Official Title: **A PHASE III, OPEN-LABEL, MULTICENTER, TWO-ARM, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF COBIMETINIB PLUS ATEZOLIZUMAB VERSUS PEMBROLIZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED *BRAF*^{V600} WILD-TYPE MELANOMA**

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STATISTICAL ANALYSIS PLAN

TITLE:	**A PHASE III, OPEN-LABEL, MULTICENTER, TWO-ARM, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF COBIMETINIB PLUS ATEZOLIZUMAB VERSUS PEMBROLIZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED *BRAF*^{V600} WILD-TYPE MELANOMA**
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STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
03-Feb-2020 12:37:52	Company Signatory	[redacted]

STATISTICAL ANALYSIS PLAN, VERSION 2

RATIONALE FOR AMENDMENT

A change has been made in Section 4.4 (“Efficacy Analyses”) to address the potential risk of over-stratification in efficacy analyses.

The stratification factors will be those used for randomization and will be obtained from the IWRS (PD-L1 status, baseline serum LDH level and geographic region). 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 PD-L1 status, baseline serum LDH level and geographic region) has fewer than 10 IRC-assessed PFS events across treatment arms, the stratification factor (one of three stratification factors: PD-L1 status, baseline serum LDH level and geographic region 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 IRC-assessed PFS events. The final set of stratification factors used in stratified analyses will be applied to all endpoints where stratified analyses are planned.

STATISTICAL ANALYSIS PLAN, VERSION 3

RATIONALE FOR AMENDMENT

Given that the study did not meet the primary endpoint and did not demonstrate a benefit of cobimetinib plus atezolizumab vs. pembrolizumab, it will be terminated early. Therefore, changes have been made in Section 2.5 (“Premature termination of study after primary analysis”) and Section 4.10 (“Interim Analysis”) to clarify when analysis of the secondary endpoint of Overall Survival (OS) will be conducted.

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1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study CO39722 (IMspire170): A Phase III, open-label, multicenter, two-arm, randomized study to investigate the efficacy and safety of cobimetinib plus atezolizumab versus pembrolizumab in patients with previously untreated advanced *BRAF*^{V600} wild-type melanoma. The background for the study can be found in the study protocol.

It is anticipated that positive results from Study CO39722 will support the submission of filing applications globally for the use of cobimetinib plus atezolizumab for the treatment of patients with previously untreated advanced *BRAF*^{V600} wild-type melanoma. For purposes of registration, the analyses outlined in this SAP will supersede those specified in the protocol.

2. STUDY DESIGN

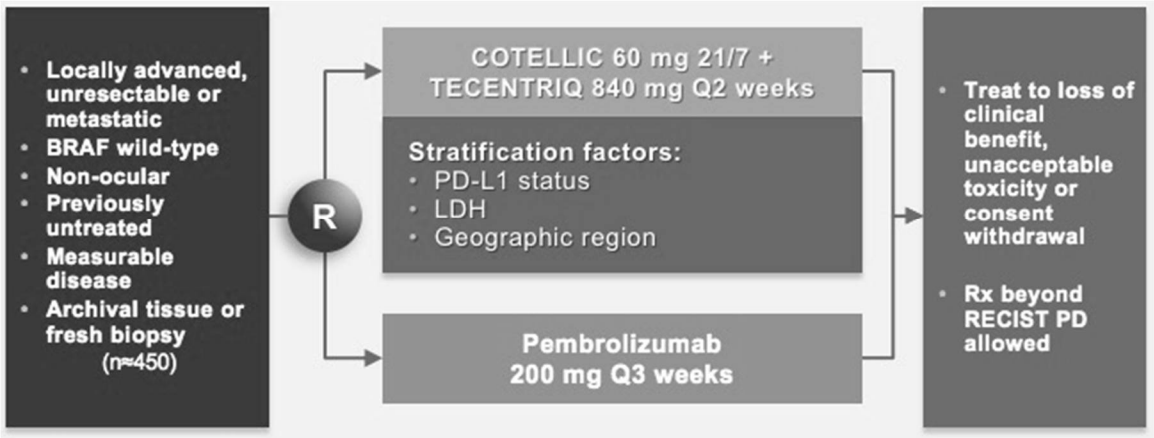
Study CO39722 is a Phase III, multicenter, open-label, randomized study designed to evaluate the efficacy, safety, and pharmacokinetics of cobimetinib plus atezolizumab compared with pembrolizumab in treatment-naive patients with advanced *BRAF*^{V600} wild-type melanoma.

This study will be conducted globally and approximately 450 patients will be randomized in a 1:1 ratio to one of two treatment arms:

- Arm A: Patients will receive 60 mg of cobimetinib by mouth (PO) on a 21 days on, 7 days off (21/7) schedule (dosing on Days 1-21, followed by no dosing on Days 22-28) plus 840 mg of atezolizumab by intravenous (IV) infusion on Days 1 and 15 of each 28-day cycle (n = 225).
- Arm B: Patients will receive 200 mg of pembrolizumab administered by IV infusion every 3 weeks (Q3W) (n = 225).

The study schema is presented in Figure 1 .

Figure 1 Study Schema



PD = progressive disease; PD-L1 = programmed death–ligand 1; Q3W = every 3 weeks; Q2W = every 2 weeks, R = randomization; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; 21/7 = 21 days on/7 days off (schedule).

Stratification factors are PD-L1 (programmed death-ligand 1) status (IC0 [tumor-infiltrating immune cell 0] vs. IC1, 2, 3), baseline serum LDH (lactate dehydrogenase) level (less than or equal to the upper limit of normal [ULN] vs. greater than the ULN), and 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 eligible patients will be randomized to treatment in a 1:1 ratio to either Arm A (cobimetinib plus atezolizumab) or Arm B (pembrolizumab).

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at the treatment discontinuation visit, and during the follow-up period. The National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0) will be used to characterize the toxicity profile of 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 response will be evaluated according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (see Appendix 4). Any evaluable and measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Investigators will assess tumor response at 8-week intervals, regardless of any dose delays or treatment cycle.

Study treatment will continue for all patients until investigator-determined disease progression according to RECIST v1.1 that is confirmed by repeat scans 4-8 weeks later, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurs first. Patients who experience disease progression must have scans repeated 4-8 weeks after initial documentation of progression to confirm disease progression. These results will be used as part of the exploratory analyses for assessing efficacy based on immune-modified RECIST. Tumor assessments are to continue according to schedule for patients who discontinue treatment for reasons other than confirmed disease progression. Clinically stable patients who have disease progression may continue study treatment, as described in protocol Section 3.1.1. 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. If a patient withdraws from the study, study staff may use a public information source (e.g., county records) to obtain information about survival status only.

The primary endpoint is Independent Review Committee (IRC)-assessed Progression-Free Survival (PFS) per RECIST v1.1, 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. The analysis of the primary endpoint of PFS will occur after a total of approximately 240 events have occurred.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2. For schedule of pharmacokinetic, immunogenicity, and biomarker sample, see Appendix 3.

2.2 ENDPOINTS

2.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is IRC-assessed PFS per RECIST v1.1, 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.

2.2.2 Secondary Efficacy Endpoints

- Overall Survival (OS), defined as the time from randomization to death from any cause
- Two-year landmark survival, defined as survival at 2 years
- Objective response, defined as a complete response or a partial response on two consecutive occasions ≥ 4 weeks apart, as determined by the IRC according to RECIST v1.1

- Objective response, defined as a complete response or a partial response on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator through use of RECIST v1.1
- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator through use of RECIST v1.1, or death from any cause, whichever occurs first
- Disease control Rate (DCR), defined as a complete response, a partial response, or stable disease at 16 weeks, as determined by the IRC through use of RECIST v1.1
- DCR, defined as a complete response, a partial response, or stable disease at 16 weeks, as determined by the investigator through the use of RECIST v1.1
- Duration of objective response, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the IRC through use of RECIST v1.1, or death from any cause, whichever occurs first
- Duration of objective response, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator through use of RECIST v1.1, or death from any cause, whichever occurs first
- The change from baseline in Health-Related Quality of Life (HRQoL) scores, as assessed through use of the two-item Global Health Status/Quality of Life (GHS/QOL) subscale of the European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) questionnaire, at specified timepoints while receiving treatment

2.2.3 Exploratory Efficacy Endpoints

- Objective response according to investigator-assessed immune-modified RECIST
- Duration of response rate (DOR) according to investigator-assessed immune-modified RECIST
- PFS according to investigator-assessed immune-modified RECIST
- Change from baseline in HRQoL, functioning and commonly reported symptoms (insomnia, pain, and fatigue), as assessed through use of the EORTC QLQ-C30 GHS, functioning and symptom scales, at specified timepoints, including progression, treatment discontinuation and post-study treatment
- The number and proportion of patients who improve, remained stable, and worsen from baseline as measured by the EORTC QLQ-C30 , GHS, functioning, and symptom scales, at specified timepoints, including progression, treatment discontinuation and post-study treatment

2.2.4 Pharmacokinetic Endpoints

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

[redacted]

2.2.5 Safety Endpoints

- Occurrence and severity of AEs, with severity determined through use of NCI CTCAE v4.0
- Change from baseline in selected vital signs
- Change from baseline in selected clinical laboratory test results

2.2.6 Immunogenicity Endpoint

- Incidence of anti-drug antibodies (ADAs) during the study relative to the prevalence of ADAs at baseline

Exploratory analysis investigating the relationship between ADA status and efficacy, safety, or PK endpoints will be performed.

2.2.7 Exploratory Biomarker Endpoint

- Relationship of immune contextures, such as PD-L1, cluster of differentiation 8 (CD8)-positive T cells, or major histocompatibility complex expression, as identified by immunohistochemistry and gene signature profiling, genetic alterations, such as *RAS* and *NF1*, with efficacy, pharmacokinetics, immunogenicity, or other biomarker endpoints.

2.2.8 Exploratory Health Utility Objective

- Health status utility score based on the European Quality of Life 5-Dimension, 5-Level (EQ-5D-5L) questionnaire

2.3 DETERMINATION OF SAMPLE SIZE

Approximately 450 patients will be randomized into the study.

The overall type I error (α) for this study is 0.05 (two-sided). Formal treatment comparisons will be performed by first evaluating the primary endpoint of IRC-assessed PFS (per RECIST v1.1) at $\alpha = 0.01$ (two-sided). If PFS is statistically significant at $\alpha = 0.01$, then the key secondary endpoints will be evaluated at $\alpha = 0.05$ (two-sided) in a hierarchical manner in the following order: OS, IRC-assessed objective response rate (ORR), and landmark OS. IRC-assessed ORR and landmark OS will be tested when OS crosses the pre-specified boundary.

The type I error (α) for the analysis of the primary endpoint of IRC-assessed PFS is 0.01 (two-sided). The analysis of the primary endpoint of IRC-assessed PFS will take place when approximately 240 PFS events have occurred. Statistical considerations are based on the following assumptions:

- Stratified log-rank test at 0.01 significance level (two-sided)
- Median PFS of 5.5 months for the pembrolizumab arm
- Median PFS of 10.0 months for the cobimetinib plus atezolizumab arm
- Enrollment period of approximately 12 months
- Annual dropout rate of 5%
- No interim analysis for PFS

A total of 240 PFS events provides approximately 98% power to detect an improvement in median PFS from 5.5 months in the pembrolizumab arm to 10.0 months in the cobimetinib plus atezolizumab arm. This corresponds to a hazard ratio (HR) of 0.55, with a minimal detectable difference of 0.72. The PFS analysis will be conducted approximately 17 months after first patient in (FPI). The final analysis of the secondary endpoint of OS will be performed after the occurrence of approximately 295 deaths. A total of 295 deaths provides approximately 60% power to detect an improvement in median OS from 28 months in the pembrolizumab arm to 37.5 months in the cobimetinib plus atezolizumab arm, corresponding to an HR of 0.75, or 80% power to detect an HR of 0.70. Two interim analyses of OS will be conducted. The final OS analysis will be conducted approximately 68 months after FPI.

2.4 ANALYSIS TIMING

The PFS primary analysis will be conducted when approximately 240 PFS events have occurred, which is expected to occur approximately 17 months after FPI. There is no planned interim analysis for PFS.

The study will incorporate three OS analyses (two interim analyses and one final analysis). The first OS interim analysis will be performed at the time of the primary PFS analysis when a projected number of 80 deaths are expected to have occurred. The second OS interim analysis will be performed after the occurrence of approximately 153 deaths and is projected to occur at approximately 28 months after the first patient is randomized. The final OS analysis will be performed after the occurrence of approximately 295 deaths and is projected to occur approximately 68 months after the first patient is randomized. Refer to Section 4.10 for the assumptions and characteristics of the interim and final analysis for OS.

2.5 PREMATURE TERMINATION OF STUDY AFTER PRIMARY ANALYSIS

Given that the study did not meet the primary endpoint and did not demonstrate a benefit of cobimetinib plus atezolizumab vs. pembrolizumab, it will be terminated early. Therefore, the second interim and final OS analyses will not be conducted as specified elsewhere in this document. Instead, a final OS analysis will be conducted at the time of final database lock.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Randomization to the two treatment arms will occur in a 1:1 ratio. A permuted-block randomization 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:

- PD-L1 status (IC0 vs. IC1, 2, 3)
- Baseline serum LDH level (less than or equal to the ULN vs. greater than the ULN)
- Geographic region (North America vs. Europe vs. Australia, New Zealand, and others).

3.2 INDEPENDENT REVIEW FACILITY

An IRC will be used for this study. PFS based on blinded independent review assessments is the primary endpoint for this study. ORR, DCR, and DOR based on blinded independent review assessments are secondary endpoints. For details about the IRC, refer to the IRC Charter.

3.3 DATA MONITORING

An independent Data Monitoring Committee (iDMC) is used to conduct periodic evaluations of safety data. All analyses for the iDMC's review will be prepared by an independent Data Coordinating Center (iDCC). For details about the iDMC, refer to the iDMC Charter.

4. STATISTICAL METHODS

The analyses described in this SAP will supersede those specified in Protocol CO39722 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 the patient received the assigned treatment.

4.1.2 Pharmacokinetic-Evaluable Population

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

4.1.3 Immunogenicity-Evaluable Population

The baseline ADA-evaluable population for each study treatment includes patients who had a baseline ADA result. The post-baseline ADA-evaluable population for each study treatment includes patients who had at least one post-baseline ADA result and had received at least one dose of that study treatment.

4.1.4 Safety Population

The safety population is defined as all patients who received at least one dose of study drug, with patients grouped according to treatment received as follows:

- Cobimetinib + atezolizumab arm (Arm A): patients who received any amount of cobimetinib or atezolizumab
- Pembrolizumab arm (Arm B): patients who received any amount of pembrolizumab without any amount of either atezolizumab or cobimetinib.

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 (e.g., Eastern Cooperative Oncology Group [ECOG] performance status), and stratification factors will be summarized by treatment arm for the ITT population. Descriptive statistics (mean, median, standard deviation [SD], and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

4.4 EFFICACY ANALYSIS

Unless otherwise noted, efficacy analyses will include all randomized patients, 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 (PD-L1 status, baseline serum LDH level and geographic region). 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 PD-L1 status, baseline serum LDH level and geographic region) has fewer than 10 IRC-assessed PFS events across treatment arms, the stratification factor (one of three stratification factors: PD-L1 status, baseline

serum LDH level and geographic region 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 IRC-assessed 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 IRC, between the two treatment arms using the stratified log-rank test at an overall 0.01 significance level (two-sided).

PFS is 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. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. Data for patients with no post-baseline tumor assessment will be censored at randomization.

The 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 provided. 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 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 cutoff, OS time will be censored at the date the patient was last known to be alive. Survival time for patients with no post-baseline survival information will be censored at randomization. The HR for OS will be estimated using a stratified Cox model, and a two-sided 95% CI for the HR will be provided. Results from an unstratified analysis will also be provided. The Kaplan-Meier approach will be used to estimate median OS and 2-year landmark survival rate. The 95% CI of the median OS will be estimated using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). The 95% CI of landmark survival rate will be calculated using the standard error derived from Greenwood's formula (Greenwood 1926).

4.4.2.2 Objective Response Rate by IRC and Investigator Using RECIST v1.1

Objective response rate is defined as the total number of patients whose objective response is a complete response or a partial response, divided by the number of patients in the ITT population with measureable disease at baseline. Objective response is defined as a complete response or partial response on two consecutive occasions ≥ 4

weeks apart, as determined by the IRC and or investigator using RECIST v1.1. 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 Progression-Free Survival by Investigator Using RECIST v1.1

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

4.4.2.4 Disease Control Rate by IRC and Investigator Using RECIST v1.1

DCR is defined as the proportion of ITT patients with measurable disease at baseline with a complete response, a partial response, or stable disease at 16 weeks after the baseline tumor assessment, as determined by the IRC or investigator according to RECIST v1.1. A 95% Clopper-Pearson CI will be calculated for the DCR for each treatment arm.

4.4.2.5 Duration of Response by IRC and Investigator Using RECIST v1.1

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 IRC or 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 estimated using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). Comparisons of DOR between treatment arms will be for descriptive purposes only.

4.4.2.6 Patient-Reported Outcomes

The data from the PRO-evaluable population, which includes all randomized patients who have a baseline and at least 1 post-baseline assessment, will be used to assess change from baseline in global health status/HRQoL (items 29 and 30 of the EORTC QLQ-C30.) Visit summary and change from baseline analyses will be performed for the EORTC QLQ-C30 GHS/HRQoL scale scores. Summary statistics (number of patients, mean, SD, median, minimum, maximum) of score(s) will be presented by treatment arm and longitudinal score change(s) from baseline to each time point while patients are receiving treatment will inform statistical differences between treatment arm (see section 4.4.3.2.4).

4.4.3 Exploratory Efficacy Endpoints

4.4.3.1 ORR, DOR, and PFS by Investigator Using Immune-Modified RECIST

Objective response, DOR, and PFS according to immune-modified RECIST will be analyzed using the methods as described above.

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 QLQ-C30 at each time point. Reasons for non-completion will be summarized if available.

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, SD, 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, time of clinical progression, at treatment discontinuation due to adverse event, and post-study treatment follow-up.

4.4.3.2.3 Proportion of patients

On the PRO-evaluable population, the number and proportion of patients with a clinically meaningful change of 10-points or greater 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 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 Health Status Utility Endpoint

The EQ-5D-5L will be scored according to its manual, and results will be reported separately from the Clinical Study Report.

4.4.5 Sensitivity Analyses

The impact of missed scheduled tumor assessments on IRC-assessed PFS will be assessed depending on the number of patients who missed assessments. If $>5\%$ of patients missed two or more 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 the last tumor assessment prior to the missed visits.

A sensitivity analysis will also be conducted on IRC-assessed PFS to determine the impact of non-protocol anti-cancer therapy. Patients who die or progress after having received non-protocol anti-cancer therapy will be censored at the date of the last evaluable tumor assessment prior to start of non-protocol anti-cancer therapy.

If more than 5% of patients have central results that indicate their tumors are BRAF mutation positive, then a sensitivity analysis will be conducted on IRC-assessed PFS with these patients excluded.

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

4.4.6 Subgroup Analyses

The consistency of the IRC-assessed 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 separately for each level of the subgroup for the comparisons between two treatment arms and displayed in a Forest plot (Lewis and Clarke 2001). Kaplan-Meier plots of OS and PFS will also be produced for selected subgroups.

Summaries of IRC-assessed ORR by subgroup will also be provided.

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)
- PD-L1 status (IC0 vs. IC1, 2, 3)
- Baseline LDH (less than or equal to the ULN, greater than the ULN)

- Region (North America, Europe, Australia, New Zealand, others)
- ECOG performance status at randomization (0, 1)
- Disease Status (Locally advanced unresectable, metastatic)

4.5 SAFETY ANALYSES

Unless specified otherwise, the safety analyses described below will be conducted for the safety population with patients grouped according to study treatment received. Specifically, the treatment arms for safety analyses will be defined as follows:

- Cobimetinib + atezolizumab arm (Arm A): patients who received any amount of cobimetinib or atezolizumab
- Pembrolizumab arm (Arm B): patients who received any amount of pembrolizumab without any amount of either atezolizumab or cobimetinib.

If a patient did not receive any amount of cobimetinib, atezolizumab, or pembrolizumab, the patient will not be included in the safety analyses.

4.5.1 Exposure of Study Medication

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

4.5.2 Adverse Events

Verbatim description of AEs will be summarized by mapped terms and appropriate 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), severe AEs (Grade $\geq$ 3), adverse events of special interest (AESI), and AEs leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. The proportion of patients who experience at least one AE event will be reported by toxicity term and treatment arm.

All deaths and causes of death will be summarized by treatment arm.

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.

4.5.3 Laboratory Data

Laboratory data will be summarized over time including change from baseline by treatment arm. 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 and treatment arm. 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

The PK analyses will include patients who have received at least one dose of study drug and for whom at least one evaluable PK sample is collected (actual dose and actual sampling time recorded for each sample). Because only a few samples will be collected from patients, data will be analyzed using existing population PK models for post-hoc estimates of apparent clearance or systemic clearance for cobimetinib and atezolizumab, respectively. The maximum or minimum concentration (C_{max} or C_{min}) will be reported for individual patients and summarized by study day, as the data permit. [redacted]

Additional PK analyses will be conducted as appropriate based on the available data.

4.7 IMMUNOGENICITY ANALYSES

The immunogenicity analyses for atezolizumab will include patients from Arm A with any ADA assessment. The numbers and proportion of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after baseline (post-baseline incidence) will be summarized by disease status (metastatic or locally advanced and unresectable). When determining the 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 unit 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 unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, pharmacokinetics, and biomarker endpoints may be analyzed and reported using descriptive statistics.

4.8 BIOMARKER ANALYSES

Efficacy will be explored in biomarker subgroups defined by PD-L1 expression, CD8 T-cell density, tumor mutation burden based on next-generation sequencing, and other significant biomarkers at the conclusion of this study.

NGS data will also be analyzed in the context of this study and explored in aggregate with data from other studies to increase researchers' understanding of disease pathobiology and guide the development of new therapeutic approaches.

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.

4.10 INTERIM ANALYSES

No interim analyses are planned for PFS.

The study will incorporate three OS analyses (two interim analyses and one final analysis).

Table 1 summarizes the assumptions and characteristics of the interim and final analyses for OS. The actual number of observed OS events at each interim analysis may differ from the estimates presented. The stopping boundaries are computed using Generalized Haybittle-Peto boundaries with unequal p-values of 0.001, 0.040, and 0.018 at the three OS analyses to control the overall type I error of the OS comparison at a two-sided 0.05 significance level.

Given that the study did not meet the primary endpoint, the second interim and final OS analysis will not be conducted as specified above. Instead, a final OS analysis will be conducted at the time of final database lock.

Table 1 Assumptions and Characteristics for the Interim and Final Analyses of Overall Survival

Assumptions	Findings
HR targeted	0.75
Targeted median (pembrolizumab)	28.0 months
Targeted median (cobimetinib + atezolizumab)	37.5 months
Projected enrollment period	12 months
First interim analysis (performed at the time of the PFS analysis)	
Estimated cutoff date [a]	17 months
Projected number of events (% of final events)	80 (27%)
Projected MDD [b] (p-value)	0.42 (< 0.001)
Second interim analysis	
Estimated cutoff date [a]	28 months
Projected number of events (% of final events)	153 (52%)
Projected MDD [b] (p-value)	0.72 (< 0.040)
Final analysis	
Estimated cutoff date [a]	68 months
Projected number of events (% of final events)	295 (100%)
Projected MDD [b] (p-value)	0.76 (< 0.018)
Power	60%
α level (two-sided)	0.05

HR = hazard ratio; MDD = minimally detectable difference; PFS = progression-free survival;

[a] Estimated data cutoff time from first randomization. Analysis results will be available after data cleaning.

[b] The largest observed HR that is projected to be statistically significant.

5. REFERENCES

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Appendix 1
Protocol Synopsis

TITLE:	**A PHASE III, OPEN-LABEL, MULTICENTER, TWO-ARM, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF COBIMETINIB PLUS ATEZOLIZUMAB VERSUS PEMBROLIZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED *BRAF*^{V600} WILD-TYPE MELANOMA**
PROTOCOL NUMBER:	CO39722
VERSION NUMBER:	5
EUDRACT NUMBER:	2016-004387-18
IND NUMBER:	135,717
TEST PRODUCTS:	Cobimetinib (RO5514041) Atezolizumab (RO5541267)
PHASE:	Phase III
INDICATION:	Metastatic *BRAF*^{V600} wild-type melanoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of cobimetinib plus atezolizumab compared with pembrolizumab in patients with treatment-naive advanced *BRAF*^{V600} wild-type melanoma. Specific objectives and corresponding endpoints for the study are outlined in the following table.

Objectives and Corresponding Endpoints

Objective(s)	Corresponding Endpoint(s)
Primary Efficacy Objective:	
• To evaluate the efficacy of cobimetinib plus atezolizumab compared with pembrolizumab, as measured by the primary endpoint of PFS by independent review	• 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

Objectives and Corresponding Endpoints (cont.)

Objective(s)	Corresponding Endpoint(s)
Secondary Efficacy Objectives:	
• To evaluate the efficacy of cobimetinib plus atezolizumab compared with pembrolizumab, as measured by OS and 2-year landmark OS • To evaluate the efficacy of cobimetinib plus atezolizumab compared with pembrolizumab, as measured by ORR • To evaluate the efficacy of cobimetinib plus atezolizumab compared with pembrolizumab, as measured by investigator-assessed PFS • To evaluate the efficacy of cobimetinib plus atezolizumab compared with pembrolizumab, as measured by DCR • To evaluate the efficacy of cobimetinib plus atezolizumab compared with pembrolizumab, as measured by DOR • To evaluate the efficacy of cobimetinib plus atezolizumab compared with pembrolizumab, as measured by the change from baseline in HRQoL	• OS, defined as the time from randomization to death from any cause • Two-year landmark survival, defined as survival at 2 years • Objective response, defined as a complete response or partial response on two consecutive occasions ≥4 weeks apart, as determined by an IRC according to RECIST v1.1 • Objective response, defined as a complete response or a partial response on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator through use of RECIST v1.1 • PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator through use of RECIST v1.1, or death from any cause, whichever occurs first • DCR, defined as the proportion of patients with a complete response, a partial response, or stable disease at 16 weeks, *as determined by the IRC through use of RECIST v1.1* • *DCR, defined as the proportion of patients with a complete response, a partial response, or stable disease at 16 weeks, as determined by the investigator through use of RECIST v1.1* • Duration of objective response, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by an IRC through use of RECIST v1.1, or death from any cause, whichever occurs first • Duration of objective response, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator through use of RECIST v1.1, or death from any cause, whichever occurs first • The change from baseline in HRQoL scores, as assessed through use of the two-item GHS/QOL subscale of the European Organization for Research and Treatment of Cancer Quality of Life Core 30 questionnaire (EORTC QLQ-C30), at specified timepoints while receiving treatment

Objectives and Corresponding Endpoints (cont.)

Objective(s)	Corresponding Endpoint(s)
Exploratory Efficacy Objectives:	
• To evaluate the efficacy of cobimetinib plus atezolizumab compared with pembrolizumab, as measured by the investigator, according to immune-modified RECIST • To evaluate the efficacy of cobimetinib plus atezolizumab compared with pembrolizumab, as measured by change from baseline in functioning and commonly reported symptoms	• Objective response according to investigator-assessed immune-modified RECIST • DOR according to investigator-assessed immune-modified RECIST • PFS according to investigator-assessed immune-modified RECIST • Change from baseline in HRQoL, functioning and commonly reported symptoms (insomnia, pain, and fatigue), as assessed through use of the EORTC QLQ-C30 GHS, functioning and symptom scales, at specified timepoints, including progression, treatment discontinuation and post-study treatment • The number and proportion of patients who improve, remained stable, and worsen from baseline as measured by the EORTC QLQ-C30 GHS, functioning, and symptom scales, at specified timepoints, including progression, treatment discontinuation and post-study treatment
Safety Objective:	
• To evaluate the safety of cobimetinib plus atezolizumab compared with pembrolizumab	• Occurrence and severity of adverse events, with severity determined through use of NCI CTCAE v4.0 • Change from baseline in selected vital signs • Change from baseline in selected clinical laboratory test results
Pharmacokinetic Objective:	
• To characterize the cobimetinib and atezolizumab pharmacokinetics when administered in combination in this patient population	• Plasma concentration of cobimetinib at specified timepoints • Serum concentration of atezolizumab at specified timepoints
Exploratory Pharmacokinetic Objective:	
[redacted]	[redacted]

Objectives and Corresponding Endpoints (cont.)

Objectives	Corresponding Endpoint(s)
Immunogenicity Objective:	
• To evaluate the immune response to atezolizumab	• Incidence of ADAs during the study relative to the prevalence of ADAs at baseline
Exploratory Immunogenicity Objective:	
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective:	
• To explore biomarkers that are associated with response or resistance to cobimetinib plus atezolizumab	• Relationship of immune contextures, such as PD-L1, CD8-positive T cells, or major histocompatibility complex expression, as identified by immunohistochemistry and gene signature profiling, genetic alterations, such as *RAS* and *NF1*, with efficacy, PK, immunogenicity, or other biomarker endpoints
Exploratory Health Utility Objective:	
• Generate health status utility scores of patients treated with cobimetinib plus atezolizumab and with pembrolizumab for pharmacoeconomic modeling	• Health status utility score based on the EQ-5D-5L

ADA=anti-drug antibody; DCR=disease control rate; DOR=duration of response; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-5L=European Quality of Life 5-Dimension, 5-Level questionnaire; IRC=independent review committee; OS=overall survival; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PD-L1=programmed death–ligand 1; PFS=progression-free survival; PK=pharmacokinetic; QLQ-C30=Cancer Quality of Life–Core 30; QOL=quality of life; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1.

Study Design

Description of Study

Study CO39722 is a Phase III, multicenter, open-label, randomized study designed to evaluate the efficacy, safety, and pharmacokinetics of cobimetinib plus atezolizumab compared with pembrolizumab in treatment-naive patients with advanced $BRAF^{V600}$ wild-type melanoma. The patient population includes patients with locally advanced and unresectable or metastatic melanoma. $BRAF^{V600}$ wild-type status will be determined using local testing and enrollment based on local testing that will be subsequently confirmed with central testing after enrollment. Patients who are enrolled based on $BRAF^{V600}$ wild-type status by local testing may continue in the study even in cases when central testing gives a different result. If local test results are not available for enrollment, $BRAF^{V600}$ wild-type status will be determined by central testing. Programmed death–ligand 1 (PD-L1) status will be determined using central testing, with $<1\%$ immune cells (IC), with IC0 defined as being PD-L1 negative versus IC1, IC2, IC3 defined as being PD-L1 positive.

The primary objective of the study is to evaluate the efficacy of cobimetinib plus atezolizumab compared with pembrolizumab in treatment-naive patients with advanced $BRAF^{V600}$ wild-type melanoma, as measured by primary endpoint of progression-free survival (PFS) assessed by independent review.

This study will be conducted globally and approximately 450 patients will be randomized in a 1:1 ratio to one of two treatment arms:

- Arm A: Patients will receive 60 mg of cobimetinib by mouth (PO) on a 21 days on, 7 days off (21/7) schedule (dosing on Days 1–21, followed by no dosing on Days 22–28) plus 840 mg of atezolizumab by intravenous (IV) infusion on Days 1 and 15 of each 28-day cycle (n = 225).
- Arm B: Patients will receive 200 mg of pembrolizumab administered by IV infusion every 3 weeks (Q3W) (n = 225).

Stratification factors are PD-L1 status (IC0 vs. IC1, 2, 3), baseline serum LDH level (less than or equal to the upper limit of normal [ULN] vs. greater than the ULN), and 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).

The Sponsor will monitor enrollment in each region (North America, Europe, Australia, New Zealand, and others). To ensure balanced global enrollment, the Sponsor may institute temporary limitations on enrollment in certain regions in the event of disproportionate accrual of patients.

Assessments and Monitoring

After signing informed consent, all patients will undergo screening procedures that include testing for *BRAF*^{V600} wild-type melanoma and PD-L1 status; laboratory tests (e.g., hematology, chemistries, liver function tests); left ventricular function evaluation (on echocardiogram [ECHO] or multiple-gated acquisition [MUGA] scan); ECG, contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scans of the brain, chest, abdomen, and pelvis; and ophthalmologic assessments.

All eligible patients will be randomized to treatment in a 1:1 ratio to either Arm A (cobimetinib plus atezolizumab) or Arm B (pembrolizumab).

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at the treatment discontinuation visit, and during the follow-up period. The National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0) will be used to characterize the toxicity profile of study treatments for all patients. Patients will be assessed for adverse events according to the schedule of activities and as necessary throughout the study.

Tumor response will be evaluated according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). Any evaluable and measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Investigators will assess tumor response at 8-week intervals, regardless of any dose delays or treatment cycle.

Study treatment will continue for all patients until investigator-determined disease progression according to RECIST v1.1 that is confirmed by repeat scans 4–8 weeks later, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurs first. Patients who experience disease progression must have scans repeated 4–8 weeks after initial documentation of progression to confirm disease progression. These results will be used as part of the exploratory analyses for assessing efficacy based on immune-modified RECIST. Tumor assessments are to continue according to schedule for patients who discontinue treatment for reasons other than confirmed disease progression. Clinically stable patients who have disease progression may continue, as described below.

Clinically stable patients who have a favorable benefit–risk ratio may continue study treatment following radiographic progression per RECIST v1.1 but approval will need to be provided by the Medical Monitor on a case-by-case basis. Patients who continue treatment beyond radiographic disease progression will be closely monitored. Treatment will be discontinued if clinical deterioration because of disease progression occurs at any time or if persistent disease growth is confirmed on follow-up scans performed 4–8 weeks later.

Patients who discontinue one study drug in Arm A may be able to continue the other study drug, 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. If a patient withdraws from the study, study staff may use a public information source (e.g., county records) to obtain information about survival status only.

This study will not allow crossover to other study drug(s) at the time of progression.

All patients who discontinue from study treatment because of radiographic disease progression or any other reasons will be asked to complete the European Quality of Life 5-Dimension, 5-Level questionnaire (EQ-5D-5L) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30), approximately every 28 days for 6 months after the last dose of study treatment.

Dosing of Study Treatment beyond Disease Progression

Dosing of study treatment beyond RECIST v1.1–defined disease progression is allowed for patients in all treatment arms.

Dosing of study treatment will continue until unacceptable toxicity 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). Because of the possibility of an initial increase in tumor burden caused by IC infiltration in the setting of a T-cell response (termed pseudoprogression) with anti-PD-1 or anti-PD-L1 treatment, radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving study treatment will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as 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
- Approval by the Medical Monitor

Safety Data Review

The Sponsor's study team will review data on adverse events, serious adverse events, the frequency of deaths from all causes, and any other safety data (for both treatment arms combined) in the study on an ongoing basis.

It is the responsibility of the study team to review accumulating safety data, to assess and monitor ongoing safety in patients, to evaluate potential changes to the clinical study protocol, and ultimately, to safeguard patient safety.

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. Specific details, including responsibilities and structure of the iDMC, will be specified in an iDMC charter.

Number of Patients

The planned enrollment specifies a total of approximately 450 patients.

Target Population

Approximately 450 patients with advanced, unresectable, or metastatic *BRAF*^{V600} wild-type melanoma who are naive to treatment will be enrolled in this study.

Inclusion Criteria

Disease-Specific Inclusion Criteria

Patients must meet the following disease-specific inclusion criteria for study entry:

- Histologically confirmed locally advanced and unresectable or metastatic melanoma
- Naive to prior systemic anti-cancer therapy for melanoma (e.g., chemotherapy, hormonal therapy, targeted therapy, immunotherapy, or other biologic therapies), with the following exceptions:
  - Adjuvant treatment with interferon-α (IFN-α), interleukin-2 (IL-2), or vaccine therapies, if discontinued at least 28 days prior to initiation of study treatment
  - Adjuvant treatment with ipilimumab, if discontinued at least 90 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} wild-type 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 [CAP], external quality assurance by European Molecular and Genetics Quality Network [EQMN], and EMQN for clinical diagnosis, CE-marked [European conformity] in vitro diagnostic in EU countries, or equivalent)
- A representative, formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or 20 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study entry. If 20 slides are not available or the tissue block is not of sufficient size, the patient may still be eligible for the study, after discussion with and approval by the Medical Monitor.

  If archival tissue is unavailable or is determined to be inadequate, tumor tissue must be obtained from a biopsy performed at screening.
- Measurable disease according to RECIST v1.1

General Inclusion Criteria

Patients must meet the following general inclusion criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Histologically or cytologically confirmed *BRAF*^{V600} wild-type melanoma
- ECOG Performance Status of 0 or 1
- Life expectancy ≥ 3 months
- Adequate hematologic and end-organ function, defined using the following laboratory results obtained within 14 days prior to first dose of study drug treatment:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL)
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9 g/dL)

    Patients may be transfused to meet this criterion.
  - Creatinine clearance ≥ 40 mL/min
  - Serum albumin ≥ 25 g/L (2.5 g/dL)
  - Serum bilirubin $\leq 1.5 \times$ ULN, with the following exception:

    Patients with known Gilbert disease: serum bilirubin level $\leq 3 \times$ ULN
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN

- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen and stable INR during the 28 days immediately preceding initiation of study treatment
- AST, ALT, and ALP $\leq 2.5 \times$ ULN, with the following exceptions:

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

  Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use at least two forms of effective contraceptive with a failure rate of $< 1\%$ per year during the treatment period and for at least 3 months after the last dose of cobimetinib and at least 5 months after the last dose of atezolizumab or pembrolizumab. *Women must refrain from donating eggs during this same period.*

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

  Examples of 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 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 (e.g. condom), and agreement to refrain from donating sperm, for at least 3 months after the last dose of cobimetinib

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of cobimetinib to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  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.

- Willingness and ability of patients to report selected study outcomes (e.g., global health status [GHS] and health-related quality of life [HRQoL]) using an electronic device or paper backup questionnaire.

Exclusion Criteria

General Exclusion Criteria

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

- Inability to swallow medications
- Malabsorption condition that would alter the absorption of orally administered medications
- Pregnancy, breastfeeding, or intention of becoming pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

- History of severe hypersensitivity reactions to components of the cobimetinib, atezolizumab, or pembrolizumab formulations
- Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation of need for such a vaccine during the study
- Any anti-cancer therapy, including chemotherapy or hormonal therapy, within 2 weeks prior to initiation of study treatment

- Treatment with systemic immunostimulatory agents (including, but not limited to, IFNs, IL-2) within 28 days or 5 half-lives of the drug, whichever is shorter, prior to Day 1 of Cycle 1
- Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis agents) within 2 weeks prior to Day 1 of Cycle 1

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study

Cancer-Related Exclusion Criteria

Patients who meet any of the following cancer-related exclusion criteria will be excluded from study entry:

- Ocular melanoma
- Any anti-cancer therapy for advanced melanoma
- Major surgery or radiotherapy within 21 days prior to Day 1 of Cycle 1 or anticipation of needing such procedure while receiving study treatment
- Uncontrolled tumor-related pain
  - Patients requiring narcotic pain medication must be on a stable regimen at study entry.
  - Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to 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 repeated drainage more than once every 28 days

  Indwelling drainage catheters (e.g., PleurX®) are allowed.
- Active or untreated CNS metastases

  Patients with treated and asymptomatic CNS metastases are eligible, if they meet all of the following:
  - Evaluable or measurable disease outside the CNS
  - No metastases to midbrain, pons, medulla or within 10 mm of the optic nerves and chiasm
  - No history or evidence of intracranial hemorrhage or spinal cord hemorrhage
  - No evidence of clinically significant vasogenic edema
  - No corticosteroids for $\geq$ 2 weeks; anti-convulsant medications at a stable dose are allowed
  - No evidence of clinical and radiographic disease progression in the CNS for $\geq$ 3 weeks after radiotherapy or surgery

Exclusion Criteria based on Organ Function or Medical History

Exclusions Related to Cardiovascular Disease

Patients who meet any of the following exclusion criteria related to cardiovascular disease will be excluded from study entry:

- Unstable angina, new-onset angina within last 3 months, myocardial infarction within the last 6 months prior to Day 1 of Cycle 1, or current congestive heart failure classified as New York Heart Association Class II or higher
- Left ventricular ejection fraction (LVEF) below institutional lower limit of normal or $<50\%$, whichever is lower
- Poorly controlled hypertension, defined as sustained, uncontrolled, non-episodic baseline hypertension consistently above 159/99 mmHg despite optimal medical management
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction

Exclusions Related to Infections

Patients who meet any of the following exclusion criteria related to infections will be excluded from study entry:

- HIV infection
- Active tuberculosis infection
- Severe infections within 4 weeks prior to Day 1 of Cycle 1, 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 Day 1 of Cycle 1
- Treatment with oral or IV antibiotics within 2 weeks prior to Day 1 of Cycle 1

  Patients receiving prophylactic antibiotics (e.g., for prevention of urinary tract infection or COPD) are eligible.
- Active or chronic viral hepatitis B or C infection

  Patients with a past or resolved hepatitis B virus (HBV) infection, defined as having a negative hepatitis B surface antigen (HBsAg) test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study if HBV DNA are negative.

  Patients with hepatitis C virus (HCV) infection are eligible if polymerase chain reaction test for HCV RNA is negative.

Exclusions Related to Ocular Disease

Patients who meet any of the following exclusion criteria related to ocular disease will be excluded from study entry:

- Known risk factors for ocular toxicity, consisting of any of the following:
  - History of serous retinopathy
  - History of retinal vein occlusion (RVO)
  - Evidence of ongoing serous retinopathy or RVO at screening

Autoimmune Conditions and Immunomodulatory Drugs

Patients who meet any of the following exclusion criteria related to autoimmune conditions and immunomodulatory drugs will be excluded from study entry:

- 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 who are on thyroid-replacement hormone are eligible for the study.

Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen 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 covering $<10\%$ of body surface area
- Well-controlled disease at baseline, requiring 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

- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents) within 2 weeks prior to Day 1, Cycle 1

Exclusions Related to Other Medical Conditions or Medications

Patients who meet any of the following exclusion criteria related to other medical conditions or medications will be excluded from study entry:

- Active malignancy (other than melanoma) or a prior malignancy within the past 3 years

  Patients with completely resected basal cell carcinoma, cutaneous squamous cell carcinoma, cervical carcinoma in situ, breast carcinoma in situ, and patients with isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer are eligible for the study.
- Any Grade ≥ 3 hemorrhage or bleeding event within 28 days of Day 1 of Cycle 1
- History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to Day 1
- Proteinuria >3.5 g/24 hr
- Consumption of foods, supplements, or drugs that are strong or moderate CYP3A4 enzyme inducers or inhibitors at least 7 days prior to Day 1 of Cycle 1 and during study treatment

  These include St. John's wort or hyperforin (strong CYP3A4 enzyme inducer) and grapefruit juice (strong cytochrome P450 CYP3A4 enzyme inhibitor)

End of Study

The study will end when all patients enrolled have been followed until death, withdrawal of consent, loss 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 withdrawal of consent. After treatment discontinuation, information on disease progression, survival, and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinical visits approximately every 3 months. Patients who start a subsequent anti-cancer treatment after study treatment discontinuation will be followed for survival and safety per protocol.

Length of Study

The total length of the study, from screening of the first patient to last patient, last visit (LPLV) is expected to be approximately 7 years.

Investigational Medicinal Products

The investigational medicinal products (IMP) for this study are cobimetinib and atezolizumab. Pembrolizumab is an approved treatment for melanoma and can be considered standard of care in some countries. Pembrolizumab is a non-investigational medicinal product in this study, unless local regulations require it to be an IMP.

Test Products

Cobimetinib

Patients randomized to Arm A will receive cobimetinib 60 mg (three tablets of 20 mg each) PO QD on Days 1–21 of each 28-day cycle. This 4-week period is considered a treatment cycle.

Cobimetinib should be taken at the same time every day. It can be taken with or without food. If a daily dose of cobimetinib is missed or if vomiting occurs when the dose is taken, resume dosing with the next scheduled dose.

Atezolizumab

Patients randomized to Arm A will receive atezolizumab 840 mg Q2W (twice in one cycle). A 4-week period is considered a treatment cycle.

Pembrolizumab

Patients randomized to Arm B will receive 200 mg of pembrolizumab by IV infusion Q3W as monotherapy. A 3-week period is considered a treatment cycle.

Statistical Methods

Unless otherwise noted, all efficacy analyses will include all randomized patients (i.e., the intent-to-treat population), and patients will be grouped according to the treatment assigned at randomization.

Primary Analysis

Unless otherwise noted, all efficacy analyses will include all randomized patients (i.e., the intent-to-treat population), and patients will be grouped according to the treatment assigned at randomization.

The primary efficacy analysis will be the comparison of PFS, as determined by the IRC, between the two treatment arms using the stratified log-rank test at an overall 0.01 significance level (two-sided).

PFS is 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. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. Data for patients with no post-baseline tumor assessment will be censored at randomization.

The HR for PFS will be estimated using a stratified Cox model, and two-sided 95% confidence intervals (CIs) for the hazard ratio (HR) will be provided. The stratification factors used for analysis will be the same as the randomization stratification factors: PD-L1 status (IC0 vs. IC1, 2, 3), baseline LDH (less than or equal to the ULN vs. greater than the ULN), and geographic region (North America vs. Europe vs. Australia, New Zealand, and others). Results from an unstratified analysis will also be provided. 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. Sensitivity analyses will be conducted to determine the impact of missed scheduled tumor assessments on PFS, depending on the number of patients with missed assessments.

Determination of Sample Size

Approximately 450 patients will be randomized into the study.

The overall type I error (α) for this study is 0.05 (two-sided).

The type I error (α) for the analysis of the primary endpoint of IRC-assessed PFS is 0.01 (two-sided). The analysis of the primary endpoint of IRC-assessed PFS will take place when

approximately 240 PFS events have occurred. Statistical considerations are based on the following assumptions:

- Stratified log-rank test at 0.01 significance level (two-sided)
- Median PFS of 5.5 months for the pembrolizumab arm
- Median PFS of 10.0 months for the cobimetinib plus atezolizumab arm
- Enrollment period of approximately 12 months
- Annual dropout rate of 5%
- No interim analysis for PFS

A total of 240 PFS events provides approximately 98% power to detect an improvement in median PFS from 5.5 months in the pembrolizumab arm to 10.0 months in the cobimetinib plus atezolizumab arm. This corresponds to a HR of 0.55, with a minimal detectable difference of 0.72. The PFS analysis will be conducted approximately 17 months after FPI.

The final analysis of the secondary endpoint of OS will be performed after the occurrence of approximately 295 deaths. A total of 295 deaths provides approximately 60% power to detect an improvement in median OS from 28 months in the pembrolizumab arm to 37.5 months in the cobimetinib plus atezolizumab arm, corresponding to an HR of 0.75, or 80% power to detect an HR of 0.70. Two interim analyses of OS will be conducted. The final OS analysis will be conducted approximately 68 months after FPI.

Interim Analyses

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

Interim Efficacy Analyses of the Secondary Efficacy Endpoint

The study will incorporate three OS analyses (two interim analyses and one final analysis). The first overall survival (OS) interim analysis will be performed at the time of the primary PFS analysis when a projected number of 80 deaths are expected to have occurred. The second OS interim analysis will be performed after the occurrence of approximately 153 deaths and is projected to occur at approximately 28 months after the first patient is randomized. The final OS analysis will be performed after the occurrence of approximately 295 deaths and is projected to occur approximately 68 months after the first patient is randomized. Generalized Haybittle-Peto boundaries with unequal p-values will be used to control the overall type I error of the OS comparison at a two-sided 0.05 significance level.

Appendix 2
Schedule of Assessments

Table 1 Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (28-Day Cycles)

Assessment/Procedure (Visit Window in Days)	Screen [a]	Cycle 1		Cycle 2		Cycles ≥ 3		Tx Discon [b]	Unscheduled Visit [e]	Survival FU [c]
	Days –35 to –1	Day 1 (+3) [d]	Day 15 (±3)	Day 1 (±3)	Day 15 (±3)	Day 1 (±3)	Day 15 (±3)	< 30 Days after Last Dose (+7)		Every 3 Months
Informed consent [f]	x									
Demographic data	x									
Medical and cancer history	x	x								
Vital signs [g, h]	x	x	x	x	x	x	x	x	x	
ECOG Performance Status	x	x		x		x		x		
Weight	x	x		x		x		x		
Height	x									
Complete physical examination	x							x		
Limited physical examination		x [i]		x		x				
Hematology [j]	x	x		x		x		x		
Coagulation (INR and aPTT)	x									
PK sample for cobimetinib		See Appendix 3								
PK sample and ADA sample for atezolizumab		See Appendix 3								
Chemistry panel [k]	x	x		x		x		x		

Appendix 2
Schedule of Activities (cont.)

Table 1 Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (28-Day Cycles)

Assessment/Procedure (Visit Window in Days)	Screen [a]	Cycle 1		Cycle 2		Cycles ≥ 3		Tx Discon [b]	Unscheduled Visit [e]	Survival FU [c]
	Days –35 to –1	Day 1 (+3) [d]	Day 15 (±3)	Day 1 (±3)	Day 15 (±3)	Day 1 (±3)	Day 15 (±3)	< 30 Days after Last Dose (+7)		Every 3 Months
ECHO or MUGA scan [l]	x			x [l]		x [l]		x [l]		
12-Lead ECG	x	As clinically indicated								
Optional WGS sample		x								
Tumor assessments	x	Scans will be performed every 8 or 12 weeks [m, n]								
Serology [o]	x									
Thyroid function [p]	x	x		x		x [p]		x		
Ophthalmologic exam [q]	x			x		x [q]		x		
Pregnancy test [r]	x	x [r]		x [r]		x [r]		x [r]		
Urinalysis [s]	x									
Concomitant medications [t]	x [t]	x [t]		x		x		x [t]	x	
Adverse events [u]	x [u]	x [u]	x	x	x	x	x	x [u]	x	x [u]
Tumor biopsy [v]	x		x					x		
EORTC QLQ-C30 and EQ-5D-5L [w]		x		see Footnote [w]				x [w]	x	
Biomarker blood samples		See Appendix 3						x		
Atezolizumab administration [x]		x	x	x	x	x	x			
Cobimetinib accountability [y]		x		x		x		x		
Dispense cobimetinib [z]		x		x		x				
Survival and anti-cancer therapy FU										x [aa]

Appendix 2
Schedule of Activities (cont.)

Table 1 Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (28-Day Cycles)

ADA = anti-drug antibody; Discon = discontinuation; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire; EQ-5D-5L = European Quality of Life 5-Dimension, 5-Level questionnaire; FU = follow-up; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IRR = infusion-related reaction; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition; PK = pharmacokinetic; PO = by mouth; PRO = patient-reported outcome; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; Tx = treatment; WGS = whole genome sequencing.

Notes: All assessments should be performed within ±3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. On treatment days, pre-infusion laboratory samples should be drawn 0–4 hours before the start of infusion, and post-infusion laboratory samples should be drawn 0–30 minutes after the end of infusion, unless otherwise specified. Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

[a] Perform screening tests within 35 days prior to treatment initiation (Day 1) unless the patient meets criteria specified in Section 4.5.1. Standard-of-care screening assessments may be performed concurrently with *BRAF*^{V600} mutation and PD-L1 testing. *BRAF*^{V600} status must be known prior to performing study-specific screening assessments. The 35-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 prior to obtaining informed consent and within 35 days prior to treatment initiation (Day 1) may be used; such tests do not need to be repeated for screening. *For a list of laboratory tests for which results must be obtained within 14 days prior to the first dose of study drug, see Section 4.1.1.2.* Test results should be reviewed prior to administration of study drug. PD-L1 will be assessed by central laboratory and the result will be used for stratification and randomization only.

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit within 30 (+7) days. The visit at which response assessment shows progressive disease may be used as the study discontinuation visit.

[c] Required follow-up information will be collected via telephone calls and/or clinic visits every 3 months until death, loss to follow-up, or study termination by the Sponsor.

[d] Day 1 of Cycle 1 can occur up to 3 days after randomization.

[e] Visit not specified by the protocol. Assessments (possibly including PK sample collection) should be performed as clinically indicated.

[f] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained up to 35 days before initiation of study treatment.

[g] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Resting oxygen saturation will be measured during screening and subsequent visits. 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.

[h] At the first atezolizumab infusion, vital signs will be recorded within 60 minutes prior to the infusion, every 15 (±5) minutes during the atezolizumab infusion, and 30 (±10) minutes after the infusion if clinically indicated. For subsequent infusions, vital signs will be collected within 60 minutes prior to the infusion and*, if the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs* should be collected during the infusion and 30 (±10) minutes after the infusion.

Appendix 2
Schedule of Activities (cont.)

Table 1 Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (28-Day Cycles)

[i] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. If physical examinations are assessed within 7 days of the Day 1, Cycle 1 visit, they do not have to be repeated on Day 1.

[j] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, reticulocyte count, platelet count, and differential count (neutrophils, bands, eosinophils, basophils, monocytes, and lymphocytes)

[k] Chemistry panel (serum) includes sodium, potassium, chloride, bicarbonate or total CO_2 (HCO_3 and CO_2 not mandatory if unavailable at site), glucose, BUN or urea, creatinine, albumin, magnesium, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, CPK, uric acid, LDH, and total protein. Fasting triglycerides, fasting cholesterol, fasting LDL cholesterol, and fasting glucose will be assessed after a minimum 8-hour fast for screening only. Non-fasting laboratory values will be accepted for subsequent visits after screening. If fasting laboratory values are clinically warranted in a subject, then it will be at the discretion of the investigator. LDH will be assessed by both local and central laboratory, and the central laboratory result will be used for stratification and randomization only.

[l] All patients will undergo evaluation of left ventricular dysfunction, either by ECHO or MUGA, at screening. Evaluation of LVEF by ECHO or MUGA scan must be performed at the following timepoints only for patients randomized to receive cobimetinib:

- Day 1 of Cycle 2 (±1 week).
- Day 1 of Cycles 5, 8, 11, 14, 17, etc. (every three treatment cycles; ±2 weeks).
- Treatment discontinuation visit evaluation of LVEF does not need to be performed at treatment discontinuation visit if an evaluation has been performed within the last 12 weeks and there are no clinically significant findings and/or changes from baseline.

[m] Tumor assessments will be performed every 8 weeks (±1 week) from the date of first study drug administration (Day 1) through 18 months (80 weeks) and then every 12 weeks (±1 week) thereafter. Refer to Section 4.5.5.

[n] Tumor assessments will continue until disease progression per RECIST v1.1, loss of clinical benefit (for patients who continue treatment after disease progression according to RECIST v1.1) (see Section 3.1.2), withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first. Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. A confirmatory scan will be needed 4–8 weeks after progression of disease to confirm progression and exclude pseudoprogression. Refer to Section 4.5.5 for details.

[o] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the study. HBV serology will include HBsAg, antibodies against HBsAg, total anti-HBcAb. HBV DNA should be obtained prior to randomization if patient has a negative serology for HBsAg and a positive serology for anti-HBcAb. HCV serology will include HCV antibody (anti-HCV). HCV RNA should be obtained prior to randomization if patient tests positive for anti-HCV.

[p] Thyroid-function testing (thyroid-stimulating hormone, free T3 [or total T3 for sites where free T3 is not performed], and free T4) collected on Day 1 of Cycles 1–5, and every second cycle thereafter (e.g., Day 1 of Cycles 7, 9, 11, etc.

Appendix 2
Schedule of Activities (cont.)

Table 1 Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (28-Day Cycles)

[q] All patients will undergo ophthalmologic examination (see Section 4.5.10 for exam requirements) at screening. Ophthalmologic examination must be performed at the following timepoints only for patients randomized to receive cobimetinib:

- Day 1 of Cycle 2 (±1 week).
- Day 1 of Cycles 5, 8, and 11 (every three treatment cycles; ±2 weeks).
- Day 1 of Cycles 15, 19, and 23 (every four treatment cycles; ±2 weeks).
- Day 1 of Cycles 29, 35, 41, 47, etc. (every six treatment cycles; ±2 weeks).
- Treatment discontinuation visit.

[r] All women of childbearing potential will have a serum pregnancy test at screening within 7 days prior to Day 1 of Cycle 1. Urine pregnancy tests will be performed on Day 1 of every cycle, at the treatment discontinuation visit, and 3 months after cobimetinib discontinuation and 5 months after atezolizumab discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[s] Includes dipstick (pH, specific gravity, glucose, protein, ketones, and blood), and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria).

[t] Includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study drug until 30 days after the last dose of study drug.

[u] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 135 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported (per Section 5.3.5.8). After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug 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 or adverse events of special interest considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[v] Archival tumor tissue with sample collection date <5 years or fresh baseline tumor tissue will be collected during screening. An optional on-treatment biopsy will be obtained at Cycle 1, Day 15 (±5 days), and a mandatory biopsy will be obtained at progression if clinically feasible.

[w] PRO instruments, the EORTC QLQ-C30 and EQ-5D-5L, will be completed in this order using an electronic device on Day 1 of Cycle 1 and every 4 weeks (±3 days) thereafter, prior to tumor assessments visits every 8 weeks, at the treatment discontinuation visit, and at unscheduled visits, as clinically indicated. Patients will also complete the questionnaires every 4 weeks for 6 months after treatment discontinuation. All PRO questionnaires are required to be completed prior to the administration of study treatment and/or prior to any other study assessment(s) that could bias a patient's responses.

[x] The initial dose will be delivered over 60 (±15) minutes. If the first infusion is well tolerated all subsequent infusions will be delivered over 30 (±10) minutes until loss of clinical benefit. Study drug administration may be ±3 days after the first cycle.

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

Appendix 2
Schedule of Activities (cont.)

Table 1 Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (28-Day Cycles)

[z] Cobimetinib 60 mg/day PO will be given on a 21 days on/7 days off dosing schedule. Study drug administration may be ± 3 days after the first cycle, commensurate with atezolizumab administration.

[aa] 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 (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 study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 2
Schedule of Activities (cont.)

Table 2 Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (28-Day Cycles)

Assessment/Procedure (Day Window)	Screening [a]	Cycle 1		Cycle 2	Cycle ≥ 3	Tx Discon [b]	Unscheduled Visit [e]	Survival FU [c]
	Days –35 to –1	Day 1 (+3) [d]	Day 15 (±3)	Day 1 (±3)	Day 1 (±3)	< 30 Days after Last Dose (+7)		Every 3 Months
Informed consent [f]	x							
Demographic data	x							
Medical and cancer history	x	x						
Vital signs [g, h]	x	x		x	x	x	x	
ECOG Performance Status	x	x		x	x	x		
Weight	x	x		x	x	x		
Height	x							
Complete physical examination	x					x		
Limited physical examination		x [i]		x	x			
Hematology [j]	x	x		x	x	x		
Coagulation (INR and aPTT)	x							
Chemistry panel [k]	x	x		x	x	x		
ECHO or MUGA scan	x							
12-Lead ECG	x	As clinically indicated					x	
Optional WGS sample		x						
Tumor assessments [l]	x	Scans will be performed every 8 or 12 weeks. [m]						

Appendix 2
Schedule of Activities (cont.)

Table 2 Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (28-Day Cycles)

Assessment/Procedure (Day Window)	Screening [a]	Cycle 1		Cycle 2	Cycle ≥ 3	Tx Discon [b]	Unscheduled Visit [e]	Survival FU [c]
	Days –35 to –1	Day 1 (+3) [d]	Day 15 (±3)	Day 1 (±3)	Day 1 (±3)	< 30 Days after Last Dose (+7)		Every 3 Months
Serology [n]	x							
Thyroid function [o]	x	x		x	x [o]	x		
Ophthalmologic exam [p]	x							
Pregnancy test [q]	x	x [q]		x [q]	x [q]	x		
Urinalysis [r]	x							
Concomitant medications [s]	x [s]	x [s]		x	x	x [s]	x	
Adverse events [t]	x [t]	x [t]		x	x	x [t]	x	x [t]
Tumor biopsy [u]	x		x			x		
EORTC QLQ-C30 EQ-5D-5L [v]		x		See Footnote [v]		x [v]	x	
Biomarker blood samples		See Appendix 3						
Pembrolizumab administration [w]		x		x	x			
Survival and anti-cancer therapy FU								x [x]

Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire; EQ-5D-5L = European Quality of Life 5-Dimension, 5-Level questionnaire; FU = follow-up; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IRR = infusion-related reaction; LVEF = left ventricular ejection fraction; PK = pharmacokinetic; PRO = patient-reported outcome; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; Tx = treatment; WGS = whole genome sequencing.

Notes: All assessments should be performed within ±3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. On treatment days, pre-infusion laboratory samples should be drawn 0–4 hours before the start of infusion, and post-infusion laboratory samples should be drawn 0–30 minutes after the end of infusion, unless otherwise specified. Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

[a] Perform screening tests within 35 days prior to treatment initiation (Day 1) unless a patient meets criteria specified in Section 4.5.1. Standard-of-care screening assessments may be performed concurrently with *BRAF*^{V600} mutation and PD-L1 testing. *BRAF*^{V600} status

Table 2 Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (28-Day Cycles)

must be known prior to performing study-specific screening assessments. The 35-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 prior to obtaining informed consent and within 35 days prior to treatment initiation (Day 1) may be used; such tests do not need to be repeated for screening. *For a list of laboratory tests for which results must be obtained within 14 days prior to the first dose of study drug, see Section 4.1.1.2.* Test results should be reviewed prior to administration of study drug. PD-L1 will be assessed by central laboratory and the result will be used for stratification and randomization only.

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit within 30 (+7) days. The visit at which response assessment shows progressive disease may be used as the study discontinuation visit.

[c] Required follow-up information will be collected via telephone calls and/or clinic visits every 3 months until death, loss to follow-up, or study termination by the Sponsor.

[d] Day 1 of Cycle 1 can occur 3 days after randomization.

[e] Visit not specified by the protocol. Assessments (possibly including PK sample collection) should be performed as clinically indicated.

[f] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained up to 35 days before initiation of study treatment.

[g] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Resting oxygen saturation will be measured during screening and subsequent visits. 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.

[h] Vital signs at the first pembrolizumab infusion will be recorded within 60 minutes prior to the infusion, every 15 (±5) minutes during the pembrolizumab infusion and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes prior to the infusion and*, if the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs* should be collected during the infusion, and 30 (±10) minutes after the infusion.

[i] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. At the baseline visit only, any abnormality should be recorded on the General Medical History and Baseline Conditions eCRF. If physical examinations are assessed within 7 days of the Cycle 1, Day 1 visit, they do not have to be repeated on Day 1.

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

Table 2 Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (28-Day Cycles)

[k] Chemistry panel (serum) includes sodium, potassium, chloride, bicarbonate or total CO_2 (HCO_3 and CO_2 not mandatory if unavailable at site), glucose, BUN or urea, creatinine, albumin, magnesium, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, CPK, uric acid, LDH, and total protein. Fasting triglycerides, fasting cholesterol, fasting LDL cholesterol, and fasting glucose will be obtained after a minimum 8-hour fast for screening only. Non-fasting laboratory values will be accepted for subsequent visits after screening. If fasting laboratory values are clinically warranted in a subject, then it will be at the discretion of the investigator. LDH will be assessed by both local and central laboratory, and the central laboratory result will be used for stratification and randomization only.

[l] Tumor assessments will be performed every 8 weeks (±1 week) from the date of first study drug administration (Day 1) through 18 months (80 weeks) and then every 12 weeks (±1 week) thereafter. Refer to Section 4.5.5.

[m] Tumor assessments will continue until disease progression per RECIST v1.1, loss of clinical benefit for patients who continue treatment after disease progression according to RECIST v1.1 (see Section 3.1.2), consent withdrawal, study termination by the Sponsor, or death, whichever occurs first. Patients who discontinue treatment for reasons other than disease progression (e.g. toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. A confirmatory scan will be needed 4–8 weeks after progression of disease to confirm progression and exclude pseudoprogression. Refer to Section 4.5.5 for details.

[n] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical study. HBV serology will include HBsAg, antibodies against HBsAg, total anti-HBcAb. HBV DNA should be obtained prior to randomization if patient has a negative serology for HBsAg and a positive serology for anti-HBcAb. HCV serology will include HCV antibody (anti-HCV). HCV RNA should be obtained prior to randomization if patient tests positive for anti-HCV.

[o] Thyroid-function testing (thyroid-stimulating hormone, free T3 [or total T3 for sites where free T3 is not performed], and free T4) collected on Day 1 of Cycles 1–5, and every second cycle thereafter (e.g., Day 1 of Cycles 7, 9, 11, etc.

[p] All patients will undergo ophthalmologic examination (see Section 4.5.10 for exam requirements) at screening.

[q] All women of childbearing potential will have a serum pregnancy test at screening within 14 days prior to Day 1 of Cycle 1. Urine pregnancy tests will be performed on Day 1 of every cycle, at the treatment discontinuation visit, and 5 months after pembrolizumab discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[r] Includes dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria).

[s] Includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study drug until 30 days after the last dose of study drug.

[t] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 135 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported (see Section 5.3.5.8). After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug 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

Table 2 Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (28-Day Cycles)

patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events or adverse events of special interest considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[u] Archival tumor tissue with sample collection date <5 years or fresh baseline tumor tissue will be collected during screening. An optional on-treatment biopsy will be obtained at Cycle 1, Day 15 (± 5 days), and a mandatory biopsy will be obtained at progression if clinically feasible.

[v] PRO instruments, the EORTC QLQ-C30 and EQ-5D-5L, will be completed in this order using an electronic device on Day 1 of Cycle 1 and every 4 weeks ($\pm$ 3 days) thereafter, prior to tumor assessments visits every 8 weeks, at the end-of-treatment visit, and at unscheduled visits, as clinically indicated. Patients will also complete the questionnaires every 4 weeks for 6 months after treatment discontinuation. All PRO questionnaires are required to be completed prior to the administration of study treatment and/or prior to any other study assessment(s) that could bias patient's responses.

[w] Pembrolizumab will be delivered over 30 (± 10) minutes. Study drug administration may occur ± 3 days after the first cycle.

[x] 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 (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 study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 3
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Visit	Timepoint	Sample Type(s)
Cycle 1, Day 1	Prior to the first infusion	Atezolizumab PK and ADA (serum)
	30 (±10) minutes following the end of atezolizumab infusion	Atezolizumab PK (serum)
	2–4 hours post-cobimetinib dose	Cobimetinib PK (plasma)
Cycle 1, Day 15	Prior to cobimetinib dose 2–4 hours post-cobimetinib dose	Cobimetinib PK (plasma) Cobimetinib PK (plasma)
Cycles 2 and 3, Day 1	Prior to the first infusion	Atezolizumab PK and ADA (serum)
Day 1 of Cycles 1 and 2, and at time of subsequent radiologic tumor assessments [a]	Prior to the first infusion	Biomarkers (plasma)
Treatment discontinuation visit [b]	At visit	Atezolizumab PK and ADA (serum)
		Biomarkers (plasma) [c]

ADA = anti-drug antibody; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

[a] *Biomarker assessments on Day 1 of Cycles 1 and 2 must be done on the day of study drug administration, prior to infusion.* A ± 7-day window for biomarker sampling will be allowed at the time of subsequent radiologic tumor assessments.

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit 30 (±7) days after the last dose of study drug. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[c] At confirmed disease progression, lack of clinical benefit, or at treatment discontinuation.

Note: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ±7 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (Eisenhauer et al. 2009), are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent [redacted]

Protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval ≤ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

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

DEFINITION OF NON-MEASURABLE LESIONS

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

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

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

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

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

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

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

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

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

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

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

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

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

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is < 5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the eCRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

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

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

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

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCE

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