baseline characteristics (e.g., ECOG performance status, histology, prior NSCLC treatment regimens [as listed in Section 3.1] and PD-L1 status)

Summaries of OS, including the unstratified HR estimated from a Cox proportional hazards model and KM estimates of median OS, will be produced separately for each level of the subgroup for the comparisons between treatment arms and displayed in a forest plot (Lewis and Clarke 2001).

Summaries of PFS by subgroup will also be provided.

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

PK samples will be collected in this study as outlined in Appendix 3. Atezolizumab serum concentration data (minimum serum concentration [C_{min}] and maximum serum concentration [C_{max}]) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Plasma concentrations of cabozantinib will be collected in this study as outlined in Appendix 3. The concentrations of cabozantinib will be summarized using descriptive statistics as described above.

Additional PK analyses may be conducted, as appropriate, based on the availability of data.

4.6 SAFETY ANALYSES

The safety population includes treated patients, defined as all randomized patients who receive any amount of the study drug. Specifically, a patient will be included in the atezolizumab plus cabozantinib experimental arm if the patient receives any amount of atezolizumab or cabozantinib, regardless of the initial treatment assignment at randomization.

4.6.1 Exposure of Study Medication

Study drug exposure, including treatment duration, dosage and dose intensity, will be summarized for each treatment arm with descriptive statistics.

4.6.2 Adverse Events

Verbatim description of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. Severity of all AEs will be graded by the investigator in accordance with the NCI CTCAE v5.0.

Treatment-emergent adverse events will be summarized by mapped term, appropriate thesaurus level, NCI CTCAE grade (wherever applicable), and treatment arm. Multiple occurrence of the same event in same patient will be counted once at the maximum grade. Common AEs, treatment-related AEs, serious adverse events (SAEs). AEs leading to study treatment discontinuation or interruption, Grade 3-4 AEs, fatal AEs (Grade 5) and immune-mediated AEs will be summarized accordingly.

For the purpose of analyses, AEs of special interest (AESIs) will be identified by a set of comprehensive definitions using standardized MedDRA queries (SMQs), High-level terms (HLTs), and Sponsor-defined adverse event grouped terms (AEGTs) from the clinical database and presented by medical concepts. AESIs will be summarized by treatment arm and NCI CTCAE grade. The medical concepts include atezolizumab-associated identified risks, potential risks and class effects reported with other immune-checkpoint inhibitors.

For the safety analyses, “treatment-emergent” is defined as AEs occurring on or after the first dose of study drug treatment or as a pre-existing condition that worsened on or after the first dose of the study treatment up to the data cutoff date.

Listings of AEs will include all treatment-emergent AEs up to the data cutoff date.

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

4.6.3 Laboratory Data

Laboratory data will be summarized by treatment arm. Laboratory data will be graded according to NCI CTCAE v5.0 and will be summarized descriptively. Shift tables from baseline to worst value post-baseline will also be presented.

4.6.4 Vital Signs

Changes in selected vital signs from baseline will be summarized by treatment arm.

4.6.5 Patient-Reported Outcome Data

Completion rates will be summarized by the number and the proportion of patients who completed the PRO questionnaires among those expected to complete the PRO questionnaires by treatment group at each timepoint. Reasons for non-completion will also be summarized if available.

Analyses of the PRO data (collected through selected items from the PRO-CTCAE item library and the overall tolerability item in the EORTC IL46) will be primarily descriptive. PRO-CTCAE data will be analyzed at the item level in line with current NCI recommendations for data handling (Basch et al. 2014). The number (percentage) of patients reporting symptoms by "frequency," "severity," "interference," and "presence" will be reported at each visit by treatment arm. PRO-CTCAE scores, and change in frequency of responses by symptom will also be summarized at each visit by treatment arm. The worst post-baseline score and the shift from baseline to the worst post-baseline will be summarized by treatment arm. For the EORTC IL46, the frequency of patients' response of the degree they are troubled with treatment symptoms will be analyzed by treatment group at each timepoint.

Results from these exploratory analyses will be presented separately from the other safety analyses.

4.7 IMMUNOGENICITY ANALYSES

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by treatment group. The evaluation of PK, efficacy, and safety endpoints by ADA status may be analyzed and reported via descriptive statistics.

4.8 EXPLORATORY BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with response to study drug, including efficacy (PFS, OS, and/or ORR). The biomarkers include but are not limited to PD-1, prevalence of immune subsets, circulating factors, gene expression, gene expression signatures of tumor and immune biology, somatic mutations, tumor mutation burden in blood and/or tumor tissue. These and additional predictive, prognostic, and pharmacodynamics exploratory

biomarkers in archival and/or fresh tumor tissue and/or blood may be examined for their association with disease status and/or clinical outcomes. These exploratory analyses will not be included in the Clinical Study Report (CSR) for this study.

4.9 HEALTH STATUS UTILITY ANALYSES

The EQ-5D-5L questionnaire will also be collected to generate health-related quality of life and utility scores for use in economic models for reimbursement. The analyses will not be included in the CSR for this study.

4.10 MISSING DATA

Please refer to Section 4.4.1 and Section 4.4.2 for methods of handling missing data for the primary and secondary efficacy endpoints.

5. REFERENCES

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Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst 2014;106:1-11.

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Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. J clin oncol. 1998;16:139-44.

Appendix 1 Protocol Synopsis

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL, CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF ATEZOLIZUMAB GIVEN IN COMBINATION WITH CABOZANTINIB VERSUS DOCETAXEL MONOTHERAPY IN PATIENTS WITH METASTATIC NON–SMALL CELL LUNG CANCER PREVIOUSLY TREATED WITH AN ANTI–PD-L1/PD-1 ANTIBODY AND PLATINUM-CONTAINING CHEMOTHERAPY**
PROTOCOL NUMBER:	GO41892
VERSION NUMBER:	3
EUDRACT NUMBER:	2020-000100-11
IND NUMBER:	146261
NCT NUMBER:	*NCT04471428*
TEST PRODUCT:	Atezolizumab (RO5541267) and cabozantinib (XL184)
PHASE:	III
INDICATION:	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 when given in combination with cabozantinib (Atezo + Cabo) compared with docetaxel monotherapy in patients with metastatic non–small cell lung cancer (NSCLC), with no sensitizing epidermal growth factor receptor (*EGFR)* mutation or anaplastic lymphoma kinas (*ALK)* translocation, who have progressed on prior treatment with both anti–PD-L1/PD-1 antibody and platinum-containing chemotherapy. Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of Atezo + Cabo compared with docetaxel monotherapy on the basis of the following endpoint:

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

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of Atezo + Cabo compared with docetaxel monotherapy on the basis of the following endpoints:

- *Progression-free survival* (PFS), defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to Response Evaluation Criteria in Solid Tumor, Version 1.1. (RECIST v1.1), or death from any cause (whichever occurs first)

- Confirmed objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1
- Duration of response (DOR) for patients with confirmed ORR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first)
- Time to confirmed deterioration in patient–reported Physical Function (PF) and global health status (GHS) as measured by the corresponding scores from the European Organisation for the Research and Treatment of Cancer Quality of Life–Core 30 (EORTC QLQ-C30)
- PFS rates assessed by the investigator at 6 months and at 1 year
- OS rates at 1 and 2 years

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of Atezo + Cabo compared with docetaxel monotherapy on the basis of the following endpoint:

- Change from baseline and proportion of patients who report deterioration, improvement or no change in their symptoms and functioning including quality of life (QoL) as measured by the EORTC Quality of Life–Lung Cancer 13-Item Questionnaire (EORTC QLQ-LC13) symptom scores (cough, dyspnea, chest pain, arm/shoulder pain, or fatigue) and EORTC QLQ-C30 functioning scores (PF, Role Function [RF], GHS)

Safety Objectives

The safety objective for this study is to evaluate the safety of Atezo + Cabo compared with docetaxel monotherapy on the basis of the following endpoint:

- Incidence and severity of adverse events with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)

The exploratory safety objective for this study is to evaluate the safety of Atezo + Cabo compared with docetaxel monotherapy from the patient's perspective on the basis of the following endpoints:

- Presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptoms frequently reported with the intake of atezolizumab, cabozantinib, or docetaxel, as determined through the use of the NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE)
- Change from baseline in selected symptoms frequently reported with the intake of atezolizumab, cabozantinib, or docetaxel, as assessed through use of the PRO-CTCAE
- Frequency of patients' response of the degree they are troubled with treatment symptoms, as assessed through use of the single item EORTC Item List (EORTC IL46)

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the PK profile of Atezo + Cabo on the basis of the following endpoints:

- Serum concentration of atezolizumab at specified timepoints
- Plasma concentration of cabozantinib at specified timepoints

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to Atezo + Cabo on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) to atezolizumab at baseline and incidence of ADAs to atezolizumab after treatment

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs to atezolizumab on the basis of the following endpoint:

- Relationship between atezolizumab ADA status and efficacy, safety, or PK endpoints

Exploratory Biomarker Objective

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to Atezo + Cabo (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to Atezo + Cabo, can provide evidence of Atezo + Cabo activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- Relationship between biomarkers in peripheral blood mononuclear cells (PBMC), plasma, serum, and tumor tissue (including, but not limited to, PD-L1, PD-1, somatic mutations, and others) and efficacy, PK, immunogenicity, or other biomarker endpoints.

Health Status Utility Objectives

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with Atezo + Cabo compared with docetaxel monotherapy to inform pharmacoeconomic modeling on the basis of the following endpoints:

- Health utility scores from the EuroQol 5-Dimension Questionnaire (5-level version; EQ-5D-5L) index-based at each timepoint
- Change from baseline at each timepoint using the EQ-5D-5L visual analog scale (VAS) scores

Study Design

Description of Study

This is a Phase III, multicenter, randomized, open-label study designed to evaluate the efficacy, safety, and pharmacokinetics of atezolizumab given in combination with cabozantinib compared with docetaxel monotherapy in patients with metastatic NSCLC, with no sensitizing *EGFR* mutation or *ALK* translocation, who have progressed following treatment with platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody, administered concurrently or sequentially.

Approximately 350 eligible patients will be randomized in a 1:1 ratio at approximately $125\ global\ sites$ in this trial.

After providing informed consent, patients will undergo screening procedures. Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form. The investigator will record reasons for screen failure in the screening log. Screening period may be extended per Medical Monitor discretion based on extenuating circumstances (i.e., delayed laboratory results).

Patients with tumors of nonsquamous histology with unknown *EGFR* or *ALK* mutational status will be required to be tested either locally using a validated health authority–approved test or via central laboratory prior to enrollment. Patients with tumors of squamous histology who have an unknown *EGFR* or *ALK* mutational status will not be required to be tested.

Eligible patients will be in a randomized 1:1 ratio to receive either atezolizumab plus cabozantinib or docetaxel monotherapy. Randomization will be stratified by:

- Histology: nonsquamous versus squamous
- Prior NSCLC treatment regimen(s) at the following four levels:
  1. Concurrent platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody combination
  2. Platinum-containing chemotherapy first, *disease progression occurs,* followed by anti–PD-L1/PD-1 antibody
  3. Anti–PD-L1/PD-1 antibody monotherapy first, *disease progression occurs,* followed by platinum-containing chemotherapy *without anti-PD-L1/PD-1 antibody*
  4. Anti–PD-L1/PD-1 antibody monotherapy first, *disease progression occurs, followed by continued anti-PD-L1/PD-1 antibody in combination with* platinum-containing chemotherapy added on

In the experimental arm, atezolizumab (fixed dose of 1200 mg) will be administered by IV infusion on Day 1 of each 21-day cycle. Cabozantinib (40 mg) will be administered orally in tablet form (two tablets of 20 mg each) once daily (QD) on Days 1–21 of each cycle. In the control arm, docetaxel (75 mg/m^2) will be administered by IV on Day 1 of each 21-day cycle.

In the experimental arm: Atezolizumab and cabozantinib treatment will continue until unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). During study treatment, patients who meet criteria for disease progression per RECIST v1.1 and show evidence for clinical benefit may continue atezolizumab and/or cabozantinib treatment at the investigator's discretion provided that the patients meet all of the following criteria:

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

Patients randomized to the experimental arm may be allowed to discontinue one component of the combination study treatment but continue to receive the other component.

In the control arm: Docetaxel treatment will continue until unacceptable toxicity or disease progression as assessed by the investigator per RECIST v1.1.

Crossover from the control-arm to the experimental-arm will not be allowed.

Patients will undergo tumor assessments at baseline, every 6 weeks (±7 days) for the first 48 weeks following Day 1 of Cycle 1, and every 9 weeks (±7 days) after completion of the Week 48 tumor assessment regardless of treatment delays. Patients will continue scanning regardless of treatment delays until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after disease progression per RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Patients in the experimental arm who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments at the frequency described above (i.e., every 6 weeks

[±7 days] for the first 48 weeks and every 9 weeks [±7 days] after 48 weeks) until study treatment is discontinued.

Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments should continue regardless of whether a patient starts a new anti-cancer therapy.

Response will be assessed according to RECIST v1.1.

During the study, patients will be asked to complete patient-reported outcome surveys at the beginning of the study (i.e., Day 1 of Cycle 1), on Day 1 of each cycle after Day 1 of Cycle 1, at treatment discontinuation, and during survival follow-up at 3 and 6.

After study treatment discontinuation, survival follow-up information will be collected by means of telephone calls, patient medical records, and/or clinic visits approximately every 3 months *or more frequently* until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from survival 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.

Number of Patients

Approximately 350 patients with metastatic NSCLC will be enrolled during the global enrollment phase of this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed informed consent form
- Age ≥ 18 years old or meeting country definition of adult, whichever is older, on the day of consent
- Ability to comply with the study protocol, in the investigator's judgment
- Histologically or cytologically confirmed metastatic NSCLC
- Documented radiographic disease progression during or following treatment with platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody, administered concurrently or sequentially for metastatic NSCLC
    - If anti–PD-L1/PD-1 antibody and platinum-containing chemotherapy are given concurrently as the first-line treatment for metastatic NSCLC, no further lines of systemic anti-cancer therapy are allowed.
    - If anti–PD-L1/PD-1 antibody and platinum-containing chemotherapy are given sequentially as first and second lines, respectively, for metastatic NSCLC, no further lines of systemic anti-cancer therapy are allowed.
    - Combination therapies with other agents are allowed with anti–PD-L1/PD-1 and/or platinum-containing chemotherapy (see exclusion criteria for exceptions).
- Measurable disease per RECIST v1.1 outside CNS as assessed by investigator
    - Previously irradiated lesions can be considered as measurable disease only if *PD* has been unequivocally documented at that site since radiation.
- Known PD-L1 status or availability of tumor tissue for central PD-L1 testing:
    - Availability of representative fresh and archival tumor specimens suitable for determination of PD-L1 status via central testing. Results of central PD-L1 testing are not required for patient to be randomized into the study.

    - If obtaining representative fresh tumor is not clinically feasible, representative archival tumor specimen is acceptable.
  - If no tissue specimen (fresh or archival) is available, documentation of known PD-L1 status as established by a health authority–approved PD-L1 assay is required.
- ECOG Performance Status score of 0 or 1
- Recovery to baseline or Grade $\leq$ 1 NCI CTCAE v5.0 from toxicities related to any prior treatments, unless adverse events are clinically nonsignificant and/or stable on supportive therapy in the opinion of the investigator
    - Grade 2 alopecia is allowed for study participation.
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to randomization:
  - ANC $\geq$ 1500/µL ($\geq 1.5 \times 10^9$/L) without granulocyte colony-stimulating factor support within 14 days of laboratory sample collection
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/µL)
  - Platelets $\geq$ 100,000/µL ($\geq 100 \times 10^9$/L) without transfusion within 14 days of laboratory sample collection
  - Hemoglobin $\geq$ 9 g/dL ($\geq$ 90 g/L) without transfusion within 14 days of laboratory sample collection
  - Serum bilirubin $\leq 1.0 \times$ upper limit of normal (ULN)
  - Liver function tests meeting one of the following criteria:
    - ALT and AST $\leq 2.5 \times$ ULN with ALP $\leq 2.5 \times$ ULN,
    - OR
    - ALT and AST $\leq 1.5 \times$ ULN with ALP $> 2.5 \times$ ULN
  - Serum creatinine $\leq 1.5 \times$ ULN or calculated creatinine clearance $\geq$ 40 mL/min (using the Cockcroft-Gault equation):
    - For males: (140 – age) $\times$ weight (kg)/(serum creatinine [mg/dL] $\times$ 72)
    - For females: Multiply above value by 0.85.
  - Albumin $\geq$ 25 g/L (2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN
  - Urine protein/creatinine ratio $\leq$ 1 mg/mg ($\leq$ 113.2 mg/mmol) or 24-hour urine protein $<$ 1 g
- Negative HIV test at screening
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening
    - The HBV DNA test will be performed only for patients who have a negative HBsAg test and a positive total HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening
    - The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

- Women must remain abstinent or use two methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment with atezolizumab in combination with cabozantinib in the experimental arm or during the treatment with docetaxel in the control arm, and for 5 months after the final dose of atezolizumab and/or 4 months after the final dose of cabozantinib, whichever is later. Women must refrain from donating eggs during this same period.
- A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
- Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. The recommended highly effective methods of contraception are defined in the protocol
- 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 adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating sperm, as defined below:
  - With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile 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 treatment with atezolizumab in combination with cabozantinib in the experimental arm or during the treatment with docetaxel in the control arm, and for 4 months after the final dose of cabozantinib, or for 6 months after the final dose of docetaxel. Men must refrain from donating sperm during this same period.
  - With a pregnant female partner, men must remain abstinent or use a condom during the treatment with atezolizumab in combination with cabozantinib in the experimental arm or during the treatment with docetaxel in the control arm, and for 4 months after the final dose of cabozantinib.
  - 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. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

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

- Prior therapy with the following agents for NSCLC:
  - Cabozantinib
  - Docetaxel
  - Combination of an anti–PD-L1/PD-1 antibody concurrently with a vascular endothelial growth factor (VEGF)R-targeting tyrosine kinase inhibitor (TKI)
- Treatment with investigational therapy within 28 days prior to initiation of study treatment

- Documentation of known sensitizing mutation in the *EGFR* gene or *ALK* fusion oncogene
  - Patients with nonsquamous NSCLC who have an unknown *EGFR* or *ALK* status will be required to be tested at screening.
  - Patients with squamous NSCLC who have an unknown *EGFR* or *ALK* status are eligible and will not be required to be tested at screening.
  - *EGFR* and/or *ALK* status may be assessed locally or at a central laboratory.
    - EGFR status assessed locally must be performed on tissue or cytology using a validated health authority–approved test that detects mutations in exons 18–21.
    - If samples are submitted for central *EGFR* and/or *ALK* testing, additional slides must be provided.
- *Patients with known ROS1 rearrangements, BRAF V600E mutations, or other actionable oncogenes with approved therapies if available*
- Symptomatic, untreated, or actively progressing CNS metastases
  - Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.
  - Asymptomatic patients with treated CNS lesions are eligible, provided that all of the following criteria are met:
    - Measurable disease, per RECIST v1.1 as assessed by investigator, must be present outside the CNS.
    - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
    - The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment.
    - The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anticonvulsant therapy at a stable dose is permitted.
    - Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
    - There is no evidence of interim progression between completion of CNS-directed therapy (if administered) and initiation of study treatment.
    - *If the patient is receiving anti-convulsant therapy, the dose is considered stable.*
- History of leptomeningeal disease
- Uncontrolled tumor-related pain
  - Patients requiring pain medication must be on a stable regimen at study entry.
  - Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.
  - Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (more frequently than once monthly)
  - Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Severe hepatic impairment (Child-Pugh C)

- Uncontrolled or symptomatic hypercalcemia
- Any other active malignancy at the time of initiation of study treatment or diagnosis of another malignancy within 3 years prior to initiation of study treatment that requires active treatment, except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, incidental prostate cancer, or carcinoma in situ of the prostate, cervix, or breast
- *Stroke, transient ischemic attack, myocardial infarction or other symptomatic ischemic events within 6 months of initiation of study treatment*
- *Significant vascular disease (e.g., aortic aneurysm or arterial dissection requiring surgical repair or recent peripheral arterial thrombosis) within 6 months of initiation of study treatment*
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, *unstable arrhythmia, or unstable angina*) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, *or any active infection that, in the opinion on the investigator, could impact patient safety*
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
    - Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease [COPD] exacerbation) are eligible for the study.
- Current treatment with anti-viral therapy for HBV
- Major surgical procedure, other than for diagnosis (e.g., gastrointestinal [GI] surgery, removal or biopsy of brain metastasis), within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
    - Minor surgeries are not allowed within 10 days prior to initiation of study treatment. Patients must have complete wound healing from major surgery or minor surgery before initiation of study treatment. Patients with clinically relevant ongoing complications from prior surgery are not eligible.
- Pregnant or lactating females, or intention of becoming pregnant during the treatment with atezolizumab in combination with cabozantinib in the experimental arm or during the treatment with docetaxel in the control arm, or within 5 months after the final dose of atezolizumab and/or 4 months after the final dose of cabozantinib, whichever is later.
    - Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Ongoing Grade $\geq$2 sensory or motor neuropathy
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see protocol for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
    - Patients with a history of autoimmune-mediated hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
    - Patients with controlled Type 1 diabetes mellitus are eligible for the study.
    - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

- Rash must cover < 10% of body surface area.
- Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
- No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.

- Pharmacologically uncompensated, symptomatic hypothyroidism
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan
  - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Prior allogeneic stem cell of solid organ transplantation
- Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor–α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
  - Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor confirmation has been obtained.
  - Patients who received mineralocorticoids (e.g., fludrocortisone), *inhaled or low-dose systemic* corticosteroids for COPD or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any component of the cabozantinib formulation
- History of severe hypersensitivity to docetaxel or to other drugs formulated with polysorbate 80
- *Concomitant anticoagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitor dabigatran, direct factor Xa inhibitor betrixaban, or platelet inhibitors (e.g., clopidogrel)*

  The following are anti-coagulants allowed in this study:
  - *Prophylactic use of low–dose* aspirin for cardio protection (per local applicable guidelines) and low dose (prophylactic), low-dose low–molecular-weight heparins (LMWH) are permitted.
  - Therapeutic doses of LMWHs *or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban are* allowed in patients without known brain metastases *who are on a stable dose of the anticoagulant for at least 1 week before randomization without* clinically significant *hemorrhagic* complications from the anticoagulation regimen *or the tumor*

- Thromboembolic event (e.g., deep vein thrombosis [DVT], pulmonary embolism) within 6 months before initiation of study treatment
    - Patients with a diagnosis of DVT within 6 months are allowed if stable and treated with LMWH for at least 1 week before initiation of study treatment.
- History of risk factors for torsades de pointes (e.g., long QT syndrome)
- Corrected QT interval corrected through use of Fridericia's formula (QTcF) $>$ 480 ms per ECG within 14 days before initiation of study treatment
    - If a single ECG shows a QTcF with an absolute value $>$ 480 ms, two additional ECGs at intervals of approximately 3 minutes must be performed within 30 minutes after the initial ECG, and the average of the three consecutive results for QTcF must be $\leq$ 480 ms for the patient to be eligible.
- Uncontrolled hypertension defined as systolic blood pressure $>$ 150 mm Hg or diastolic BP $>$ 90 mm Hg despite optimal antihypertensive treatment
- Tumors invading the GI-tract, active peptic ulcer disease, acute pancreatitis, acute obstruction of the pancreatic or biliary duct, appendicitis, cholangitis, cholecystitis, diverticulitis, gastric outlet obstruction, or inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
- Abdominal fistula, bowel obstruction, GI perforation, or intra-abdominal abscess within 6 months before initiation of study treatment
    - Complete healing of an intra-abdominal abscess must be confirmed before initiation of study treatment.
- Known cavitating pulmonary lesion(s) or known endobronchial disease manifestation
- Lesions invading major pulmonary blood vessels
- Clinically significant hematuria, hematemesis, hemoptysis of $>$ 0.5 teaspoon (2.5 mL) of red blood, coagulopathy, or other history of significant bleeding (e.g., pulmonary hemorrhage) within 3 months before initiation of study treatment
- Serious non-healing wound/ulcer/bone fracture
- Malabsorption syndrome
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption are also excluded.
- Requirement for hemodialysis or peritoneal dialysis
- Inability to swallow tablets

Length of Study

The end of this study will occur when the required number of deaths for the final analysis of OS has been observed.

In addition, the Sponsor may decide to terminate the study at any time.

The approximate total length of the study, from screening of the first patient to the end of the study, is expected to be approximately $47\ months$.

Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are atezolizumab, cabozantinib, and docetaxel.

Test Products (Investigational Drug)

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Cabozantinib will be administered orally, QD at a dose of 40 mg ($2 \times$ 20-mg tablets) on Days 1–21 of each cycle.

Comparator

Docetaxel will be administered by IV infusion at a starting dose of 75 mg/m^2 every 3 weeks according to the locally approved label.

Statistical Methods

Primary Analysis

The analysis population for the efficacy analyses will consist of all randomized patients (i.e., the intent-to-treat [ITT] population), with patients grouped according to their assigned treatment.

Primary Efficacy Endpoint

The primary efficacy endpoint of this study is OS.

OS is defined as the time from randomization to death from any cause. Data for patients who are not reported as having died at the time of analysis will be censored at the date when they were last known to be alive. Data for patients who do not have postbaseline information will be censored at the date of randomization. The primary endpoint of OS will be compared between treatment arms with the use of the stratified log-rank test. If the estimate of the HR is < 1 and the two-sided p-value corresponding to the stratified log-rank test is less than the specified α level, then the null hypothesis will be rejected, and it will be concluded that the combination of Atezo + Cabo prolongs the duration of OS relative to the control treatment. The HR and associated 95% CI will be estimated using a stratified Cox proportional hazard model. The stratification factors will be the same as those recorded in the interactive voice or web-based response system at randomization. Results from an unstratified analysis will also be provided.

Kaplan-Meier methodology will be used to estimate the median OS for each treatment arm, and Kaplan-Meier curves will be constructed to provide a visual description of the difference between treatment arms. Brookmeyer-Crowley methodology will be used to construct the 95% CI of the median OS for each treatment arm.

One interim analysis is planned for OS. The timing and stopping boundaries of the OS analyses are described in the sections of sample size determination and planned interim analyses of the protocol.

To assess the consistency of the study results in subgroups defined by demographic (e.g., age, sex, and race/ethnicity) and baseline characteristics (e.g., ECOG Performance Status, histology, and PD-L1 status), the primary efficacy endpoint in these subgroups will be examined. Additional analyses may be performed to evaluate the potential effect of non−protocol-specified anti-cancer therapy on OS. Details of these analyses will be provided in the SAP.

Determination of Sample Size

The study is designed to test the hypothesis that atezolizumab in combination with cabozantinib prolongs the duration of OS compared to the control arm (docetaxel) in the ITT population.

The sample size determination is based on the number of events required to demonstrate efficacy with regard to OS in the ITT population. The estimate of the number of events required is based on the following assumptions:

- 1:1 randomization ratio
- OS curve that follows the exponential distributions
- Two-sided significance level of 0.05 for the comparison of OS
- 90% power to detect an HR of 0.64 in OS in the ITT population, corresponding to an improvement in median OS from 9 to 14.1 months
- One planned interim analysis of OS
    - The interim analysis of OS is to be performed when approximately 83% of the total number of OS events required for the final analysis are expected to have occurred. Crossing boundaries are determined based on the Hwang-Shih-DeCani alpha spending function with the gamma parameter of −2.5.
- Accrual duration of approximately 16 months
- Dropout rate of 5% per 24 months for each treatment arm for OS

With these assumptions, approximately 350 patients (approximately 175 per arm) in total will be randomized into the study. The interim OS analysis will be conducted after approximately 182 OS events have occurred. The final OS analysis will be conducted when approximately 220 OS events have occurred, which is expected to occur approximately 28 months after the first patient is enrolled. This number of final OS events corresponds to a minimum detectable difference corresponding to an HR of approximately 0.757.

Interim Analyses

One interim analysis is planned for OS. To control the type I error for OS at two-sided alpha of 0.05, the stopping boundaries for OS interim and final analyses are to be computed with use of the Hwang-Shih-DeCani alpha spending function with the gamma parameter of −2.5.

Due to logistical considerations in event ascertainment and operational planning and conduct, the actual analyses may include more or fewer events than the target information fractions. The actual critical values employed at the interim and final analyses of OS will depend upon the actual information fraction at the time of the analyses.

Appendix 2 Schedule of Activities

Assessments	Screening [a]	Treatment	Post-Treatment Follow-Up	
	Days –28 to –1	Day 1 (every 21 days) (± 3 days)	≤ 30 Days after Final Dose	Survival Follow-Up
Informed consent	x [b]			
Tumor tissue specimens [c]	x			
Demographic data	x			
Medical history, including NSCLC history, PD-L1 status (if available), and baseline conditions [d]	x			
ALK and/or *EGFR* assessment if status is unknown (may be done locally or centrally) [e]	x			
Viral serology [f]	x			
C-reactive protein	x			
Height	x			
Vital signs [g]	x	x [gg]	x [gg]	
Weight	x	x	x	
Complete physical examination [h]	x		x	
Limited physical examination [i]		x [j]		
ECOG Performance Status	x	x [j]	x	
ECG (12-lead)	x [k]	x [j, k]		
Hematology [m]	x [l]	x [j, gg]	x [gg]	
Chemistry [n]	x [l]	x [j, gg]	x [gg]	
Pregnancy test [o]	x [l]	x [j, gg]	x [gg]	
Coagulation (INR, aPTT)	x [l]		x [gg]	
TSH, free T3 (or total T3), free T4 [p]	x	x [j, p, gg]	x [gg]	

Appendix 2 Schedule of Activities (cont.)

Assessments	Screening [a]	Treatment	Post-Treatment Follow-Up	
	Days –28 to –1	Day 1 (every 21 days) (± 3 days)	≤ 30 Days after Final Dose	Survival Follow-Up
Urine chemistry including UPCR *or 24-hour urine protein*	x [l]	x [j]	x	
Urinalysis [r]	x	x [q]	x	
Concomitant medications [s]	x	*x* [gg]	*x* [gg]	
Adverse events [t]	x	*x* [gg]	*x* [gg]	x
Atezolizumab administration [u]		x		
Cabozantinib dispensing/reconciliation [v]		x		
Docetaxel administration [w]		x		
Patient-reported outcomes [x]		x [y]	x [z]	x [z]
Plasma PK samples for cabozantinib		See Appendix 2		
Serum PK samples for atezolizumab		See Appendix 2.		
Serum ADA samples for atezolizumab		See Appendix 2.		
PBMC, plasma, and serum samples for biomarkers (central laboratory)[gg]		See Appendix 2.		
Tumor biopsy, if clinically feasible		At time of radiographic progression [aa]		
Optional tumor biopsy at other timepoints [bb]		Any time during study treatment, observation FU or survival FU (at investigator's discretion)		
Tumor response assessments	x [cc]	x [dd, ee]		
Anti-cancer treatment information [ff]			x	x
Survival follow-up				x [ff]

Appendix 2 Schedule of Activities (cont.)

ADA = anti-drug antibody; Atezo = atezolizumab; Cabo = cabozantinib; CT = computed tomography (scan); ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; FFPE = formalin-fixed, paraffin-embedded; FU = follow-up; GHS = global health status; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IL46 = Item List 46; NSCLC = non–small cell lung cancer; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PK = pharmacokinetic; PRO = patient-reported outcome; QLQ-C30 = Quality of Life–Core 30 Questionnaire, Version 1.1; QLQ-LC13 = Quality of Life–Lung Cancer 13-Item Questionnaire; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; UPCR = urine protein/creatinine ratio.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

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

[b] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[c] Representative fresh and archival tumor tissue sample obtained at baseline for exploratory research on biomarkers (e.g., PD-L1 status via central testing), including biomarker assay development. Tumor tissue samples should be submitted before or within 4 weeks of randomization.

[d] If no tissue specimen is available, known PD-L1 status, as defined by a health authority–approved PD-L1 assay, is required.

[e] For patients with nonsquamous NSCLC histology with unknown *EGFR* and/or *ALK* status, test results are required at screening. *EGFR* and/or *ALK* status must be assessed locally or at a central laboratory. If samples are submitted for central testing, additional tissue sample is required. See laboratory manual for details.

[f] At screening, patients will be tested for HIV, HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

[g] Includes respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion, after the infusion of atezolizumab

but prior to the administration of cabozantinib, and, if clinically indicated, every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion, and, if clinically indicated or if symptoms occurred during the previous infusion, every 15 (±5) minutes during the infusion and at 30 (± 10) minutes after the infusion. *Vital signs should be measured prior to docetaxel infusions.*

[h] Includes evaluation of the skin, head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, blood and lymphatic, and neurologic systems.

[i] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints.

[j] If screening assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated for Day 1 of Cycle 1. At all cycles subsequent to Day 1 of Cycle 1, laboratory assessments, ECOG Performance Status, ECG (through Cycle 5), and limited physical examination must be performed within 96 hours prior to administration of drug.

[k] ECG recordings will be obtained during screening, on Day 1 of every cycle through Cycle 5, and then as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[l] Specific screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells [if applicable]).

[n] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH.

[o] All women of childbearing potential will have a serum pregnancy test at screening, within 14 days prior to initiation of study treatment. Urine pregnancy tests will be performed at every cycle during study treatment, at treatment discontinuation, and as clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[p] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening, on Day 1 of Cycle 1, and every four cycles thereafter (i.e., Cycles 5, 9, 13, etc.).

[q] Urinalysis should be performed as clinically indicated during study treatment.

[r] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

Appendix 2 Schedule of Activities (cont.)

[s] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[t] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment.

[u] The initial infusion of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[v] Cabozantinib tablets will be given on Day 1 of Cycle 1 after atezolizumab infusion. Patients will take tablets once daily at home thereafter until study treatment is discontinued.

[w] For docetaxel, study drug will be administered according to the local prescribing information, including premedication with steroids.

[x] PRO assessments (EORTC QLQ-C30, *EORTC IL17*, EORTC QLQ-LC13, EORTC IL46, *selected items from the PRO-CTCAE* and EQ-5D-5L questionnaires) will be completed before the patient receives any information on disease status and prior to the performance of non-PRO assessments that could bias patients' rating and the administration of study treatment. Study personnel should confirm all questionnaires for completeness before the patient leaves the investigational site.

[y] Patient-completed questionnaires should be completed by the patients prior to any assessments, tests or interactions that might bias patients' view on their health status.

[z] PRO assessments *(EORTC QLQ-C30, EORTC QLQ-LC13, EORTC IL46, selected items from the PRO-CTCAE, and EQ-5D-5L)* will be completed at the end-of-treatment visit. Following treatment discontinuation, patients will complete selected scales from the EORTC QLQ-C30 *(EORTC IL17)* and the EQ-5D-5L questionnaires at *the 3-month (±30 days)* and 6-month *(±30 days) survival* follow-up *visits*. The questionnaires might be administered by the site over the telephone if patients are not coming in-person to the clinic.

Appendix 2 Schedule of Activities (cont.)

[aa] Patients will undergo a tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of radiographic disease progression per RECIST v1.1. Biopsies should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner.

[bb] Biopsies collected at the investigator's discretion are preferred at the time of clinical events (e.g., clinical response). Patients must sign a separate Optional Biopsy Informed Consent Form to undergo optional biopsies. See Section 4.5.10 for details.

[cc] Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. All known sites of disease, including measurable and/or non-measurable disease, must be documented at screening and re-assessed at each subsequent tumor evaluation. Screening assessments must include CT scans (with oral or IV contrast) of chest, abdomen, and pelvis, as wells as a CT scan (with oral or IV contrast) or MRI of the head. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest must be performed and MRI scans of the abdomen, pelvis, and head must be performed. A CT scan with contrast or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. At subsequent (post-screening) tumor assessments, patients with a history of irradiated brain metastasis at screening are not required to undergo brain scan unless clinically indicated. The same radiographic modality (e.g., CT scan with contrast) and procedures (e.g., the same contrast protocol for CT scans) used to assess disease sites at screening should be used for subsequent tumor assessments. Bone scans and CT scans of the neck should also be performed at screening, if clinically indicated.

[dd] All patients will undergo tumor assessments at baseline, every 6 weeks (±7 days) for the first 48 weeks following Day 1 of Cycle 1, and every 9 weeks (±7 days) after completion of the Week 48 tumor assessment regardless of treatment delays. Patients will continue scanning regardless of treatment delays until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after disease progression per RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Patients in the experimental arm who are treated beyond disease progression per RECIST v1.1 will continue to undergo tumor assessments at the frequency described above until (i.e., every 6 weeks [±7 days] for the first 48 weeks and every 9 weeks [± 7 days] after 48 weeks) until study treatment is discontinued. Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of

consent, death, or study termination by the Sponsor, whichever occurs first. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments should continue regardless of whether a patient starts a new anti-cancer therapy.

[ee] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[ff] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months *(every 12 weeks [±7 days]) or more frequently* until death (unless the patient withdraws consent or the Sponsor terminates the study). If a 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, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

[gg] *For patients in either arm at participating sites who have provided written informed consent to participate in mobile nursing visits, this assessment or procedure may be performed by a trained nursing professional at the patient's home or another suitable location.*

Appendix 3 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Visit	Timepoint	Experimental Arm (Atezo + Cabo)	Control Arm (Docetaxel)
Day 1 of Cycle 1	Predose (same day as treatment administration)	• Atezolizumab PK (serum) • Cabozantinib PK (plasma) • Atezolizumab ADA (serum) • Biomarker (PBMC, plasma, serum) • Biomarker (blood for RBR, optional [a])	• Biomarker (PBMC, plasma, serum) • Biomarker (blood for RBR, optional [a])
Day 1 of Cycle 1	30 (±10) minutes after end of atezolizumab infusion	• Atezolizumab PK (serum)	
Day 1 of Cycle 2	Predose (same day as treatment administration)	• Atezolizumab PK (serum) • Cabozantinib PK (plasma) • Atezolizumab ADA (serum) • Biomarker (PBMC, plasma, serum)	• Biomarker (PBMC, plasma, serum)
Day 1 of Cycle 3	Predose (same day as treatment administration)	• Atezolizumab PK (serum) • Cabozantinib PK (plasma) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)	• Biomarker (plasma, serum)
Day 1 of Cycle 4	Predose (same day as treatment administration)	• Atezolizumab PK (serum) • Cabozantinib PK (plasma) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)	• Biomarker (plasma, serum)

Appendix 3 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

Visit	Timepoint	Experimental Arm (Atezo + Cabo)	Control Arm (Docetaxel)
Day 1 of Cycle 5	Predose (same day as treatment administration)	• Cabozantinib PK (plasma)	
Day 1 of Cycle 8	Predose (same day as treatment administration)	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)	• Biomarker (plasma, serum)
Day 1 of Cycle 12	Predose (same day as treatment administration)	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)	• Biomarker (plasma, serum)
Day 1 of Cycle 16	Predose (same day as treatment administration)	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)	• Biomarker (plasma, serum)
Post-treatment follow-up visit (≤ 30 days after final dose)[c]	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (*PBMC,* plasma, serum)	• Biomarker (*PBMC,* plasma, serum)
Disease Progression [c]	At time of radiographic progression per RECIST v1.1 [b]	• Biomarker (PBMC, plasma, serum)	• Biomarker (PBMC, plasma, serum)

Appendix 3 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

ADA = anti-drug antibody; Atezo = atezolizumab; Cabo = cabozantinib; eCRF = electronic Case Report Form; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Notes: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ± 3 days of the scheduled date.

Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

Collection of PK samples may be halted early, or sampling frequency may be modified at the discretion of the Sponsor.

Blood sampling for cabozantinib PK analyses: After Day 1 of Cycle 1, PK samples should be collected approximately 8 or more hours after the previous dose of cabozantinib, and if cabozantinib will be administered on that day, PK samples should be collected prior to cabozantinib administration. The investigator will ask the patient for the date and time of the most recent prior dose of cabozantinib, and this information will be recorded on the appropriate eCRF.

[a] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate. *RBR samples are preferred to be collected on Day 1 of Cycle 1; however, they may be collected predose on Day 1 of any subsequent cycle visit.*

[b] Blood collections should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner.

[c] *For patients in either arm at participating sites who have provided written informed consent to participate in mobile nursing visits, collection of this sample may be performed by a trained nursing professional at the patient's home or another suitable location.*