Official Title: A Phase III, Double-Blinded, Randomized, Placebo-Controlled Study of Atezolizumab Plus Cobimetinib and Vemurafenib Versus Placebo Plus Cobimetinib and Vemurafenib in Previously Untreated BRAFv600 Mutation-Positive Patients With Unresectable Locally Advanced or Metastatic Melanoma

NCT Number: NCT02908672

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STATISTICAL ANALYSIS PLAN

TITLE:	**A PHASE III, DOUBLE-BLINDED, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB PLUS COBIMETINIB AND VEMURAFENIB VERSUS PLACEBO PLUS COBIMETINIB AND VEMURAFENIB IN PREVIOUSLY UNTREATED *BRAF*^{V600} MUTATION POSITIVE PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC MELANOMA**
PROTOCOL NUMBER:	CO39262
STUDY DRUG:	Atezolizumab (RO5541267) Cobimetinib (RO5514041) Vemurafenib (RO5185426)
VERSION NUMBER:	2
IND NUMBER:	111271
EUDRACT NUMBER:	2016-002482-54
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted], Ph.D.
DATE FINAL:	Version 1: .02 August 2018
DATE AMENDED	Version 2: See electronic date stamp below

STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
18-Jun-2019 18:28:56	Company Signatory	[redacted]

STATISTICAL ANALYSIS PLAN, VERSION 2.0

RATIONALE FOR AMENDMENT

Two changes have been made in Section 4.4 ("Efficacy Analyses") and Section 4.4.5 ("Sensitivity Analyses") to address the potential risk of over-stratification in efficacy analyses and the potential risk of delayed treatment effect. The rationale for each change is outlined below:

The stratification factors will be those used for randomization and will be obtained from the IWRS (geographic region and baseline LDH). Due to the potential risk of over-stratification (Akazawa et al., 1997), if at least one stratum (i.e., a combination of stratification factor levels across geographic region and baseline LDH) has fewer than 10 PFS events across treatment arms, the stratification factor (one of two stratification factors: geographic region and baseline LDH per IWRS) which contains the level with the smallest number of patients will be removed from the stratified analyses. The removal of the stratification factors will continue until there is no stratum with fewer than 10 PFS events. The final set of stratification factors used in stratified analyses will be applied to all endpoints where stratified analyses are planned.

The log-rank test has been the most commonly used method for analyzing survival endpoints under proportional hazards. Due to the potential risk of non-proportional hazards due to delayed treatment effect, the weighted log-rank test will be performed as a sensitivity analysis.

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1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study CO39262 (IMspire150): a Phase III, double-blinded, randomized, placebo-controlled study of atezolizumab plus cobimetinib and vemurafenib versus placebo plus cobimetinib and vemurafenib in previously untreated *BRAF*^{V600} mutation positive patients with unresectable locally advanced or metastatic melanoma. The background for the study can be found in the study protocol.

It is anticipated that positive results from Study CO39262 will support the submission of filing applications globally for the use of atezolizumab plus cobimetinib and vemurafenib for the treatment of the previously untreated *BRAF*^{V600} mutation positive patients with unresectable locally advanced or metastatic melanoma. For registration purposes, the analyses outlined in this SAP will supersede those specified in the protocol.

2. STUDY DESIGN

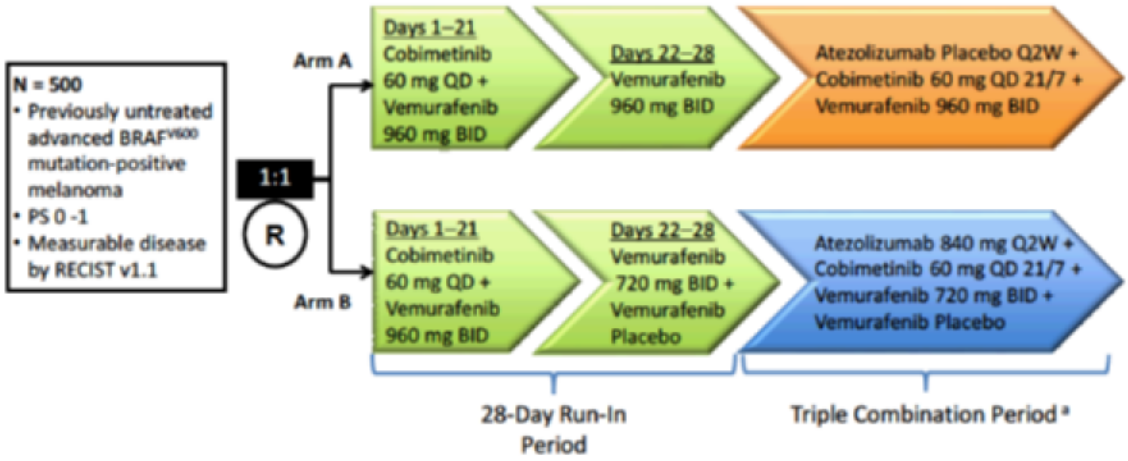
Study CO39262 is a Phase III, double-blinded, placebo-controlled, randomized, multicenter study designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of atezo+cobi+vem compared with placebo+cobi+vem in patients with previously untreated *BRAF*^{V600} mutation-positive metastatic or unresectable locally advanced melanoma. The primary endpoint of the study is investigator-assessed progression-free survival (PFS).

Approximately 500 patients will be randomized in the study. Patients will be randomized in a 1:1 ratio to one of the two treatment arms:

- Arm A (placebo+cobi+vem): Patients will receive cobimetinib and vemurafenib during a run-in period of 28 days, and then atezolizumab placebo, cobimetinib, and vemurafenib (960 mg twice daily) post run-in.
- Arm B (atezo+cobi+vem): Patients will receive cobimetinib and vemurafenib during a run-in period of 28 days, and then atezolizumab, cobimetinib, and vemurafenib (720 mg twice daily).

The study schema is presented in Figure 1.

Figure 1 Study Schema



21/7=treatment on Days 1–21 followed by no treatment on Days 22–28; BID=twice daily; PS=performance status; QD=once daily; Q2W=every 2 weeks; R=randomization; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1.

[a] Study treatment will continue until investigator-determined disease progression according to RECIST v1.1 (or subsequent clinical deterioration or confirmed disease progression 4–8 weeks later, for clinically stable patients with a favorable benefit-risk ratio), death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurs first.

Stratification factors are:

- Baseline Lactic Acid Dehydrogenase (LDH) (≤the upper limit of normal [ULN] vs.>ULN, using central laboratory result);
- Geographic region (North America vs. Europe vs. Australia, New Zealand, and others).

A permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm. Randomization and stratification will be managed through an interactive web-based response system (IWRS).

All patients will be closely monitored for safety and tolerability throughout the study. The National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0) will be used to characterize the toxicity profile of the study treatments for all patients. Patients will be assessed for adverse events (AEs) according to the schedule of activities (see Appendix 2) and as necessary throughout the study.

Tumor assessments will be performed by the investigator and by an independent review committee (IRC) according to RECIST v1.1. Tumor assessments according to [redacted] will only be performed by the investigator. All measurable and non-measurable lesions will be documented at screening. Response will be assessed by the investigator at 8- or 12-week intervals until investigator-determined disease progression (according to RECIST v1.1), or death, whichever occurs first. Patients who experience disease progression (RECIST v1.1) must have scans following the

protocol-specified tumor assessment schedule after initial documentation of progression to confirm disease progression. Tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than confirmed disease progression. Clinically stable patients who have a favorable benefit-risk ratio should continue on study treatment following radiographic progression per RECIST v1.1. Patients who continue treatment beyond radiographic disease progression will be closely monitored.

Study treatment will continue for all patients until investigator-determined disease progression according to RECIST v1.1 that is confirmed by repeat scans approximately 4-8 weeks later or subsequent clinical deterioration, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurs first. Patients who discontinue one study drug may be able to continue other study drugs, per guidelines for management of specific AEs provided in the Protocol Section 5.1. After treatment discontinuation, patients will be followed for disease progression if applicable and followed for survival until death, withdrawal of consent, or loss to follow-up, whichever occurs first. Patients in the control arm cannot crossover to the treatment arm at disease progression. An independent Data Monitoring Committee (iDMC) will be employed to conduct periodic evaluations of safety data.

2.1 PROTOCOL SYNOPSIS

The protocol synopsis is in Appendix 1. The schedule of assessments is provided in Appendix 2. For additional details, see the study protocol.

2.2 ENDPOINTS

2.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the investigator-assessed PFS per RECIST v1.1, defined as the time from randomization to the first occurrence of disease progression, as determined by an investigator according to RECIST v1.1, or death from any cause, whichever occurs first.

2.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- IRC-assessed PFS per RECIST v1.1, defined as the time from randomization to the first occurrence of disease progression, as determined by the IRC according to RECIST v1.1, or death from any cause, whichever occurs first
- Overall survival (OS), defined as the time from randomization to death from any cause
- Objective response, defined as a complete response or a partial response on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1

- 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
- Time to deterioration in global health status, defined as the time from randomization to first observed ≥10-point decrease in European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) linearly transformed global health status scale score that is sustained for two consecutive assessments or followed by death while the patient is on treatment
- Time to deterioration in physical functioning, defined as the time from randomization to first observed ≥10-point decrease in EORTC QLQ-C30 linearly transformed physical functioning scale score that is sustained for two consecutive assessments or followed by death while the patient is on treatment

2.2.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

- [redacted]

2.2.4 Pharmacokinetic Endpoints

The PK endpoints are as follows:

- Serum concentration of atezolizumab at specified timepoints
- Plasma concentration of cobimetinib and vemurafenib at specified timepoints

2.2.5 Safety Endpoints

The safety endpoints are as follows:

- Occurrence, frequency, and severity of AEs
- Change from baseline in targeted vital signs during and following treatment
- Change from baseline in targeted clinical laboratory test results during and following treatment

2.3 DETERMINATION OF SAMPLE SIZE

Approximately 500 patients will be randomized into the study.

The final analysis of the primary endpoint of PFS will take place when approximately [redacted] PFS events have occurred. Statistical considerations are based on the following assumptions:

- Stratified log-rank test at 0.05 significance level (two sided)
- [redacted]

A total of [redacted] PFS events provides approximately [redacted] % power to detect an improvement in median PFS from [redacted]

2.4 ANALYSIS TIMING

The primary analysis will be conducted when approximately [redacted] PFS events have occurred, which is expected to occur approximately [redacted] months after first-patient-in (FPI). There is no planned interim analysis for PFS.

The study will incorporate [redacted] OS analyses ([redacted] interim analyses and [redacted] final analysis). The [redacted] OS interim analysis will be performed at the time of the primary PFS analysis, at which time a number of [redacted] deaths are projected to have occurred. [redacted] Refer to Section 4.10 for the assumptions and characteristics of the interim and final analysis for OS.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Randomized to the two treatment arms will occur in a 1:1 ratio. A permuted-blocked will be applied to ensure a balanced assignment to each treatment arm.

Randomization and stratification will be managed through an IWRS. Randomization will be stratified by the following factors:

- Geographic region (North America vs. Europe vs. Australia, New Zealand, and others)

- Baseline LDH (≤the ULN vs. >ULN, using central laboratory results)

3.2 INDEPENDENT REVIEW FACILITY

An independent review committee (IRC) will be used for this study. PFS based on the IRC assessments is the secondary endpoint. Specific details, including responsibilities and structure of the IRC are specified in the IRC Charter.

3.3 DATA MONITORING

An iDMC will be employed to conduct periodic evaluations of safety data. All analyses for the iDMC's review will be prepared by an independent data coordinating center (iDCC). Specific details, including responsibilities and structure of the iDMC, are specified in the iDMC Charter.

4. STATISTICAL METHODS

The analyses described in this SAP will supersede those specified in protocol for Study CO39262 for the purpose of a regulatory filing.

4.1 ANALYSIS POPULATIONS

4.1.1 Randomized Population

The randomized population or intent-to-treat (ITT) population is defined as all randomized patients, whether or not study treatment was received. The ITT population will be analyzed according to the treatment assigned at randomization.

4.1.2 Safety Population

The safety population will include all patients who received any amount of any study drug (e.g., atezolizumab, cobimetinib, or vemurafenib), with patients grouped as follows:

- Atezolizumab+cobimetinib+vemurafenib arm: patients who received any amount of atezolizumab with or without any amount of cobimetinib or vemurafenib
- Placebo+cobimetinib+vemurafenib arm: patients who received any amount of cobimetinib or vemurafenib without any amount of atezolizumab

4.1.3 Pharmacokinetic-Evaluable Population

The PK-evaluable population is defined as all patients who have received any dose of study drug and for whom at least one evaluable PK sample is collected.

4.2 ANALYSIS OF STUDY CONDUCT

Study enrollment, major protocol deviations, including major deviations of inclusion/exclusion criteria, and reasons for study discontinuation 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, race/ethnicity, baseline disease characteristics, and stratification factors will be summarized for the ITT population. Descriptive statistics (mean, median, SD, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

4.4 EFFICACY ANALYSES

Unless otherwise noted, all efficacy analyses will include the ITT population, and patients will be grouped according to the treatment assigned at randomization. The stratification factors will be those used for randomization and will be obtained from the IWRS (geographic region and baseline LDH). Due to the potential risk of over-stratification (Akazawa et al., 1997), if at least one stratum (i.e., a combination of stratification factor levels across geographic region and baseline LDH) has fewer than 10 PFS events across treatment arms, the stratification factor (one of two stratification factors: geographic region and baseline LDH per IWRS) which contains the level with the smallest number of patients will be removed from the stratified analyses. The removal of the stratification factors will continue until there is no stratum with fewer than 10 PFS events. The final set of stratification factors used in stratified analyses will be applied to all endpoints where stratified analyses are planned.

4.4.1 Primary Efficacy Endpoint

The primary efficacy analysis will be the comparison of PFS, as determined by the investigator, between the two treatment arms using the stratified log-rank test at an overall 0.05 significance level (two-sided).

The statistical hypothesis of this study is as follows:

- H_0: PFS (Arm A)=PFS (Arm B)
- H_1: PFS (Arm A)≠PFS (Arm B)

PFS (Arm A) represents the survival function of PFS in the placebo+cobi+vem arm, and PFS (Arm B) represents the survival function of PFS in the atezo+cobi+vem arm.

PFS, as assessed by the investigator, is defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or death at the time of analysis data cut-off will be censored at the date of last tumor assessment. Data for patients without post-baseline tumor assessment will be censored at randomization date.

The hazard ratio (HR) for PFS will be estimated using a stratified Cox model, and two-sided 95% CIs for the HR will be provided. Results from an unstratified analysis will

also be presented. Kaplan-Meier methodology will be used to estimate the median PFS for each treatment arm, and Kaplan-Meier curves will be produced. The 95% CI of the median PFS for each treatment arm will be constructed using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982).

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 Progression-Free Survival

PFS, as determined by the IRC according to RECIST v1.1, will be analyzed using the same methods described for PFS analysis in Section 4.4.1.

4.4.2.2 Objective Response Rate

Objective response rate (ORR) is defined as the proportion of patients who had an objective response as assessed by the investigator. Objective response is defined as a CR or PR on two consecutive occasions at least 4 weeks apart, as determined by the investigator using RECIST v1.1. Patients evaluable for objective response will be all randomized patients with measurable disease at baseline. Randomized patients with measurable disease at baseline, who had no post-baseline tumor assessments, are considered non-responders.

A 95% Clopper–Pearson CI will be calculated for the ORR for each treatment arm. The difference in ORR between treatment arms will be tested using the stratified Cochrane-Mantel-Haenszel test. A 95% Hauck-Anderson CI will be calculated for the difference in ORR between treatment arms.

4.4.2.3 Duration of Response

For patients who achieve an objective response, DOR is 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. The censoring method for DOR will be the same as that for PFS. The Kaplan-Meier approach will be used to estimate median DOR. The 95% CI of the median DOR will be constructed using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982).

4.4.2.4 Overall Survival

OS is defined as the time from randomization to death from any cause. For patients who are alive at the time of analysis data cut-off, OS time will be censored at the date the patient was last known to be alive. Survival time for patients without post-baseline survival information will be censored at randomization date.

The OS will be compared between the two treatment arms using a two-sided stratified log-rank test at an overall two-sided 0.05 significance level. The HR for OS will be estimated using a stratified Cox model, and two-sided 95% CIs for the HR will be provided.

The OS will be compared between the two treatment arms at [redacted] interim analyses and [redacted] final analysis. [redacted]

To control the overall type I error rate at the 0.05 level (two sided), the secondary endpoint OS will be evaluated for statistical significance at the 5% level (two sided) only if the primary PFS endpoint meets statistical significance. The Lan–DeMets implementation (Lan and DeMets 1983) of the O'Brien-Fleming use function will be used to control the type I error at the 5% level (two-sided) for the OS evaluation in the interim and final analyses. See Section 4.10.2 for details.

Stratified analyses will incorporate the same stratification factors for the analysis of PFS.

Kaplan-Meier methodology will be used to [redacted]. The 95% CI of the [redacted] will be constructed using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982).

As a sensitivity analysis, an unstratified log-rank test will be performed and the unstratified HR will be provided.

4.4.2.5 Patient-Reported Outcomes

The data from the ITT population will be used to assess time to deterioration (TTD) in global health status (items 29 and 30 of the EORTC QLQ-C30) and TTD in physical functioning (items 1-5 of the EORTC QLQ-C30) for each treatment arm. TTD in global health status is defined as the time from randomization to first observed ≥10 point decrease in EORTC QLQ-C30 linearly transformed global health status scale score that is sustained for two consecutive assessments or followed by death while the patient is on treatment. TTD in physical functioning is defined as the time from randomization to first observed ≥10-point decrease in EORTC QLQ-C30 linearly transformed physical functioning scale score that is sustained for two consecutive assessments or followed by death while the patient is on treatment. Data for patients who do not achieve a 10-point decrease will be censored at the last time patient-reported outcome (PRO) data are available. Randomized patients without baseline PRO assessment or post-baseline PRO assessment will be censored at randomization.

TTD in global health status and physical functioning will be compared between the treatment groups using the same method as the analysis of PFS.

4.4.3 Exploratory Efficacy Endpoints

4.4.3.1 PFS, DOR, and ORR

[redacted]

4.4.3.2 Patient-Reported Outcomes

4.4.3.2.1 Analyses of Study Conduct

On the ITT population, completion analysis will be performed for the overall EORTC QLQ-C30 questionnaire. Completion rates will be summarized by number and proportion of patients among those expected to complete the EORTC QLQ-C30 at each time point. Reasons for non-completion may be summarized.

4.4.3.2.2 Visit Score Summary and Change from Baseline

PRO-evaluable population will include all randomized patients who have a baseline and at least 1 post-baseline assessment. On the PRO-evaluable population, visit summary and change from baseline analyses will be performed for the EORTC QLQ-C30 scales. Summary statistics (number of patients, mean, standard deviation, median, minimum, maximum) of score(s) and score change(s) will be presented by treatment arm from baseline to each time point including time of disease progression per RECIST v1.1, at treatment discontinuation, and post-study treatment.

4.4.3.2.3 Responder Analysis

On the PRO-evaluable population, the number and proportion of patients with a clinically 10-point meaningful change will be summarized by treatment arm, for the EORTC QLQ-C30 scores at the same timepoints listed in Section 4.4.3.2.2. The 95% CI around the proportion will be calculated using the Clopper–Pearson method for each treatment arm.

The difference in the proportions between the two treatment arms will be presented with a two-sided 95% CI based on a normal approximation to the binomial distribution.

4.4.3.2.4 Mixed-Effect Model Repeated Measures Analysis

On the PRO-evaluable population, mixed-effects model repeated measures (MMRM) will be used for comparing the EORTC QLQ-C30 Role Functioning (RF), Physical Functioning (PF), and Global Health Status/Health-Related Quality of Life (GHS/HRQoL) scores between treatment arms. The model may include a term for intercept, a term for linear time trend, a term for treatment group, and a term for treatment-by-time interaction. Repeated measures over time may be accounted for by covariance structure. Time points with less than 20% patients who completed the RF, the PF, or the GHS/HRQoL scales, where all subsequent time points also have less than 20% completion will be excluded.

4.4.4 Exploratory [redacted]

[redacted]

4.4.5 Sensitivity Analyses

4.4.5.1 Missing Tumor Assessment

The impact of missed scheduled tumor assessments on PFS will be assessed. If patients missed two or more consecutive assessments scheduled immediately prior to the date of disease progression per RECIST v1.1 or death, a sensitivity analysis will be performed where patients who missed two or more scheduled assessments immediately prior to the date of disease progression per RECIST v1.1 or death will be censored at date of the last tumor assessment prior to the missed visits, or at randomization date if no post-baseline tumor assessment prior to the missed visits.

4.4.5.2 Non-Protocol Anti-Cancer Therapy

A sensitivity analysis will also be conducted on PFS to determine the impact on non-protocol anti-cancer therapy. Patients who received non-protocol anti-cancer therapy will be censored at the date of the last tumor assessment prior to start of non-protocol anti-cancer therapy, or randomization date if no post-baseline tumor assessment prior to start of non-protocol anti-cancer therapy.

4.4.5.3 Delayed Treatment Effect

The weighted log-rank analysis (Fleming and Harrington 1991) that weights more on late events (Fine et al. 2007) will be conducted to assess a potential delayed treatment effect for the treatment group.

Statistical methodologies analogous to those used in the analysis of PFS or OS as specified in Section 4.4.1 and Section 4.4.2.4 will be used for these sensitivity analyses. The sensitivity analysis is based on the stratified analyses.

4.4.6 Subgroup Analyses

The consistency of the PFS and OS results will be examined in subgroups defined by demographic and baseline characteristics and stratification factors. Summaries of PFS and OS, including the unstratified HR estimated from a Cox proportional hazards model and Kaplan-Meier estimates of median PFS and OS, will be produced by treatment arm for each of the defined subgroups, and displayed in a Forest plot (Lewis and Clarke 2001).

The subgroups to be considered include but are not limited to the following:

- Age (≤65 years,>65 years) at randomization
- Race (non-White, White)
- Sex (female, male)
- Geographic Region (North America, Europe, Australia/New Zealand/Others)

- LDH (≤ ULN, >ULN)
- Eastern Cooperative Oncology Group (ECOG) performance status (0, 1)
- Melanoma staging
- PD–L1 expression

4.5 SAFETY ANALYSES

Safety analyses will be performed on the safety population and will include all randomized patients who received any amount of any study drug, with patients grouped as follows:

- Atezolizumab+cobimetinib+vemurafenib arm: patients who received any amount of atezolizumab with or without any amount of cobimetinib or vemurafenib
- Placebo+cobimetinib+vemurafenib arm: patients who received any amount of cobimetinib or vemurafenib without any amount of atezolizumab

4.5.1 Exposure of Study Medication

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

4.5.2 Adverse Events

Verbatim description of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus levels and graded according to NCI CTCAE v4.0. All AEs that occur during or after the first study drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events (SAEs), AEs (Grade 3–5), [redacted] and AEs leading to study drug discontinuation or interruption will be summarized accordingly. AEs leading to dose reduction will be summarized for cobimetinib and vemurafenib.

Multiple occurrences of the same event will be counted once at the maximum severity. The proportion of patients who experience at least one AE will be reported by toxicity term and treatment arm.

All deaths and causes of death will be summarized.

Listings of AEs will include all AEs with an onset that occurred on or after the first study drug treatment up to the data cutoff date.

In addition, deaths, SAEs, [redacted], and AEs (Grade 3–5) during the study run-in period, will be summarized. To evaluate safety during triple combination period (i.e., post run-in), SAEs, AEs (Grade 3–5), and AE leading to any study drug discontinuation will be summarized.

4.5.3 Laboratory Data

Laboratory data will be summarized over time including change from baseline. Values outside the normal ranges will be summarized. Additionally, selected laboratory data will be classified in accordance with NCI CTCAE v4.0 and will be summarized by grade. Highest NCI CTCAE grade post-baseline will also be reported, and shift tables from baseline to worst value during the study post-baseline will be presented.

4.5.4 Vital Signs

Changes in selected vital signs will be summarized by treatment arm and by change over time including change from baseline.

4.6 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

PK samples of cobimetinib, vemurafenib, and atezolizumab concentration-time data will be overlaid with typical concentration-time profiles for each molecule using existing population PK models to determine if exposures in this study are consistent with previously characterized pharmacokinetics. In addition, individual patient PK parameters will be determined using the non-linear mixed-effects modeling. The results of PK analyses may be reported in a standalone report and may not be reported in the CSR.

4.7 IMMUNOGENICITY ANALYSES

The numbers and proportions of atezolizumab anti-drug antibody (ADA)-positive patients and ADA-negative patients at baseline (baseline prevalence) and after baseline (post-baseline incidence) will be summarized. When determining post-baseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 0.60 titer units greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60 titer units greater than the titer of the baseline sample (treatment unaffected).

The relationship between [redacted] may be analyzed and reported descriptively via subgroup analyses.

4.8 BIOMARKER ANALYSES

[redacted]

[redacted]

The biomarker analyses will be reported separately from the CSR.

4.9 MISSING DATA

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

Any incomplete or missing death date will be handled separately for safety and efficacy analyses. In safety analyses, all deaths will be included, regardless of completeness of death date; patients who died with a partial or missing death date will be included as an event. In efficacy analyses, a death is considered an event only if a complete death date is available; patients who died with only a partial or missing death date will not be considered as a death event.

4.10 INTERIM ANALYSES

4.10.1 Interim Analysis of the Primary Efficacy Endpoint

No interim analyses of the primary endpoint (PFS) will be performed.

4.10.2 Interim Analysis of the Secondary Efficacy Endpoint

The study will incorporate [redacted] OS analyses ([redacted] interim analyses and [redacted] final analysis). [redacted] The Lan-DeMets implementation of the O'Brien and Fleming use function will be used to control the overall type I error for the OS comparison at a two-sided 0.05 significance level. Table 1 summarizes the assumptions and characteristics of the interim and final analyses for OS.

[redacted]

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Appendix 1
Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, DOUBLE-BLINDED, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB PLUS COBIMETINIB AND VEMURAFENIB VERSUS PLACEBO PLUS COBIMETINIB AND VEMURAFENIB IN PREVIOUSLY UNTREATED *BRAF*^{V600} MUTATION–POSITIVE PATIENTS WITH METASTATIC OR UNRESECTABLE LOCALLY ADVANCED MELANOMA**
PROTOCOL NUMBER:	CO39262
VERSION NUMBER:	4
Eudract Number:	2016-002482-54
IND NUMBER:	111, 271
TEST PRODUCTS:	Atezolizumab (RO5541267) Cobimetinib (RO5514041) Vemurafenib (RO5185426)
PHASE:	Phase III
INDICATION:	Metastatic or unresectable locally advanced melanoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of atezolizumab plus cobimetinib plus vemurafenib (atezo + cobi + vem) compared with placebo plus cobimetinib plus vemurafenib (placebo + cobi + vem) in patients with previously untreated, *BRAF*^{V600} mutation–positive, metastatic or unresectable locally advanced melanoma. Specific objectives and corresponding endpoints for the study are outlined in the table below.

Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of atezo + cobi + vem compared with placebo + cobi + vem	• PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first

Objectives and Corresponding Endpoints (cont.)

Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of atezo + cobi + vem compared with placebo + cobi + vem	• PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by an IRC according to RECIST v1.1, or death from any cause, whichever occurs first • Objective response, defined as a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1 • DOR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first • OS, defined as the time from randomization to death from any cause • 2-year landmark survival, defined as survival at 2 years • Time to deterioration in global health status, defined as the time from randomization to first observed ≥ 10-point decrease in EORTC QLQ-C30 linearly transformed global health status scale score that is sustained for two consecutive assessments or followed by death while the patient is on treatment • Time to deterioration in physical functioning, defined as the time from randomization to first observed ≥ 10-point decrease in EORTC QLQ-C30 linearly transformed physical functioning scale score that is sustained for two consecutive assessments or followed by death while the patient is on treatment

Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objective	Corresponding Endpoints
• [redacted]	• [redacted]
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of atezo + cobi + vem compared with placebo + cobi + vem	• Occurrence, frequency, and severity of adverse events, with severity determined through use of NCI CTCAE v4.0 • Change from baseline in targeted vital signs during and following treatment • Change from baseline in targeted clinical laboratory test results during and following treatment
PK Objective	**Corresponding Endpoints**
• To characterize the pharmacokinetics of atezolizumab, cobimetinib, and vemurafenib when administered together and to characterize the pharmacokinetics of cobimetinib and vemurafenib when administered together	• Serum concentration of atezolizumab at specified timepoints • Plasma concentration of cobimetinib and vemurafenib at specified timepoints
Exploratory PK Objectives	**Corresponding Endpoint**
• [redacted]	• [redacted]
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to atezolizumab in the atezo + cobi + vem arm	• Presence of ADAs against atezolizumab during the study relative to the presence of ADAs at baseline

Objectives and Corresponding Endpoints (cont.)

Exploratory Immunogenicity Objective	Corresponding Endpoint
• [redacted]	• [redacted]
Exploratory Biomarker Objective	**Corresponding Endpoint**
• [redacted]	• [redacted]
Exploratory Health Status Utility Objective	**Corresponding Endpoint**
• [redacted]	• [redacted]

ADA = anti-drug antibody; atezo = atezolizumab; cobi = cobimetinib; CR = complete response; DOR = duration of response; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire, Version 3.0; [redacted] IRC = independent review committee; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; VAS = visual analog scale; vem = vemurafenib.

Study Design

Description of Study

Study CO39262 is a Phase III, double-blinded, placebo-controlled, randomized, multicenter study designed to evaluate the efficacy, safety, and pharmacokinetics of atezo + cobi + vem compared with placebo + cobi + vem in patients with previously untreated *BRAF*^{V600} mutation–positive metastatic or unresectable locally advanced melanoma. The primary endpoint of the study is progression-free survival (PFS).

Approximately 500 patients will be randomized in the study. Patients will be randomized in a 1:1 ratio to Arm A (placebo + cobi + vem) or Arm B (atezo + cobi + vem). Patients in both arms will be treated with cobimetinib and vemurafenib during a run-in period of 28 days. Patients in Arm A (control arm) will receive atezolizumab placebo, cobimetinib, and vemurafenib (960 mg twice daily [BID]). Patients in Arm B (experimental arm) will receive active atezolizumab, cobimetinib, and vemurafenib (720 mg BID).

As the vemurafenib doses are different between in the two treatments arms, vemurafenib will be blinded in both study arms. To ensure adequate blinding, patients in both arms will receive the

same number of vemurafenib tablets, with patients in Arm A receiving all active vemurafenib tablets and patients in Arm B receiving a combination of active vemurafenib tablets and vemurafenib placebo tablets.

Following randomization, patients will enter a 28-day run-in period to receive treatment with cobi + vem, followed by treatment with either atezo placebo + cobi + vem (Arm A) or atezo + cobi + vem + vem placebo (Arm B) in the triple combination period.

A stratified, permuted-block randomization scheme will be used for treatment allocation and will be based on the following stratification factors:

- Geographic region (North America vs. Europe vs. Australia, New Zealand, and others)
- Baseline LDH (≤ the upper limit of normal [ULN] vs. > ULN, using central laboratory result)

After signing informed consent, eligible patients will undergo screening procedures that include testing for the *BRAF*^{V600} mutation, laboratory tests, 12-lead ECGs, left ventricular function evaluation (echocardiogram or multigated acquisition scan), contrast–enhanced brain computed tomography (CT) or magnetic resonance imaging (MRI), contrast-enhanced CT or MRI scan of the chest, abdomen, and pelvis, and ophthalmologic and dermatologic assessments. All standard-of-care assessments performed prior to signing the Informed Consent Form do not require repeating, if the assessment was completed within the time frame outlined in this protocol.

All patients will be closely monitored for safety and tolerability throughout the study. The National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 4.0 will be used to characterize the toxicity profile of the study treatments for all patients. The protocol includes a detailed risk management plan for monitoring and managing molecule-specific and potential combination toxicities.

Tumor response will be evaluated by the investigator and by an independent review committee (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. [redacted] will only be assessed by the investigator. All measurable and non-measurable lesions will be documented at screening. Response will be assessed by the investigator at 8- or 12-week intervals until investigator-determined disease progression (according to RECIST v1.1) *or* death, whichever occurs first. Patients who experience disease progression (RECIST v1.1) must have scans repeated 4–8 weeks after initial documentation of progression to confirm disease progression as required per the protocol. Tumor assessments (RECIST v1.1 and [redacted]) are to continue according to schedule in patients who discontinue treatment for reasons other than confirmed disease progression.

Clinically stable patients who have a favorable benefit-risk ratio will continue on study treatment following radiographic progression per RECIST v1.1 *at least until a follow-up scan 4–8 weeks later*. Patients who continue treatment beyond radiographic disease progression will be closely monitored. Treatment will be discontinued if clinical deterioration due to disease progression occurs at any time or if persistent disease growth is confirmed by follow-up scans performed 4–8 weeks later. *If the follow-up scans do not confirm disease progression, the patient may continue on study treatment.*

Study treatment will continue for all patients until investigator-determined disease progression according to RECIST v1.1 (or subsequent clinical deterioration or confirmed disease progression 4–8 weeks later), for clinically stable patients with a favorable benefit-risk ratio), death, unacceptable toxicity, or pregnancy, whichever occurs first. Patients who discontinue one study drug may be able to continue other study drugs, per guidelines for management of specific adverse events. After treatment discontinuation, patients will be followed for disease progression if applicable, and followed for survival until death, withdrawal of consent, or loss to follow-up, whichever occurs first.

Patients in the control arm are not eligible for crossover to the treatment arm at disease progression.

An independent Data Monitoring Committee (iDMC) will be employed to conduct periodic evaluations of safety data. All analyses for the iDMC's review will be prepared by an independent Data Coordinating Center. Sponsor personnel will not have access to by-arm data summaries or listings prior to the formal reporting of the primary efficacy results. Specific details, including responsibilities and structure of the iDMC, will be specified in the iDMC charter.

Number of Patients

Approximately 500 patients with previously untreated, *BRAF*^{V600} mutation–positive metastatic melanoma will be randomized in the study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Able to comply with the study protocol, in the investigator's judgment
- Histologically confirmed Stage IV (metastatic) or unresectable Stage IIIc (locally advanced) melanoma, as defined by the American Joint Committee on Cancer, 7th revised edition
- Naïve to prior systemic anti-cancer therapy for melanoma (e.g., chemotherapy, hormonal therapy, targeted therapy, immunotherapy, or other biologic therapies), with the following exceptions:
  - Neoadjuvant and or adjuvant treatment with chemotherapy, if discontinued at least 28 days prior to initiation of study treatment
  - Adjuvant treatment with interferon, interleukin-2, or vaccine therapies, if discontinued at least 28 days prior to initiation of study treatment
  - Adjuvant treatment with herbal therapies, if discontinued at least 7 days prior to initiation of study treatment
- Documentation of *BRAF*^{V600} mutation–positive status in melanoma tumor tissue (archival or newly obtained) through use of a clinical mutation test approved by the local health authority (e.g., U.S. Food and Drug Administration [FDA]-approved test, College of American Pathologists, External Quality Assurance by EMQN [European Molecular and Genetics Quality Network], EMQN for clinical diagnosis,CE-marked [European conformity] in vitro diagnostic in E.U. countries, or equivalent)

- Eastern Cooperative Oncology Group Performance Status of 0 or 1
- Measurable disease according to RECIST v1.1 (must be outside of CNS)
- 
- Life expectancy ≥ 18 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment, with the exception of amylase, lipase, and LDH where up to 28 days is acceptable (using central laboratory result)
  - ANC ≥ 1.5 × 10^9/L without granulocyte colony-stimulating factor support
  - WBC count ≥ 2.5 × 10^9/L
  - Lymphocyte count ≥ 0.5 × 10^9/L
  - Platelet count ≥ 100 × 10^9/L without transfusion
  - Hemoglobin ≥ 90 g/L without transfusion
  - Serum albumin ≥ 25 g/L
  - Total bilirubin ≤ 1.5 × ULN

- AST and ALT ≤ 2.0 × ULN
- Amylase and lipase ≤ 1.5 × ULN
- Alkaline phosphatase (ALP) ≤ 2.5 × ULN or, for patients with documented liver or bone metastases, ALP ≤ 5 × ULN
- Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CrCl) ≥ 40 mL/min on the basis of measured CrCl from a 24-hour urine collection or Cockcroft-Gault glomerular filtration rate estimation:

$$\text{CrCl} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})} \quad (\times 0.85 \text{ if female})$$

- For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 × ULN within 28 days prior to initiation of study treatment
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen and stable INR during the 28 days immediately preceding initiation of study treatment
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of < 1% per year during the treatment period and for 6 months after the last dose of study treatment

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

  Examples of 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.

  Hormonal contraceptive methods must be supplemented by a barrier method.

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

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

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of study treatment to avoid exposing the embryo.

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

Exclusion Criteria

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

Cancer-Related Exclusion Criteria

- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the course of the study
- Traumatic injury within 2 weeks prior to initiation of study treatment
- Palliative radiotherapy within 14 days prior to initiation of study treatment

- Active malignancy (other than *BRAF*^{V600} mutation–positive melanoma) or malignancy within 3 years prior to screening are excluded, with the exception of resected melanoma, resected basal cell carcinoma (BCC), resected cutaneous squamous cell carcinoma (SCC), resected carcinoma in situ of the cervix, resected carcinoma in situ of the breast, in situ prostate cancer, limited-stage bladder cancer, or any other curatively treated malignancies from which the patient has been disease-free for at least 3 years

  Patients with a history of isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer are eligible for the study.

Ocular Exclusion Criteria

- History of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment, central serous chorioretinopathy, retinal vein occlusion (RVO), or neovascular macular degeneration

  Patients will be excluded from study participation if they currently are known to have any of the following risk factors for RVO:

  - History of serous retinopathy
  - History of retinal vein occlusion
  - Evidence of ongoing serous retinopathy or RVO at baseline

Cardiac Exclusion Criteria

- History of clinically significant cardiac dysfunction, including the following:
  - Poorly controlled hypertension, defined as sustained, uncontrolled, nonepisodic baseline hypertension consistently above 159/99 mmHg despite optimal medical management
  - Unstable angina, or new-onset angina within 3 months prior to initiation of study treatment
  - Symptomatic congestive heart failure, defined as New York Heart Association Class II or higher
  - Myocardial infarction within 3 months prior to initiation of study treatment
  - Unstable arrhythmia
  - History of congenital long QT syndrome
  - Mean (average of triplicate measurements) QTc interval corrected using Fridericia's method (QTcF) $\geq$ 480 ms at screening, or uncorrectable abnormalities in serum electrolytes (sodium, potassium, calcium, magnesium, and phosphorus)
  - Left ventricular ejection fraction below the institutional lower limit of normal or below 50%, whichever is lower

Central Nervous System Exclusion Criteria

- Untreated or actively progressing CNS lesions (carcinomatous meningitis)

  Patients with a history of CNS lesions are eligible, provided that all of the following criteria are met:

  - Measurable disease, per RECIST v1.1, must be present outside the CNS.
  - All known CNS lesions have been treated with radiotherapy or surgery.
  - CNS lesions have not been treated with whole-brain radiotherapy, except in patients who underwent definitive resection of or stereotactic therapy for all radiologically detectable parenchymal brain lesions.

- Absence of interim progression must be confirmed by radiographic study within 4 weeks prior to initiation of study treatment. If new CNS metastases are suspected during the screening period, a confirmatory radiographic study is required prior to initiation of study treatment.
- Any radiotherapy or surgery must be completed ≥ 4 weeks prior to initiation of study treatment.
- There is no ongoing requirement for corticosteroids, and any prior corticosteroid treatment must be discontinued ≥ 2 weeks prior to initiation of study treatment. Treatment with an anticonvulsant at a stable dose is allowed.
- No history of intracranial hemorrhage from CNS lesions

- History of metastases to brain stem, midbrain, pons, or medulla, or within 10 mm of the optic apparatus (optic nerves and chiasm)
- History of leptomeningeal metastatic disease

Additional Exclusion Criteria

- Current severe, uncontrolled systemic disease (including, but not limited to, clinically significant cardiovascular, pulmonary, or renal disease) other than cancer
- Anticipated use of any concomitant medication during or within 7 days prior to initiation of study treatment that is known to cause QT prolongation (which may lead to torsades de pointes)
- Uncontrolled diabetes or symptomatic hyperglycemia
- Any psychological, familial, sociological, or geographical condition that may hamper compliance with the protocol and follow-up after treatment discontinuation
- History of malabsorption or other clinically significant metabolic dysfunction that may interfere with absorption of oral study treatment
- Pregnant or breastfeeding, or intending to become pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.
- Prior allogeneic stem cell or solid organ transplantation
- 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 CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- 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, anti–phospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for the study after discussion with and approval by the Medical Monitor.

  Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for the study after discussion with and approval by the Medical Monitor.

  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

- Known clinically significant liver disease, including alcoholism, cirrhosis, fatty liver, and other inherited liver disease as well as active viral disease including:
  - Positive HIV test at screening
  - Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening

  Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody test at screening, are eligible for the study.
  - Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test and a positive HCV RNA test at screening
- 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
- Signs or symptoms of clinically relevant infection within 2 weeks prior to initiation of study treatment
- Any Grade $\geq$ 3 hemorrhage or bleeding event within 4 weeks prior to initiation of study treatment
- History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to initiation of study treatment
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Treatment with therapeutic oral or intravenous (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 exacerbation) are eligible for the study.
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study
- Treatment with systemic immunosuppressive medication (including, but not limited to, prednisone, 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 the course of the study

  Patients who have received acute, low-dose systemic immunosuppressant medication ($\leq$ 10 mg/day oral prednisone or equivalent) $\geq$ 4 weeks prior to initiation of study treatment 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.

  The use of inhaled corticosteroids for chronic obstructive pulmonary disease or asthma, mineralocorticoids (e.g., fludrocortisone), or low-dose corticosteroids for patients with orthostatic hypotension or adrenocorticol insufficiency is allowed.
- Known hypersensitivity to biopharmaceutical agents produced in Chinese hamster ovary cells
- Known hypersensitivity to any component of the atezolizumab, cobimetinib, or vemurafenib formulations
- History of severe allergic, anaphylactic or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent
- Inability or unwillingness to swallow pills
- Requirement for concomitant therapy or food that is prohibited during the study

End of Study

The study will end when all patients enrolled have been followed until death, withdrawal of consent, lost to follow-up, or the Sponsor decides to end the trial, whichever occurs first. Patients may continue on study treatment until the development of progressive disease, unacceptable toxicity, and/or consent withdrawal. Patients who discontinue study treatment for any reason will be followed for safety according to protocol, followed for disease progression and followed for survival until death, withdrawal of consent, or they are lost to follow-up. Patients who start subsequent anti-cancer treatment after study treatment discontinuation will still need to be followed for disease progression, survival, and safety per the protocol.

Length of Study

The length of the study, from screening of the first patient to the last patient last visit, is expected to be approximately 90 months.

Investigational Medicinal Products

Test Products (Investigational Drugs)

Atezolizumab 840 mg or placebo will be administered by IV infusion on Days 1 and 15 of Cycle 1 and Days 1 and 15 (every 2 weeks) of subsequent cycles.

All patients will receive cobimetinib at a dose of 60 mg (three 20-mg tablets) orally (PO) once daily on Days 1–21 of each 28-day cycle during the run-in and triple combination periods. Cobimetinib should be taken approximately the same time each day, with the morning vemurafenib dose, and no later than 4 hours after the scheduled time. Cobimetinib may be taken with or without a meal. Cobimetinib should be swallowed whole with a glass of water and should not be chewed, cut, or crushed. If a dose of cobimetinib is missed (i.e., not taken within 12 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

Each dose of vemurafenib will consist of four tablets, with patients in Arm A (atezo placebo + cobi + vem) receiving four active tablets and patients in Arm B (atezo + cobi + vem + vem placebo) receiving three active tablets plus one placebo tablet. All patients will receive vemurafenib at a dose of 960 mg (four 240-mg tablets) PO BID on Days 1–21 of the run-in period. Patients in Arm A will continue to receive vemurafenib at a dose of 960 mg PO BID on Days 22–28 of the run-in period and Days 1–28 of each 28-day cycle during the triple combination period. Patients in Arm B will receive vemurafenib at a dose of 720 mg (three 240-mg tablets) plus vemurafenib placebo (one tablet) PO BID on Days 22–28 of the run-in period and Days 1–28 each 28-day cycle during the triple combination period.

Statistical Methods

Primary Analysis

The primary analysis will be a comparison of PFS as determined by the investigator between the two treatment arms using a stratified log-rank test at an overall 0.05 significance level (two sided).

The statistical hypothesis of this study is as follows:

- H_0: PFS (Arm A) = PFS (Arm B)
- H_1: PFS (Arm A) ≠ PFS (Arm B)

PFS (Arm A) represents the survival function of PFS in the placebo + cobi + vem arm, and PFS (Arm B) represents the survival function of PFS in the atezo + cobi + vem arm.

PFS, as assessed by investigator, will be the primary endpoint evaluated. PFS is defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or have died will be censored at the last tumor assessment date. Data for patients with no post-baseline tumor assessment will be censored at randomization.

The hazard ratio (HR) for PFS will be estimated using a stratified Cox model. Two-sided 95% CIs for the HR will be provided. The stratified analyses will incorporate two stratification factors: geographic region (North America vs. Europe vs. Australia, New Zealand, and others) and baseline LDH (≤ ULN vs. > ULN, using central laboratory result). Results from an unstratified log-rank test and the unstratified HR will also be presented. Kaplan-Meier methodology will be used to estimate median PFS for each treatment arm, and Kaplan-Meier curves will be provided.

Determination of Sample Size

Progression-Free Survival

The type I error (α) for the analysis of the primary endpoint of PFS is 0.05 (two sided).

Approximately 500 patients will be randomized to treatment. The final analysis of the primary endpoint of PFS will take place when approximately [redacted] PFS events have occurred. Statistical considerations are based on the following assumptions:

- Stratified log-rank test at 0.05 significance level (two sided)
- [redacted]

Approximately [redacted] PFS events provides approximately [redacted]% power to detect an improvement in median PFS from [redacted]

Overall Survival

The type I error (α) for the analysis of the secondary endpoint of overall survival (OS) is 0.05 (two sided). The final analysis of OS will be performed after the occurrence of approximately [redacted] deaths.

A total of [redacted] deaths provides approximately [redacted]% power to detect an improvement in median OS from [redacted] months in the placebo + cobi + vem arm to [redacted] months in the atezo + cobi + vem arm (corresponding to an HR of [redacted]) at an overall two-sided 0.05 significance level.

Interim Analyses

Planned Interim Analysis of the Primary Efficacy Endpoint

[redacted]

Interim Efficacy Analysis of Secondary Efficacy Endpoint

The study will incorporate [redacted] OS analyses ([redacted] interim analyses and [redacted] final analysis). The [redacted] OS interim analysis will be performed at the time of the primary PFS analysis. [redacted] The Lan-DeMets implementation of the O'Brien and Fleming use function will be used to control the overall type I error for the OS comparison at a two-sided 0.05 significance level.

Appendix 2
Schedule of Assessments

	Screening [a]		Run-In Period (Days 1–28) [b]			Triple Combination Period [c]										Treatment Discon. [d]	Follow-Up	
						Cycle 1				Cycle 2				Cycles 3+				
Day	−28 to −1	−14 to −1	1	15	21	1	8	15	22 [e]	1	8	15	22	1	15	28	3 mos	6 mos
Visit window (days) [f]	x [f]			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14
Informed consent	x [g]																	
Randomization			x [i]															
BRAF^{V600} mutation status	x [a]																	
Demographic data [j]	x																	
Medical history [k]	x																	
EORTC QLQ-C30 [l]			x			x		x		x		x		x		x		x [m]
Height and weight	x																	
ECOG performance status	x					x				x				x		x		
Complete physical examination [n]	x		x [o]													x		
Limited physical examination [n]						x				x				x			x	x
Head and neck examination [p]	x													x [p]		x [p]	x [p]	x [p]
Anal and gynecological examinations [q]	x															x		x [q]
Dermatologic examination [r]	x					x								x [r]		x [r]		x [r]

Appendix 2
Schedule of Assessments (cont.)

	Screening [a]		Run-In Period (Days 1–28) [b]			Triple Combination Period [c]										Treatment Discon. [d]	Follow-Up	
						Cycle 1				Cycle 2				Cycles 3+				
Day	−28 to −1	−14 to −1	1	15	21	1	8	15	22 [e]	1	8	15	22	1	15	28	3 mos	6 mos
Visit window (days) [f]	x [f]			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14
Cutaneous SCC tumor tissue or suspicious neoplasms [t]			Any new primary neoplasms that develop from the start of study treatment through 6 months following vemurafenib discontinuation [s]															
Vital signs [u]		x [u, v]		x		x	x	x	x	x	x	x	x	x	x	x		
Hematology [w]		x	x [o]			x				x				x		x		
Chemistry [x]		x	x [o]	x		x	x	x	x	x	x	x	x	x	x	x		
Thyroid-function tests [y]	x					x				x				x [y]		x		
Viral serology [z]	x																	
Pregnancy test [aa]		x [v, aa]				x [aa]				x [aa]				x [aa]		x [aa]		
Fasting blood glucose and lipids [bb]	x																	
INR and aPTT	x																	
12-Lead ECG [cc]		x		x				x				x			x [cc]	x		
Radiologic tumor assessment [dd]	x [ee]								Last week of Cycle 1 and every 8 or 12 weeks thereafter [ee]									
Additional chest CT or MRI scan																		x [ff]
Brain CT or MRI scan	x [gg]		As clinically indicated [ff]															

Appendix 2
Schedule of Assessments (cont.)

	Screening [a]		Run-In Period (Days 1–28) [b]			Triple Combination Period [c]										Treatment Discon. [d]	Follow-Up	
						Cycle 1				Cycle 2				Cycles 3+				
Day	−28 to −1	−14 to −1	1	15	21	1	8	15	22 [e]	1	8	15	22	1	15	28	3 mos	6 mos
Visit window (days) [f]	x [f]			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±14
ECHO or MUGA scan	x					x								x [hh]		x		
[redacted]																		
PK sample						Refer to Appendix 2												
Sample for ADAs						Refer to Appendix 2												
[redacted]																		
Concomitant medications [ii]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Adverse events [kk]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [kk]	x [kk]	x [kk]
Study drug accountability [ll]			x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Dispense cobimetinib and vemurafenib (± vemurafenib placebo) [mm, nn, oo]			x		x	x				x				x				
Atezolizumab or atezolizumab placebo administration [oo, pp]						x		x		x		x		x	x			
Survival assessment and initiation of subsequent anti-cancer therapy																	x [qq]	q12w x [qq]

Appendix 2
Schedule of Assessments (cont.)

ADA = anti-drug antibody; BID = twice daily; CT = computed tomography; discon. = discontinuation; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV = hepatitis C virus; HEENT = head, eyes, ears, nose, and throat; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition; OCT = optical coherence tomography; PCR = polymerase chain reaction; PK = pharmacokinetic; QD = once daily; Q12W = every 12 weeks; Q2W = every 2 weeks; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria in Solid Tumors; RVO = retinal vein occlusion; SCC = squamous cell carcinoma; T3 = triiodothyronine; TSH = thyroid-stimulating hormone.

Note: Assessments scheduled on study drug administration days should be performed prior to study drug dosing, unless otherwise specified.

[a] Perform screening tests within 28 days prior to treatment initiation (Run-In Day 1). Standard-of-care screening assessments may be performed concurrently with the *BRAF*^{V600} mutation testing. BRAF^{V600} status must be known prior to performing study-specific screening assessments. The 28-day window begins at the time of the first standard-of-care screening assessment or the first study-specific screening assessment after the *BRAF*^{V600} mutation test result is available, whichever is earlier. Results of standard-of-care tests or examinations performed before obtaining informed consent and within 28 days prior to Run-In Day 1 may be used for screening assessments; such tests do not need to be repeated for screening. Test results should be reviewed prior to administration of study treatment.

[b] Dose modifications (including treatment interruption and dose reductions) for treatment–related toxicities are allowed during the run-in period (see guidelines for management of specific adverse events in Section 5.1.5.4). Treatment can be withheld for a maximum of 28 consecutive days, and the run-in period can be extended to a maximum of 56 days (28 days + 4 weeks).

[c] Study treatment will continue until disease progression (as assessed by the investigator according to RECIST v1.1) or (for patients who are clinically stable) confirmation of disease progression, death, unacceptable toxicity, or pregnancy, whichever occurs first.

[d] Patients who discontinue all study treatment will be asked to return to the clinic for a treatment discontinuation visit within 28 (±7) days after the last dose of study treatment or before subsequent anti-cancer therapy is initiated. The visit at which response assessment shows disease progression may be used as the treatment discontinuation visit, provided all required assessments have been performed and it is 28 (±7) days after the last dose of study drug.

[e] Cycle 1 Day 22 has a window of ±3 days.

[f] During the screening period, a visit window of upto –35 days in is permitted for the following safety assessments: ECOG, ECHO/MUGA, anal and gynecological examinations, and ophthalmologic examinations, if the results are within the expected range. During the study treatment, a ±3 day window is deemed acceptable, only if the visit cannot be scheulded on the required day. All safety assessments, such as laboratory tests, EGCs, etc. should be performed before the treatment cycle starts (visit window –3 days). Additional visit windows such as ±7 days may be included for individual assessment if deemed appropriate (see individual footnote for each assessment).

[g] Informed consent must be documented before any study-specific screening assessments are performed.

Appendix 2
Schedule of Assessments (cont.)

[h] [redacted]

[i] Randomization must occur within 24 hours prior to Run-In Day 1.

[j] Demographic data include age, sex, and self-reported race/ethnicity (where permissible).

[k] Medical history includes clinically significant diseases and surgeries within 5 years prior to initiation of study treatment, cancer history (including prior cancer therapies, surgeries, and procedures), and use of use of alcohol.

[l] PRO assessments (EORTC QLQ-C30 and [redacted] scheduled for administration during a clinic visit are required to be completed by the patient at the investigational site at the start of the clinic visit (or the first clinic visit for that cycle if multiple visits are scheduled, allowing upto a −3 day visit window) before discussion of the patient's health state, lab results or health record, before administration of study treatment, and/or prior to any other study assessment(s) that could bias patients' responses to ensure that the validity of the instrument is not compromised and that data quality meets regulatory requirements. *In addition, questionnaires may be completed at the site at an unscheduled timepoint.*

[m] The global health status questions (29 and 30) and physical functioning questions (1–5) from the EORTC QLQ-C30 and the entire [redacted] will be administered at 2, 4, and 6 months after the last dose of study treatment. Questionnaires during follow up period do not need to be conducted in person (i.e., do not require an office visit).

[n] Patients should be asked specifically about skin and vision changes at each physical examination. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Complete physical examination includes evaluation of the HEENT and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Limited, symptom-directed physical examination includes evaluation of the lungs, heart, abdomen, neurological systems, and skin (at a minimum).

[o] If performed within 7 days prior to Run-In Day 1, assessments do not need to be repeated at that visit.

[p] To monitor for the occurrence of SCC in the upper aerodigestive tract, a head and neck examination will be performed at screening, Day 1 of Cycle 3 and every three cycles thereafter during treatment (i.e., Day 1 of Cycles 6, 9, 12, etc.) (± 1 week), at the treatment discontinuation visit (unless performed within the previous 12 weeks), at 3 and 6 months (± 2 weeks) after the last dose of study treatment, and as clinically indicated (e.g., if any new head and neck lesions are suspected of being non-cuSCC). Assessments will include (at a minimum) examination of the HEENT and neck, visual inspection of the oral mucosa, and lymph node palpation.

[q] To monitor for anal SCC, visual inspection and digital examination of the anus and anal canal will be performed at screening, at the treatment discontinuation visit, 6 months (±2 weeks) after the last dose of vemurafenib, and as clinically indicated. Colonoscopy, sigmoidoscopy, or anoscopy is not required but may be performed if clinically indicated. To monitor for cervical carcinoma, all female patients will undergo a pelvic examination, including visual inspection of the uterine cervix and Papanicolaou (Pap) smear, at screening, at the treatment discontinuation visit, 6 months (±2 weeks) after the last dose of vemurafenib, and as clinically indicated. Pelvic examinations performed within 12 months prior to screening need not be repeated if found to be normal.

Appendix 2
Schedule of Assessments (cont.)

[r] A complete dermatologic evaluation (as described in Section 4.5.6.1) should be performed at screening, on Day 1 of Cycle 1 and every three cycles thereafter during treatment (i.e., Day 1 of Cycles 4, 7, 10, etc.) (± 1 week), at the treatment discontinuation visit (unless performed within the previous 12 weeks), 6 months (±2 weeks) after the last dose of study treatment, and as clinically indicated.

[s] Ophthalmologic examinations (as described in Section 4.5.6.2) should be performed at screening; on Day 1 of Cycle 1 (±1 week), Cycles 4, 7, 10, 14, 18, 22, and every six cycles thereafter (i.e., Cycles 28, 34, 40, etc.) (±2 weeks for each); at the treatment discontinuation visit (unless examination performed within the previous 12 weeks showed no clinically significant findings or changes since the prior examination); and as clinically indicated.

[t] If a patient develops a new skin lesion that is suspected of being cuSCC or another new primary cutaneous neoplasm during the study or up to 6 months after the last dose of vemurafenib, a biopsy and/or excision should be formed and a tissue specimen, along with a paired normal skin sample (one sample per patient) must be sent to a Roche-designated central laboratory for confirmation of diagnosis, further molecular characterization, and exploratory biomarker analyses. All new primary neoplasms (benign or malignant), including new primary melanoma, will be reported until 6 months after the last dose of vemurafenib. Any new primary neoplasm other than cuSCC should be reported as a serious adverse event.

[u] Vital signs include measurement of heart rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position, as well as oral or tympanic temperature. Blood pressure and heart rate measurements will be recorded after a 5-minute rest while the patient is in a seated position. Resting oxygen saturation will be measured during screening. Vital signs should be measured within 60 minutes prior to each atezolizumab infusion and, if clinically indicated, during or after the infusion.

[v] Vital signs and serum pregnancy test must be performed within 7 days prior to Run-In Day 1.

[w] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, reticulocyte count, differential count (neutrophils, bands (if available), eosinophils, basophils, monocytes, lymphocytes,).

[x] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (HCO_3 and CO_2 not mandatory if unavailable at site), BUN or urea, creatinine, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, LDH, CPK, glucose (non-fasting). LDH will be assessed by both local and central laboratory, and the central laboratory result will be used for stratification and randomization only. At Cycle 6 and thereafter, the chemistry panel should be done at Day 1 only and as clinically indicated. *Amylase and lipase is required at screening (if not feasible, then either amylase or lipase) and if clinically indicated during study treatment.*

[y] Includes thyroid-stimulating hormone, free T3 (or total T3 for sites where free T3 is not performed), free thyroxine. Thyroid-function tests are to be performed at screening, on Day 1 of Cycles 1–5 and every second cycle thereafter (e.g., Day 1 of Cycles 7, 9, 11, etc.), and at the treatment discontinuation visit

Appendix 2
Schedule of Assessments (cont.)

[z] At screening, patients will be tested for HIV, HBsAg, HBsAb, 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 should be performed. 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 active HCV infection.

[aa] For women of childbearing potential, a serum pregnancy test is required at screening (within 7 days prior to Run-In Day 1) and at the treatment discontinuation visit. Urine pregnancy tests will be performed on Day 1 (or within 7 days) of every cycle (e.g., Day 1 of Cycles 1, 2, 3 etc.). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

[bb] Both blood glucose and lipid panel must be obtained after at least an 8-hour fast, at screening only. Lipid panel should include total cholesterol, low-density lipoprotein, and triglycerides.

[cc] ECG recordings will be obtained at screening. ECG recordings will be obtained prior to the morning doses of cobimetinib and vemurafenib on Run-In Day 15 (±3 days); on Day 15 (±3 days) of Cycles 1, 2, 3, and every three cycles thereafter (i.e., Day 15 of Cycles 6, 9, 12, etc.) (±3 days); at the treatment discontinuation visit (±3 days); and as clinically indicated. EGCs should be performed prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws unless pre-authorized by the Medical Monitor) and after the patient has been resting in a supine position for at least 10 minutes (see Section 4.5.6.3 for additional details).

[dd] Tumor assessments will include contrast-enhanced CT or MRI scans of the chest, abdomen, and pelvis. Imaging of the neck should be included if clinically indicated. Clinical disease assessments by physical examination should be performed for patients with palpable/superficial lesions. Tumor measurements for each patient should be made by the same investigator or radiologist, if feasible, using the same assessment technique or procedure throughout the study. Tumor response and progression will be evaluated according to RECIST v1.1 (see Appendix 4) and [redacted].

[ee] All measurable and non-measurable lesions must be documented at screening (within 28 days prior to Run-In Day 1), and previously irradiated lesions should not be selected as measurable lesions. Patients will undergo subsequent tumor assessments during the last week of Cycle 1 and every 8 weeks (±1 week) through 24 months (e.g., *Weeks 8, 16, 24, 32,* etc.) and then every 12 weeks (±1 week) thereafter, until investigator-determined disease progression (according to RECIST v1.1) or death, whichever occurs first. Thus, tumor assessments as outlined are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression. At the investigator's discretion, CT or MRI scans may be repeated at any time if disease progression is suspected. Patients who experience disease progression must have scans repeated 4–8 weeks after initial documentation of progression to confirm disease progression. Tumor assessments must be performed independently of changes to the study treatment administration schedule (e.g., treatment interruptions). If a tumor assessment has to be performed early or late, subsequent assessments should be conducted according to the original schedule based on the date of first study treatment administration (Run-In Day 1). Objective response (complete or partial response) must be confirmed by repeat assessments ≥ 4 weeks after initial documentation. In the case of stable disease, tumor measurements must meet criteria for stable disease ≥ 6 weeks after initiation of study treatment.

Appendix 2
Schedule of Assessments (cont.)

ff To monitor for SCC, an additional chest CT or MRI scan must be performed 6 months (±2 weeks) after the last dose of study treatment.

gg Patients must have a screening brain CT or MRI scan to assess for brain metastasis. Stable brain metastases (as defined in Section 4.1.2) must be evaluated at each tumor assessment with the same radiographic procedure as the baseline study. Patients without brain metastases do not need brain scans for tumor assessment unless clinically warranted.

hh Evaluation of left ventricular function, either by ECHO or MUGA scan, will be performed at screening, on Day 1 of Cycle 1 (±1 week), and on Day 1 of every three treatment cycles thereafter starting at Cycle 4 (± 2 weeks for each), at the treatment discontinuation visit (unless evaluation performed within the previous 12 weeks showed no clinically significant findings or changes from baseline), and as clinically indicated. All patients who restart treatment with a reduced dose of cobimetinib because of a decrease in LVEF should have LVEF measurements taken after approximately 2, 4, 10, and 16 weeks (or as clinically indicated) and then resume monitoring LVEF every 12 weeks (three cycles). Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF assessment. For patients (asymptomatic and symptomatic) who discontinue cobimetinib, LVEF assessments should continue 6 weeks post-treatment or as clinically indicated until the LVEF recovers to LLN or 50% and or symptoms. These evaluations are not required for patients who have permanently discontinued cobimetinib and who do not have reduced left ventricular function.

ii [redacted]

jj Includes any 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 study treatment from 7 days prior to signing of the Informed Consent Form through 30 days after the last dose of study treatment.

kk 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, adverse events will be reported as follows: All adverse events will be reported until 30 days after the last dose of study treatment or until initiation of subsequent anti-cancer therapy, whichever occurs first. Serious adverse events and [redacted] will continue to be reported until 90 days after the last dose of study treatment or until initiation of subsequent anti-cancer therapy, whichever occurs first. All new primary neoplasms (benign or malignant), including new primary melanoma, will be reported until 6 months after the last dose of vemurafenib. After the 6 month safety follow-up 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 (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

Appendix 2
Schedule of Assessments (cont.)

[ll] Medication diaries should be issued, collected, and reviewed, and unused medications should be collected for assessment of compliance.

[mm] All patients will receive cobimetinib at a dose of 60 mg (three 20-mg tablets) PO QD on Days 1–21 of each 28-day cycle during the run-in and triple combination periods. At least 7 days off cobimetinib are required prior to starting a new treatment cycle. Cobimetinib will be dispensed on Day 1 of each treatment cycle.

[nn] All patients will receive vemurafenib at a dose of 960 mg (four 240-mg tablets) PO BID on Days 1–21 of the run-in period. Patients in Arm A will continue to receive vemurafenib at a dose of 960 mg PO BID on Days 22–28 of the run-in period and Days 1–28 of each 28-day cycle during the triple combination period. Patients in Arm B will receive vemurafenib at a dose of 720 mg (three 240-mg tablets) plus vemurafenib placebo (one tablet) PO BID on Days 22–28 of the run-in period and Days 1–28 each 28-day cycle during the triple combination period. Vemurafenib will be dispensed on Day 1 of each treatment cycle and on Day 21 or 22 of the run-in period.

[oo] Study treatment will continue for all patients until investigator-determined disease progression (or confirmed progression 4–8 weeks later, for clinically stable patients with a favorable benefit-risk ratio), death, unacceptable toxicity, or pregnancy, whichever occurs first.

[pp] Atezolizumab 840 mg or placebo will be administered by IV infusion on Days 1 and 15 of Cycle 1 and Days 1 and 15 of subsequent cycles. The initial dose 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. The morning dose of vemurafenib and the once daily dose of cobimetinib may occur prior to the atezolizumab infusion.

[qq] After treatment discontinuation, all patients will be monitored for survival and initiation of subsequent anti-cancer therapy via telephone calls patient medical records, and/or clinic visits every 12 weeks until death (unless the Sponsor terminates the study). If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) if permissible by local regulations to obtain information about survival status only.