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

NCT Number: NCT03273153

Document Date: Protocol Version 6: 05 February 2021

PROTOCOL

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:	6
EUDRACT NUMBER:	2016-004387-18
IND NUMBER:	135,717
NCT NUMBER:	NCT03273153
TEST PRODUCTS:	Cobimetinib (RO5514041) Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 8 May 2017
DATES AMENDED:	Version 2 (VHP): 8 August 2017 Version 3: 8 August 2017 Version 4: 12 March 2018 Version 5: 19 September 2018 Version 6: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
05-Feb-2021 16:47:30	Company Signatory	[redacted]

PROTOCOL AMENDMENT, CO39722 VERSION 6: RATIONALE

Protocol CO39722 has been amended primarily to update atezolizumab safety information. Changes to the protocol, along with a rationale for each change, are summarized below:

- The list of approved indications for atezolizumab has been updated to include small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma (Section 1.2.2).
- Lists of identified risks for atezolizumab have been revised to include myositis and severe cutaneous adverse reactions for consistency with the list of identified risks in the Atezolizumab Investigator's Brochure (Section 5.1.2).
- Language has been added to clarify that hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) are considered potential risks for atezolizumab (Sections 5.1.2 and Appendix 11).
- To address a request by the French National Agency for the Safety of Medicines and Health Products (ANSM), systemic immune activation has been replaced by HLH and MAS in the list of potential risks for atezolizumab (Section 5.1.2) and the management guidelines for systemic immune activation have been replaced with management guidelines for hemophagocytic lymphohistiocytosis and macrophage activation syndrome (Appendix 11). In addition, systemic immune activation has been removed from the list of adverse events of special interest (Section 5.2.3).
- To align with the Atezolizumab Investigator's Brochure, "immune-related" has been changed to "immune-mediated" when describing events associated with atezolizumab (Sections 5.1.2 and 5.1.5.3; Appendices 10 and 11).
- To address a request by the French ANSM, HLH and MAS have replaced systemic inflammatory response syndrome on the list of atezolizumab-associated adverse events of special interest (Section 5.2.3).
- To address a request by the French ANSM, the management guidelines for infusion-related reactions associated with atezolizumab have been updated to include guidelines for CRS to align with the definition, grading, and management of CRS reflected in a recent publication (Lee et al. 2019) (Section 5.3.5.1; Appendices 10 and 11).
- Appendix 6 has been revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent.
- Anaphylaxis Precautions (Appendix 7) has been modified to remove the requirement for use of a tourniquet. The application of a tourniquet is no longer recommended due to the limited therapeutic benefit and risk of losing time for more important measures (Ring J, Beyer K, Biedermann T, et al. Allergo J Int. 2014;23:96–112).

- Guidelines for management of atezolizumab-associated dermatologic adverse events have been revised to provide guidance on severe cutaneous adverse reactions of Stevens-Johnson syndrome and toxic epidermal necrolysis (Appendices 10 and 11).
- Guidelines for managing patients who experience atezolizumab-associated adverse events have been revised to include myositis (Appendix 11).
- To address a request by the French ANSM, the atezolizumab adverse event management guidelines have been revised to add laboratory (e.g., B-type natriuretic peptide) and cardiac imaging abnormalities as signs or symptoms that are suggestive of myocarditis (Appendix 11).
- To address a request by the French ANSM, the management guidelines for HLH and MAS have been modified to indicate that HLH should be considered when cytokine-release syndrome (CRS) presentation is atypical or prolonged, to add anti-cytokine therapy as an option for treating HLH or MAS, and to suggest that published guidelines should be followed for HLH or MAS events that do not respond to treatment within 24 hours (Appendix 11).

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

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:	6
EUDRACT NUMBER:	2016-004387-18
IND NUMBER:	135,717
NCT NUMBER:	NCT03273153
TEST PRODUCTS:	Cobimetinib (RO5514041) Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return the signed original of this form to the Sponsor or its designee. Please retain a copy of the signed copy for your study files.

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:	6
EUDRACT NUMBER:	2016-004387-18
IND NUMBER:	135,717
NCT NUMBER:	NCT03273153
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:	
• To investigate the relationship between cobimetinib exposure and efficacy and safety outcomes using population approaches	• Relationship between cobimetinib plasma concentration and efficacy or safety endpoints

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 anti-tumor 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.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody; also known as anti-therapeutic antibody (ATA)
APC	antigen-presenting cell
CI	confidence interval
CPK	creatine phosphokinase
CRC	colorectal cancer
CRS	*cytokine-release syndrome*
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating-tumor DNA
CTLA-4	cytotoxic T lymphocyte–associated protein-4
DCR	disease control rate
DOR	duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D-5L	European Quality of Life 5-Dimension, 5-Level questionnaire
EDC	electronic data capture
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EU	European Union
FDA	(U.S.) Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FPI	first patient in
GHS	global health status
HBcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HLH	*hemophagocytic lymphohistiocytosis*
HR	hazard ratio
HRQoL	health-related quality of life

Abbreviation	Term
IC	immune cell
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IFN-α	interferon-α
IL-2	interleukin-2
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRC	independent review committee
IRR	infusion-related reaction
ITT	intent to treat
IWRS	interactive Web-based response system
LVEF	left ventricular ejection fraction
LLN	lower limit of normal
LPLV	last patient, last visit
LS	least square (means)
MAPK	mitogen-activated protein kinase
MAS	*macrophage activation syndrome*
MDSC	myeloid-derived suppressor cell
MEK	mitogen-activated protein/extracellular signal-regulated kinase
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NCI CTCAE v4.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
NCCN	National Comprehensive Cancer Network
NGS	next-generation sequencing
ORR	overall response rate
OS	overall survival
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PO	by mouth (orally)
PRO	patient-reported outcome

Abbreviation	Term
QD	once a day
Q3W	every 3 weeks
Q2W	every 2 weeks
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RVO	retinal vein occlusion
TCR	T-cell receptor
TNF-α	tumor necrosis factor–α
T3	triiodothyronine
T4	Thyroxine
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON MELANOMA

Melanoma is a potentially deadly form of skin cancer originating from melanocytes. The clinical outcome of patients with melanoma is highly dependent on the stage at presentation. The outcome for promptly diagnosed superficial tumors is good. In the metastatic setting, high rates of mortality and disease-related morbidity have improved significantly with recent therapeutic advances. The 5-year overall survival (OS) rates were at 15.7% based on Surveillance, Epidemiology, and End Results data from 2012 (Siegel et al. 2016). In the KEYNOTE-006 study (pembrolizumab vs. ipilimumab) in advanced melanoma, the 1-year OS rates ranged from 58% to 74% (Robert et al. 2015b).

In 2012, there were approximately 232,000 new cases and 55,000 deaths from melanoma worldwide, with more than 100,000 new cases and 22,000 deaths in Europe (Ferlay et al. 2013). In the United States in 2016, an estimated 76,380 new diagnoses of melanoma were projected and approximately 10,130 patients are expected to die of the disease (American Cancer Society 2016). The incidence of melanoma is particularly high among Caucasian populations in Australia (42.4 per 100,000) and Western Europe (10.6 per 100,000) (American Cancer Society 2016). Moreover, the number of melanoma cases worldwide is increasing faster than any other cancer. The annual increase in incidence rate varies between populations, but in general, the rate has been in the order of 3%–7% per year for fair-skinned Caucasian populations (Diepgen and Mahler 2002). Estimates suggest a doubling of the incidence of melanoma every 10–20 years (Garbe and Leiter 2009).

Until recently, treatment options for metastatic melanoma were limited. Dacarbazine was considered to be the standard first-line treatment; however, outcomes were poor, with response rates of 5%–12%, median progression-free survival (PFS) of less than 2 months, and median OS of 6.4 to 9.1 months (Middleton et al. 2000; Bedikian et al. 2006; Chapman et al. 2011; Robert et al. 2011). Combination chemotherapy and chemotherapy combined with interferon-α (IFN-α) or interleukin-2 (IL-2), although showing improved response rates, have not resulted in improved OS (Chapman et al. 1999; Ives et al. 2007).

The mitogen-activated protein kinase (MAPK) signaling cascade is a key intracellular signaling network that transduces multiple proliferative and differentiating signals from the extracellular environment to the nucleus of cells to activate cellular growth and differentiation (Johnson and Lapadat 2002; Roberts and Der 2007). This pathway is highly implicated in pathogenesis of melanoma. Approximately 40%–50% of all melanomas harbor an activating mutation in *BRAF*, a major driver of RAS, RAF, MEK, ERK, and MAPK signaling (Davies et al. 2002; Curtin et al. 2005; Jakob et al. 2012), and an additional 15%–30% harbor an activating mutation of neuroblastoma *RAS* (*NRAS*) (Lee et al. 2011; Cancer Genome Atlas Network 2015). Approximately 14% harbor

mutations of NF1, an inhibitory protein of the MAPK pathway (Cancer Genome Atlas Network 2015). Thus, the MAPK pathway is an important driver of pathogenesis in *BRAF*^{V600} wild-type melanoma, as well as in *BRAF*^{V600}-mutated melanoma. In recent years, targeting of the MAPK pathway has emerged as an effective treatment strategy in *BRAF*^{V600}-mutated melanoma and several targeted therapies are now approved globally for treatment of this indication specifically (Richman et al. 2015).

Treatment options for *BRAF*^{V600} wild-type melanoma have also improved dramatically with approvals of several immunotherapeutic agents. Melanoma cells are highly immunogenic and thus an appropriate target for these agents (Zhu et al. 2016). Several immunotherapeutic agents, which interrupt T-cell suppression and render melanoma cells susceptible to immune attack, are currently available or are in development for the treatment of melanoma (Zhu et al. 2016). The two-signal model of activation to overcome T-cell suppression, involves interaction of the T-cell receptor (TCR) with its antigen (signal one), followed by signal two, which is a co-stimulatory interaction between CD28 on the T-cell surface and its ligand B7-1 on antigen-presenting cells (Chen and Flies 2013). Expression of co-inhibitory receptors, also known as “immune checkpoints” by tumor cells, including cytotoxic T lymphocyte–associated protein-4 (CTLA-4) and programmed death–1 (PD-1) receptor, can prevent TCR ligand interaction and downregulate the immune system, thus rendering cancer cells immune to cytotoxic T cells (Freeman et al. 2000). Targeting of these checkpoint inhibitors disables this mechanism and allows T cells to recognize and attack the cancer cells.

Immunotherapeutic agents currently approved for advanced *BRAF* wild-type melanoma include the following:

- The anti–CTLA-4 antibody, ipilimumab
- Two anti–PD-1 antibodies, nivolumab and pembrolizumab
- Combination therapy with nivolumab and ipilimumab

Both single-agent and combination immunotherapy with pembrolizumab, ipilimumab, and/or nivolumab have demonstrated an increased overall response rate (ORR) and improved PFS for the treatment of *BRAF* wild-type unresectable or metastatic melanoma with prolonged duration of responses (DORs). Across multiple clinical trials responses to anti–PD-1 agents are limited to 30%–40% of patients, with median PFS of 5–6 months (Robert et al. 2015a, 2015b; Weber et al. 2015) and OS of approximately 20–24 months (Hodi et al. 2016; Robert et al. 2016). For ipilimumab monotherapy, reported response rates are 10%–15% and OS is 10–11 months (Hodi et al. 2010; Robert et al. 2011). Of note, these response rates and PFS outcomes both in patients with *BRAF*-mutant melanoma and *BRAF* wild-type melanoma are still lower than the rates achieved with combined BRAF and MEK inhibition. Combination immunotherapy, in particular, results in challenging toxicity. In Phase III testing in previously untreated patients with advanced melanoma, the combination of ipilimumab and nivolumab demonstrated an increased ORR and improved PFS relative to either agent as

monotherapy but resulted in challenging toxicity, with more than 50% of patients experiencing Grade ≥3 adverse events. The OS benefit for this combination is not yet known (Larkin et al. 2015).

Despite the therapeutic advances achieved by development of these agents, high unmet need still exists for patients with advanced *BRAF*^{V600} wild-type melanoma.

1.2 BACKGROUND ON STUDY TREATMENTS

1.2.1 Cobimetinib

Cobimetinib is a potent and highly selective inhibitor of MEK, a central component of the MAPK pathway. Activated MEK triggers downstream signaling through ERK to promote growth. Cancer cells transformed by *BRAF*^{V600} are exceptionally sensitive to MEK inhibition in vitro. Allosteric MEK inhibitors can result in G_1 phase growth arrest in melanoma cells (Solit et al. 2006; Haass et al. 2008). In vitro, MEK inhibitors reduce cell proliferation, soft agar colony formation, and matrigel invasion of *BRAF*^{V600} mutation–positive melanoma cells, and are also effective against *BRAF*^{V600} mutation–positive melanoma xenografts, which is suggestive of a potentially important role for MEK inhibitors in melanoma and other tumors that harbor the *BRAF*^{V600} mutation (Solit et al. 2006).

Cobimetinib (Cotellic®), in combination with vemurafenib, is approved in the United States, European Union, and multiple other countries across the world for use with vemurafenib for the treatment of advanced *BRAF*-mutated melanoma.

Cobimetinib shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies and in combination with chemotherapy, other targeted therapies, and cancer immunotherapy.

Refer to the Cobimetinib Investigator's Brochure for details on nonclinical and clinical studies.

1.2.2 Atezolizumab

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death–ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer*, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma*.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 Rationale for Combining Cobimetinib and Atezolizumab in Advanced BRAF^{V600} Wild-Type Melanoma in Treatment-Naive Patients

The rationale for combining cobimetinib, a MEK inhibitor, with atezolizumab, an anti–PD-L1 antibody, in the treatment of patients with advanced *BRAF*^{V600} wild-type melanoma is based on the complementary mechanisms of action of these agents. The effects of MAPK pathway inhibition on tumor microenvironment may enhance anti-tumor T cell–mediated immunity and is supported by preclinical and clinical data as summarized in this section. The nonclinical data elucidating the effect of MAPK inhibition on tumor immune contexture are presented in Section 1.3.2. The effects of MAPK inhibitors on tumor immune contexture in patients treated with BRAF and MEK inhibitors in clinical trials are summarized in Section 1.3.3.

1.3.2 Effect on MAPK Inhibition on Tumor Immune Contexture

1.3.2.1 Nonclinical Data

The MAPK pathway has been implicated in the regulation of the immune microenvironment of tumors. In in vitro cell lines, blocking the MAPK pathway was shown to increase antigen expression and enhance reactivity to antigen-specific T lymphocytes (Boni et al. 2010). MEK inhibition has also been shown to increase tumor major histocompatibility complex (MHC) expression and PD-L1 expression in triple-negative breast cancer cells in vivo and in vitro (Loi et al. 2016).

Additional MAPK inhibition effects may further modulate the tumor microenvironment in ways that could enable an improved immune reaction against the tumor. These effects include increased recruitment and activation status of CD8-positive and CD4-positive T cells and reduced secretion of granulocyte-colony stimulating factor, which reduces mobilization and activity of CD11-positive GRL-positive myeloid-derived suppressor cells (Phan et al. 2013; Ebert et al. 2016) as well as reduces expression of angiogenesis factors with altered tumor vascular support (Ciuffreda et al. 2009; Chang et al. 2013; Mohan et al. 2015).

The MEK inhibitor G-38963, which is mechanistically similar to cobimetinib, promotes the effector phenotype and longevity of tumor-infiltrating T cells in a CT26 colon cancer mouse model and combines synergistically with anti–PD-L1 in inhibiting growth of CT26 tumors (Ebert et al. 2016).

1.3.2.2 Clinical Data

This section describes the tumor biopsy data from patients treated with MAPK inhibitors in clinical trials. Clinical data from cobimetinib and atezolizumab monotherapy trials are presented in Sections 1.3.3 and 1.3.4, respectively. Clinical efficacy, safety, and biomarker data from patients treated with the combination in Study GP28363 are provided in Section 1.3.5.

In tumor biopsies from patients with melanoma, BRAF and MEK inhibitors, alone or in combination, have been shown to increase melanoma antigen expression, MHC Class I expression, T-cell infiltration, and PD-L1 expression (Wilmott et al. 2012; Frederick et al. 2013; Hu-Lieskovan et al. 2015; Kavakand et al. 2015; Liu et al. 2015). Furthermore, pretreatment biopsies in which there were increased tumor-infiltrating lymphocytes demonstrated a larger increase in tumor-infiltrating lymphocytes and PD-L1 expression after treatment with a BRAF inhibitor and MEK inhibitor (Kakavand et al. 2015; Liu et al. 2015).

Collectively, and as presented in Section 1.3.4, the data demonstrate that inhibition of the MAPK pathway leads to an increase in immune effector cells in the tumor, thus priming the microenvironment to enable the immune system to attack the tumor.

1.3.3 Activity of Cobimetinib and Other MEK Inhibitors in *BRAF*^{V600} Wild-Type Melanoma

In the Phase Ia study MEK4592g, activity of cobimetinib given as a single agent was limited to *BRAF*-mutated melanoma.

Clinical evidence for modest anti-tumor activity of MEK inhibition in a subset of patients with *BRAF*^{V600} wild-type melanoma has recently been provided by the NEMO Phase III study, which demonstrated improved PFS for single-agent binimetinib, a small molecule MEK inhibitor, in patients with *BRAF*^{V600} wild-type *NRAS*-mutated advanced melanoma relative to dacarbazine (hazard ratio [HR] = 0.62). Even binimetinib has limited efficacy in the *NRAS*-mutated population for which a MEK inhibitor would be expected to have optimal efficacy (Dummer et al. 2016).

As described in Section 1.1, the MAPK pathway is also highly implicated in *BRAF* wild-type melanoma.

1.3.4 Activity of Atezolizumab in Advanced Melanoma

1.3.4.1 Study PCD4989g: Atezolizumab Monotherapy

In the Phase Ia setting (Study PCD4989g), atezolizumab monotherapy has demonstrated anti-tumor efficacy in melanoma with a response rate comparable to that of two PD-1 inhibitors that are currently approved for the treatment of melanoma (pembrolizumab and nivolumab) (Hodi et al. 2014). Among patients with metastatic non-ocular melanoma (n = 37) enrolled in this study, as of the updated data cutoff date of December 2015, the ORR according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) was 32% and median PFS was 5.5 months. In addition, atezolizumab monotherapy was well tolerated by patients with metastatic melanoma.

1.3.5 Clinical Data for Combination Treatment with Cobimetinib and Atezolizumab in Advanced Melanoma

1.3.5.1 Study GP28363

Study GP28363 is an ongoing Phase Ib, open-label, multicenter study designed to assess the safety, tolerability, and pharmacokinetics of cobimetinib plus atezolizumab in patients with advanced solid tumors who are naive to anti–PD-1 therapy and for whom no standard therapy is available.

The study has two stages: Stage 1 (dose escalation) and Stage 2 (expansion). Stage 1 is designed to establish the combination maximum tolerated dose or maximum administered dose for cobimetinib plus atezolizumab. In Stage 2, the recommended Phase II dose and schedule were investigated in tumor-specific expansion cohorts: metastatic melanoma, *KRAS*-mutant and wild-type metastatic colorectal cancer (CRC), and non–small cell lung cancer.

In a separate mandatory biopsy cohort, patients with diverse solid tumors (n = 16), including CRC, received 60 mg of cobimetinib once a day (QD) as monotherapy before initiation of atezolizumab treatment and underwent mandatory fresh biopsy collection before initiation of cobimetinib dosing and at the end of the 14-day period of cobimetinib monotherapy.

In a separate mandatory biopsy cohort, patients with diverse solid tumors (n = 16), including CRC, received 60 mg of cobimetinib once daily (QD) as monotherapy before initiation of atezolizumab treatment and underwent mandatory fresh biopsy collection before initiation of cobimetinib dosing and at the end of the 14-day period of cobimetinib monotherapy.

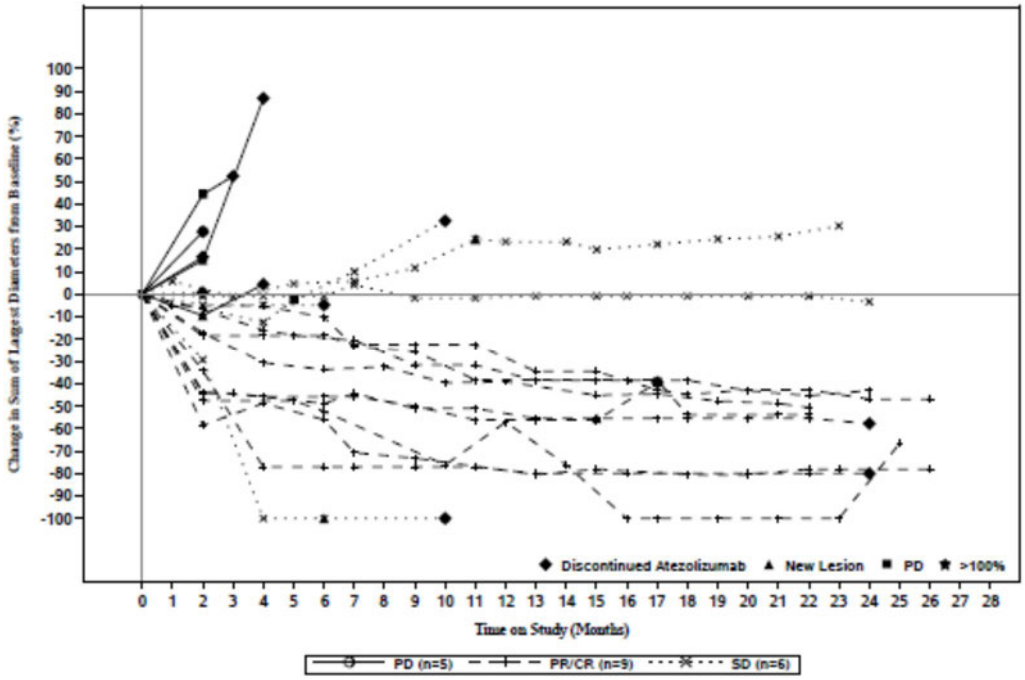
During the Stage 1 dose-escalation phase, there were no dose-limiting toxicities, and 60 mg of cobimetinib on a 21 days on/7 days off schedule with 800 mg of atezolizumab every 2 weeks (Q2W) was determined to be the recommended Phase II dose.

1.3.5.1.1 Efficacy in Non-Ocular Melanoma

As of the data cutoff (17 January 2017), 20 patients with non-ocular melanoma, including 10 patients with *BRAF*^{V600}-mutated disease and 10 patients with *BRAF*^{V600} wild-type disease who had received no prior anti–PD-1 or anti–PD-L1 therapy, were evaluable for efficacy (Miller et al. 2017). The data were comparable in both *BRAF*^{V600}-mutant and *BRAF*^{V600} wild-type melanoma. Of note, 3 of the patients with *BRAF*^{V600}-mutated melanoma who progressed without any tumor shrinkage had received prior trametinib, a MEK inhibitor. Figure 1 and Figure 2 show the RECIST v1.1 responses for all patients with melanoma and all patients with *BRAF*^{V600} wild-type melanoma, respectively.

Among these patients (n = 20), the ORR was 45% (confirmed response per RECIST v1.1), disease control rate (DCR; defined as a complete response, a partial response, or stable disease) was 75%, and median PFS was 12 months (95% CI: 2.8 months, not evaluable). Patients with metastatic melanoma had durability of response, as shown over time in Figure 1.

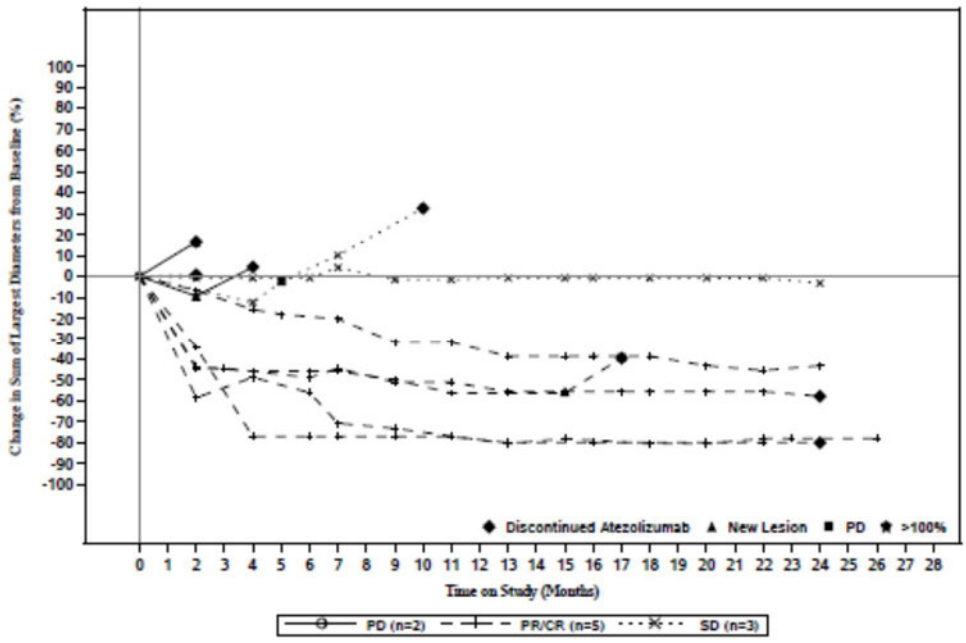
Figure 1 Tumor Burden over Time by Investigator-Confirmed Response per RECIST v1.1 in All Melanoma Patients: Study GP28363



CR = complete response; PD = progressive disease; PR = partial response;
RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SD = stable disease.
Note: n = 10.

For patients with *BRAF*^{V600} wild-type melanoma, the ORR was 50% (confirmed response per RECIST v1.1), the DCR was 80%, and median PFS was 15.7 months (95% CI: 2.8 months, not evaluable). Patients with *BRAF*^{V600} wild-type metastatic melanoma had durability of response (confirmed response per RECIST v1.1), as shown in Figure 2.

Figure 2 Tumor Burden over Time by Investigator-Confirmed Response per RECIST v1.1 in Patients with *BRAF*^{V600} Wild-Type Melanoma: Study GP28363



CR = complete response; PD = progressive disease; PR = partial response;
RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SD = stable disease.
Note: n = 10.

Biomarker Data

Biomarker evaluation from the serial tumor biopsy cohort showed a 4-fold increase in CD8-positive T-cell infiltration in 75% of tumors, as well as increases in PD-L1 and MHC-I expression (Bendell et al. 2016). The data support the hypothesis that cobimetinib has beneficial immunomodulatory effects at the tumor site that allow for immune anti-tumor activity.

Safety in Patients with Melanoma

In the 17 January 2017 data cut for melanoma, the safety data were generally similar for the 22 patients with melanoma and the overall treated population (N=150). The mean duration of safety follow-up was 14 months (range: 2–26 months). For treatment-related adverse events, 100% of patients experienced at least one adverse event; 59.0% of patients experienced a Grade ≥3 adverse event; and 14.0% of patients experienced a serious adverse event, which included pulmonary embolism, bacterial infection, and pain management. There were no Grade 5 (fatal) adverse events in the melanoma cohort.

The most common treatment-related adverse events (occurring in ≥20% of melanoma patients) as of 17 January 2017 were diarrhea (86.0%), rash (68.0%), fatigue (45.0%), nausea (45.0%), pruritus (45.0%), blood creatine phosphokinase increased (32.0%), vomiting (32.0%), abdominal pain (23.0%), decreased appetite (23.0%), and dermatitis acneiform (23.0%). In this cohort, the most common Grade ≥3 events (occurring in ≥5% of patients) were diarrhea (14.0%), anemia (9.0%), dermatitis acneiform (9.0%), amylase increased (5.0%), asthenia (5.0%), bacterial infection (5.0%), edema peripheral (5%), lipase increased (5.0%), maculopapular rash (5.0%), musculoskeletal pain (5.0%), myalgia (5.0%), rash (5.0%), pain management (5.0%), pulmonary embolism (5.0%), pruritus (5.0%), seizure (5.0%), and vomiting (5.0%).

Safety in All Patients

As of 12 July 2016, a total of 150 patients were enrolled in the study and evaluable for safety. Fourteen patients had been accrued in the dose-escalation phase (Stage 1, Cohorts 1–3), and 136 patients had been accrued in the expansion phase (Stage 2).

To be considered evaluable for safety, patients must have received at least one dose of cobimetinib or atezolizumab. All patients who received atezolizumab also received cobimetinib. The mean duration of safety follow-up was 6.59 months (range: 0.7–26.4 months). Safety follow-up is defined as the number of days from the date of the first dose to the minimum date of the last dose plus 30 days, discontinuation date, initiation date of another anti-cancer therapy, cutoff date, or the date of death.

Overall, 96.7% of patients experienced at least one adverse event regardless of attribution; 65.3% of patients experienced a Grade ≥3 adverse event; and 44.0% of patients experienced a serious adverse event. There were five Grade 5 (fatal) adverse events (3.3%) in the study, of which four were assessed as unrelated to study drug. The patient whose death was considered to be related to atezolizumab was being treated

with chronic steroids for preexisting hypopituitarism and succumbed to sepsis; cobimetinib was discontinued prior to the event and was considered not related.

The most common adverse events (occurring in ≥20% of patients) were diarrhea (69.3%), fatigue (52.7%), rash (46.0%), vomiting (38.7%), nausea (34.0%), pruritus (32.7%), decreased appetite (30.0%), constipation (28.0%), peripheral edema (26.0%), pyrexia (23.3%), acneiform dermatitis (23.3%), increased CPK (22.7%), dyspnea (20.0%), and anemia (20.0%). The most common Grade≥3 events (occurring in ≥5% of patients) were fatigue (9.3%), anemia (8.7%), and diarrhea (8.0%).

1.3.5.1.2 Summary

The improved ORR and DCR suggest that the combination of cobimetinib and atezolizumab may lead to longer PFS than either agent given as monotherapy in patients with metastatic melanoma. Together with the biomarker data from the mandatory biopsy cohort, the data suggest that cobimetinib may alter tumor immune contexture, thereby enhancing atezolizumab activity. The safety profile was consistent with other cobimetinib studies, and no new safety concerns were reported.

1.3.6 Benefit–Risk Assessment

This Phase III protocol is based on a strong scientific rationale for combining cobimetinib and atezolizumab for the treatment of patients with advanced *BRAF*^{V600} wild-type melanoma (see Section 1.3.1) and is supported by compelling clinical data from melanoma patients treated with the combination in Study GP28363 (see Section 1.3.5.1). The protocol includes eligibility criteria, baseline measurements, and recommendations for management of adverse events, including guidelines for dose modifications, delays, and discontinuation of one or more of the study drugs that are designed to enhance the safety of patients in this trial. Oversight of this study will be provided by the Sponsor's Medical Monitor (see Section 3.1.3). Additionally, an independent data monitoring committee (iDMC) will be employed to monitor and evaluate patient safety throughout the study.

Treatment options are limited for patients with advanced *BRAF*^{V600} wild-type melanoma whose disease is unresectable or metastatic. Given the unmet need in this indication, the efficacy and safety data for cobimetinib and atezolizumab given as single agents and in combination (Study GP28363) in advanced melanoma, the biomarker data from Study GP28363 that suggest that the effects of cobimetinib on tumor immune contexture may sensitize tumors to anti–PD-1 and anti–PD-L1 agents, together with a potentially much improved tolerated safety profile and the extent of safety monitoring proposed, the potential benefits for patients with this indication outweigh the potential risks.

Given the unmet need that still exists in advanced *BRAF*^{V600} wild-type melanoma, these data support development of cobimetinib plus atezolizumab in this indication.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of cobimetinib plus atezolizumab compared with pembrolizumab in treatment-naive patients with advanced or unresectable *BRAF*^{V600} wild-type melanoma. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 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
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 according to RECIST v1.1, or death from any cause • 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 EORTC QLQ-C30, at specified timepoints while receiving treatment

Table 1 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:	
• To investigate the relationship between cobimetinib exposure and efficacy and safety outcomes using population approaches	• Relationship between cobimetinib plasma concentration and efficacy or safety endpoints
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

Table 1 Objectives and Corresponding Endpoints (cont.)

Objective(s)	Corresponding Endpoint(s)
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 MHC 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 QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = European Quality of Life 5-Dimension, 5-Level questionnaire; GHS = global health status; HRQoL = health-related quality of life; IRC = independent review committee; MHC = major histocompatibility complex; 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; QoL = quality of life; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of 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. 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 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. PD-L1 status will be determined using central testing, with $<1\%$ immune cells ([IC] 0 vs. IC1, 2, 3) defined as being PD-L1 negative for PD-L1 status.

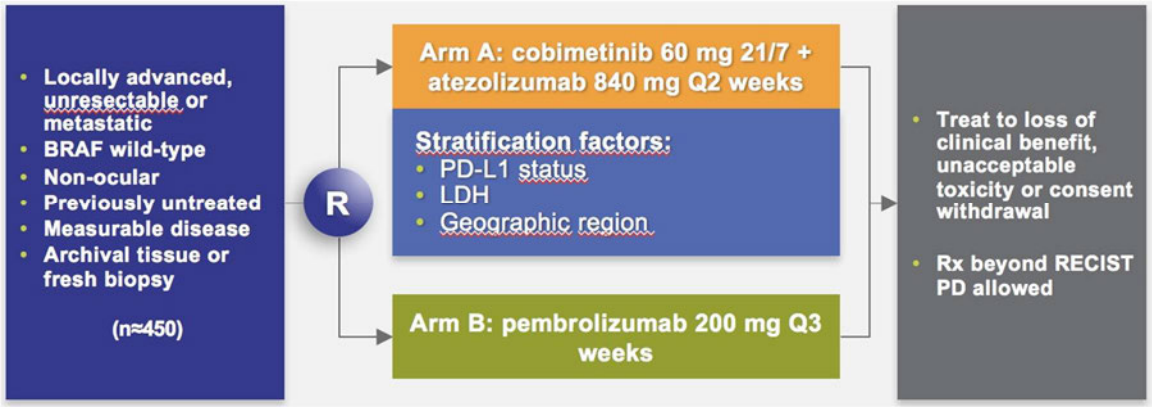
The primary objective of the study is to evaluate the efficacy of cobimetinib plus atezolizumab compared with pembrolizumab in treatment-naive patients with advanced $BRAF^{V600}$ wild-type melanoma, as measured by primary endpoint of PFS assessed by independent review.

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).

The study schema is presented in Figure 3.

Figure 3 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 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 (see Appendix 1) and as necessary throughout the study.

Tumor response will be evaluated according to RECIST v1.1 (see Appendix 3). 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.

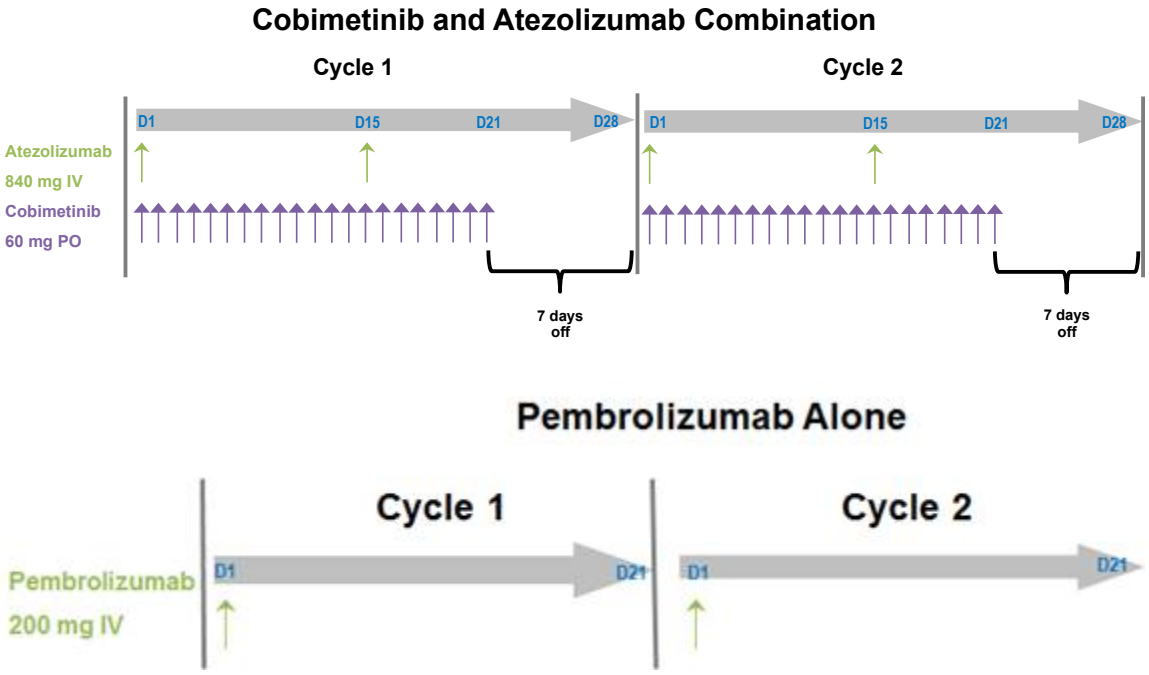
Patients who discontinue one study drug in Arm A may be able to continue the other study drug, per guidelines for management of specific adverse events provided in Section 5.1.5 and Appendix 10. After treatment discontinuation, patients will be followed for disease progression if applicable and followed 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 for 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 (EQ-5D-5L) questionnaire 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.

A schedule of activities is provided in Appendix 1 (see Table 1 for the cobimetinib and atezolizumab arm and Table 2 for the pembrolizumab arm). The treatment and schedule for cobimetinib and atezolizumab combination treatment and pembrolizumab are shown in Figure 4.

Figure 4 Treatment and Schedule



D = Day; PO = by mouth.

3.1.2 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. Treatment will be discontinued if clinical deterioration due to disease progression occurs at any time or if persistent disease growth is confirmed on follow-up scans performed 4–8 weeks later.

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 disease progression
- 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

3.1.3 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 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.

3.2 END OF STUDY AND LENGTH 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.

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

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Cobimetinib and Atezolizumab Dose and Schedule (Arm A)

Concomitant administration of atezolizumab and cobimetinib was studied in Study GP28363. Cobimetinib and atezolizumab in combination were found to be safe and tolerable with cobimetinib on the approved dose and schedule of 60 mg QD 21/7, and atezolizumab 800 mg IV Q2W, which is equivalent to the approved dose and schedule for treatment of bladder cancer of 1200 mg IV Q3W.

Cobimetinib will be administered at the approved dose and schedule of 60 mg QD 21/7 for each 28-day cycle. The 800-mg Q2W dose of atezolizumab was evaluated in Study GP28363, which is the pharmacokinetic (PK) equivalent of the dose of 1200 mg Q3W in bladder cancer. To simplify dosing, the dose was rounded up to 840 mg (1 mL of drug), which is further supported by the nonclinical dosing data and is not expected to be different from the 800-mg dose.

3.3.2 Rationale for Pembrolizumab Dose and Schedule (Arm B, Control)

Pembrolizumab will be administered at the approved dose and schedule of 200 mg IV Q3W. Pembrolizumab is considered standard of care and is approved for the treatment of unresectable or metastatic melanoma. Please refer to pembrolizumab (Keytruda®) local prescribing information for a list of approved indications and a complete summary of safety information.

Based on the KEYNOTE-006 Phase III trial of pembrolizumab versus ipilimumab in advanced melanoma, the estimated 6-month PFS rate was 46.4% and 26.5% for pembrolizumab Q3W and ipilimumab, respectively (HR = 0.58). The median estimates of PFS were 5.5 months versus 2.8 months. The estimated 12-month OS rates were 68.4% and 58.2% for pembrolizumab and ipilimumab, respectively (HR = 0.69). The ORR with pembrolizumab was 32.9% relative to 11.9% with ipilimumab (Robert et al. 2015b). In KEYNOTE-001, a Phase Ib trial of pembrolizumab in patients with ipilimumab-naive and ipilimumab-treated advanced melanoma, the median OS for all patients (n = 655) was 24.4 months. Of note, the median OS for patients who had not received any prior systemic treatment (n = 152) was 32.2 months. Three-year OS rates were 40% and 45%, respectively (Robert et al. 2016). Refer to the prescribing information for more details.

3.3.3 Rationale for Patient Population and Cohorts

Arm A and Arm B of Study CO39722 will enroll patients with advanced *BRAF* ^{V600} wild-type melanoma without a history of systemic therapy for locally advanced or metastatic disease. Despite the recent advances in treatment options provided by

immunotherapies, this patient population continues to have high unmet need. The known effects of MAPK inhibitors, including cobimetinib, on the tumor microenvironment (see Section 1.3.2) include effects that may enable conversion to an immunoresponsive phenotype, sensitize refractory tumors to anti–PD-1 and anti–PD-L1 agents, and suggest that combination therapy with cobimetinib and atezolizumab may be efficacious in this population. This hypothesis is supported by clinical data from Study GP28363 (see Section 1.3.5), indicating that combination therapy with cobimetinib and atezolizumab in advanced melanoma results in improved ORR and PFS relative to anti–PD-1, anti–PD-L1, or MEK inhibitor monotherapy.

In order to ensure *BRAF*^{V600} wild-type status, the inclusion criteria require that *BRAF* status be confirmed using an approved clinical test before randomization.

In order to ensure that the primary endpoint of PFS by independent review, and the secondary endpoints of ORR and DOR can be adequately assessed, patients must have measurable disease (per RECIST v1.1) and locally advanced and unresectable or metastatic melanoma.

Additional eligibility criteria have been incorporated that are pertinent to the safety profiles of cobimetinib and atezolizumab (and anti–PD-L1 targeted therapies as a therapeutic class). These have been informed by the known safety profiles of each drug and supplemented by experience in Study GP28363, which evaluated the combination of atezolizumab and cobimetinib in patients with diverse solid tumors, including advanced melanoma.

3.3.4 Rationale for Control Arm

The control arm will receive 200 mg of pembrolizumab administered by IV infusion Q3W.

The intent of this study is to evaluate the magnitude of benefit achievable with the combination of cobimetinib plus atezolizumab, relative to current standard of care, in treatment-naive patients with advanced *BRAF*^{V600} wild-type melanoma.

Several therapies are currently available for this indication (refer to Section 1.1). The current guidelines from the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology clinical practice guidelines (Dummer et al. 2015; NCCN 2016) are the anti–PD-1 monotherapies pembrolizumab and nivolumab and the combination of nivolumab with ipilimumab. The choice of treatment is based on evaluation of the individual patient by the treating physician.

The anti–PD-1 monotherapies pembrolizumab and nivolumab have demonstrated comparable efficacy in patients with advanced melanoma across multiple clinical trials. Efficacy has been established for survival endpoints, as well as for the correlated surrogate endpoints of PFS and ORR (median PFS for these agents in advanced melanoma is 5–6 months, with an ORR of approximately 30% [Hodi et al. 2014; Robert

et al. 2015a, 2015b; Weber et al. 2015] and OS of approximately 20–24 months [Hodi et al. 2016; Robert et al. 2016]).

Both pembrolizumab and nivolumab are used for the treatment of *BRAF*^{V600} wild-type advanced melanoma in clinical practice. Recently, a Phase III trial (KEYNOTE-006; Schachter et al. 2016) demonstrated improved PFS and survival rates for pembrolizumab relative to ipilimumab in patients with advanced melanoma. In this trial, patients were randomized in a 1:1:1 ratio to receive pembrolizumab at a dose of 10 mg/kg either Q2W or Q3W or four cycles of ipilimumab at a dose of 3 mg/kg Q3W. The final OS analysis at 24 months demonstrated survival rates of 55%, 55%, and 43%, respectively (HR for pembrolizumab Q2W = 0.68; 95% CI: 0.53, 0.87; p = 0.00085; HR for pembrolizumab Q3W = 0.68; 95% CI: 0.53, 0.86; p = 0.00083) (Schachter et al. 2016). Pembrolizumab is preferred over nivolumab for this open-label study because the dosing frequency is reduced relative to that of nivolumab (Q3W vs. Q2W [Keytruda® and Opdivo® U.S. Package Inserts and EU Summary of Product Characteristics]), which reduces the visit burden for patients enrolled in the control arm.

On the basis of anti–PD-1 monotherapy being a currently approved, widely used standard of care, which affords the longest established survival benefit of currently available therapies and is recommended by advisory bodies for treatment of patients with *BRAF*^{V600} wild-type melanoma, pembrolizumab is considered an appropriate comparator arm for Study CO39722. Pembrolizumab is the preferred treatment option compared with nivolumab because of the reduced dosing frequency.

3.3.5 Rationale for Confirmation of Progressive Disease per RECIST v1.1

In this study, all patients will have confirmatory scans performed 4–8 weeks after initial documentation of progression per RECIST v1.1. Studies with immunotherapeutic agents indicate that conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Initial increase in tumor size caused by IC infiltration in the setting of a T-cell response can occur with immunotherapy and has been termed pseudoprogression (Hales et al. 2010). However, the implications of atypical anti-tumor responses in the setting of immunotherapy combined with targeted therapy are currently unknown.

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

3.3.6 Rationale for Pharmacokinetic Sample Collection

The proposed PK sampling scheme for assessment of cobimetinib and atezolizumab concentration, together with available data from other clinical studies, will be used to investigate any drug interaction between the two molecules by comparing the PK data from this study with single-agent data from previous studies. PK samples will not be obtained from patients in the control arm (pembrolizumab) since it is an established product.

Atezolizumab is primarily eliminated by catabolism to inactive metabolites and therefore has a low potential for drug interactions. Cobimetinib is metabolized primarily by CYP3A, and to a lesser extent by UGT2B7, based on in vitro studies. Strong and moderate inhibitors and inducers of CYP3A can alter cobimetinib exposure, and no other clinically relevant drug–drug interactions have been observed. There is an approximate 7-fold increase in the area under the concentration–time curve with potent CYP3A inhibitors (see Section 4.4.2). Because of the differences in metabolism, no drug–drug interaction is anticipated between cobimetinib and atezolizumab. PK samples of cobimetinib and atezolizumab will be obtained as indicated in Appendix 2 to evaluate the pharmacokinetics of each molecule when administered in combination.

3.3.7 Rationale for Biomarker Assessments

3.3.7.1 Rationale for Biomarker Assessments in Tumor Tissue

To characterize the heterogeneity of tumors among patients and its relationship to clinical response, tumor tissue will be collected at screening (archival tissues of sample collection date $<$ 5 years or pretreatment biopsies), on Day 15 of Cycle 1 (optional biopsy), and at disease progression (fresh biopsy to be obtained either at first evidence of progression or confirmation of progression, whichever is closest to the last date of study treatment administration).

Tumor tissue will be evaluated for tumor immunity contextures, such as CD8-positive T-cell infiltrate, PD-L1, and MHC expression, and other components of tumor immunity. In addition, DNA and/or RNA will be extracted from these tumor samples to enable next-generation sequencing (NGS) of DNA and RNA to identify tumor-specific somatic mutations, immune and stromal signatures, and the clonalities of TCRs to aid the understanding of disease pathobiology. These molecular characterizations of tumors will be analyzed in relation to clinical response to identify patients who will likely benefit more from the treatment. Because these biomarkers may also have prognostic value, their potential association with disease progression will also be explored. Comparison of biomarkers between tissue acquired before treatment and tissue acquired at the time of progression will further elucidate the potential mechanism of acquired resistance to this combination. Detailed mutation and immune profiles from biopsies obtained from patients at disease progression may also provide data for consideration of subsequent therapeutic options.

3.3.7.2 Rationale for Biomarker Assessments in Blood

An exploratory objective of this study is to evaluate biomarkers in available blood samples. Factors in blood samples may hold important clues regarding the disease pathobiology of cancer patients. Potential blood biomarkers may include, but are not limited to, mutations in circulating-tumor DNA (ctDNA) such as, *NRAS* or *NF-1* mutations, total mutation load, or protein factors such as S100. Analysis of the characteristics of biomarkers from each patient before treatment, during treatment, and at disease progression, along with clinical data collected in this study, may increase the opportunity for developing new approaches for monitoring disease dynamics or that would be predictive of clinical benefit for this treatment combination.

3.3.8 Rationale for Open-Label Design

Study CO39722 is intended to evaluate the efficacy of cobimetinib in combination with atezolizumab in patients with $BRAF^{V600}$ wild-type unresectable, locally advanced, or metastatic melanoma compared with pembrolizumab, a widely used standard-of-care treatment in this indication. Study CO39722 is designed as an open-label study for the following reasons:

- Patients receiving cobimetinib are required to undergo safety monitoring tests for MEK inhibitor–associated adverse events, including extensive ophthalmologic tests (requiring a time commitment of approximately 1 hour) and left ventricular ejection fraction (LVEF) monitoring by ECHO or MUGA scan. Both of these investigations will be performed at baseline, after 1 month, and every 3 months thereafter, with additional testing if an abnormality is detected. These assessments are not indicated for patients receiving pembrolizumab monotherapy and would therefore present an excessive and unnecessary burden to patients in the control arm in a blinded study.
- Several adverse events observed with cobimetinib, including serous retinopathy, elevated CPK, and decreased LVEF, are recognized class effects of MEK inhibitors. In the Phase III study GO28141, at the time of the primary analysis, for patients in the cobimetinib plus vemurafenib arm relative to the vemurafenib plus placebo arm, the incidence of these adverse events was as follows: serous retinopathy, 24% versus 2.1%; Grade $\geq$3 elevated CPK, 10.6% versus 0.4%; and Grade $\geq$2 LVEF reductions, 8.5% versus 3.7%. Although the majority of these events have been asymptomatic or mild in nature, they are prospectively monitored in cobimetinib trials and will be monitored in this trial. Because patients in the pembrolizumab control arm will not receive a MEK inhibitor, occurrence of these adverse events would likely alert investigators and patients to the treatment assignment of patients receiving cobimetinib and atezolizumab in the experimental arm, compromising blinding in many cases.

Study CO39722 has been designed to prevent compromise of study outcomes by the absence of blinding. The primary endpoint is independent review committee (IRC)-assessed PFS, and IRC members will be blinded to patient treatment assignment. IRC-assessed PFS will be supported by a secondary endpoint of investigator-assessed

PFS. Furthermore, the secondary endpoints of OS, 2-year landmark OS, and IRC-assessed ORR and DOR will provide additional information for patients and physicians that is unaffected by knowledge of treatment assignment.

3.3.9 Rationale for Selection of Primary Endpoint: Progression-Free Survival, as Assessed by the Independent Review Committee

PFS is established as a clinically relevant measure of treatment benefit and a correlate of OS in advanced melanoma, which in recent years has been an approvable endpoint in the setting of metastatic or unresectable melanoma for both targeted and immunotherapies (European Medicines Agency 2012). In a meta-analysis of 4416 metastatic melanoma patients, PFS was found to be a robust surrogate for OS in dacarbazine-controlled randomized trials of metastatic melanoma. Furthermore, PFS has also been demonstrated to be predictive of landmark OS for pembrolizumab (Robert et al. 2015a). In addition, owing to the increased number of active treatment options available and under investigation, resulting in patients receiving more lines of therapy than have previously been available, OS would likely be confounded by the use of effective subsequent-line therapies or by mortality unrelated to cancer (Flaherty et al. 2012).

Finally, full powering for OS requires large numbers of patients, and for this study, it would result in a significantly longer timeline, such that analysis of clinical benefit would not be available to patients with remaining unmet need and their physicians in a reasonable timeframe. As progression events provide reliable information on the treatment effect observed and generally are not confounded by subsequent lines of therapy, PFS provides a meaningful efficacy endpoint with earlier time to evaluation (Di Leo et al. 2003). In addition, 2-year landmark survival may provide a meaningful measure of benefit to patients and physicians.

In summary, multiple drugs, including both targeted therapy and immunotherapies, have been approved in metastatic melanoma in recent years on the basis of PFS, and extensive clinical experience validates PFS as a consistent strong correlate of survival across different treatment modalities.

3.3.10 Rationale for Choice of Stratification Factors

In Study CO39722, randomization will be stratified by three 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).

- PD-L1 expression has recently been recognized as a strong favorable prognostic factor in melanoma and is associated with improved outcome for anti–PD-1/PD-L1–directed therapy (Carbognin et al. 2015; Hauschild et al. 2016; Wang et al. 2016).

- Baseline LDH level is recognized as a strong prognostic factor in melanoma for long-term OS. Elevated LDH level is associated with poorer outcomes across multiple therapies and is reflective of other factors associated with aggressive disease, such as tumor stage and burden (Balch et al. 2009; Chapman et al. 2011; Hauschild et al. 2012, 2015, 2016; Ascierto 2013; Kelderman et al. 2014; Long et al. 2014, 2015; McArthur et al. 2014; Diem et al. 2015; Robert et al. 2015b).
- Different regions employ different treatment paradigms based on regulatory approvals and economic considerations. These factors can influence the population of patients enrolled in clinical trials. It is therefore appropriate to include geographic region as a stratification factor.

3.3.11 Rationale for Patient-Reported Outcome Assessments

Metastatic melanoma is a deadly cancer that impacts patients' health-related quality of life (HRQoL) (Cornish et al. 2009). Current treatment goals include improving survival, managing disease or treatment-related symptoms (insomnia, pain, and fatigue), and preserving HRQoL outcomes as feasible (NCCN 2016). Studies have shown that patients with advanced melanoma tend to experience a decrease in global health status (GHS) and physical functioning while undergoing treatment, which can vary by therapy and presence of disease progression (Schadendorf et al. 2015; Long et al. 2016).

Results from the KEYNOTE-002 study (pembrolizumab vs. chemotherapy) indicate that newer treatments such as pembrolizumab are more tolerable than chemotherapy and that by extending PFS, maintenance of patients' HRQoL is prolonged as well (Schadendorf et al. 2015).

In this study (CO39722), the EORTC QLQ-C30, a generic cancer questionnaire that assesses commonly reported symptoms, functioning, and GHS/HRQoL, will be used to obtain patient-relevant information and therefore address a measurement needed to understand patients' experience with treatment of melanoma (see Section 4.5.11.1). The EQ-5D-5L (see Section 4.5.11.2) will be used to derive utility scores for use in economic models.

Assessment of the effects of combination treatment with atezolizumab and cobimetinib in relation to disease and treatment burden is important and will allow oncologists to appropriately educate patients on the benefits and risks of treatment with this doublet combination therapy. The measurement hypothesis is whether the combination of atezolizumab with cobimetinib will result in maintained HRQoL until progression compared with pembrolizumab.

4. MATERIALS AND METHODS

4.1 PATIENTS

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

4.1.1 Inclusion Criteria

4.1.1.1 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 IFN-α, 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 [EMQN], 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 (see Appendix 3)

4.1.1.2 General Inclusion Criteria

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

- Signed Informed Consent Form
- Age $\geq$ 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 (see Appendix 5)
- Life expectancy $\geq$ 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 $\geq$90 g/L (9 g/dL)

– Patients may be transfused to meet this criterion.

Creatinine clearance $\geq$40 mL/min

Serum albumin $\geq$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., GHS and HRQoL) using an electronic device or paper backup questionnaires.

4.1.2 Exclusion Criteria

4.1.2.1 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 anti−TNF] 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

4.1.2.2 Cancer-Related Exclusion Criteria

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

- Ocular 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

4.1.2.3 Exclusion Criteria based on Organ Function or Medical History

4.1.2.3.1 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 the 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
- 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

4.1.2.3.2 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 at screening, are eligible for the study if HBV DNA is negative.

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

4.1.2.3.3 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

4.1.2.4 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 (see Appendix 6 for a more comprehensive list of autoimmune diseases and immune deficiencies), 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

4.1.2.5 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

  No previous cancer immunotherapy including anti-PD-1 or anti-PD-L1
- Any Grade $\geq$ 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)

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label trial. After written informed consent has been obtained and eligibility has been established, each patient will be assigned an identification number and be randomized to one of the two treatment arms through use of an IWRS.

Randomization will be stratified by 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). A stratified, permuted block randomization scheme will be used to obtain approximately a 1:1 ratio between the two treatment arms.

Patients should receive their first dose of study treatment as soon as possible and within 3 days of randomization, unless approved by Medical Monitor.

4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) 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 (NIMP) in this study, unless local regulations require it to be an IMP.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Cobimetinib

Cobimetinib will be supplied as 20-mg, film-coated tablets packaged in blister packs (21 tablets per pack; 3 packs per box) for oral administration.

For information on the formulation and handling of cobimetinib, see the Cobimetinib Investigator's Brochure and pharmacy manual.

4.3.1.2 Atezolizumab

Atezolizumab will be supplied as sterile liquid in 20-mL glass vials. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution, but it may contain more than the stated volume to enable delivery of the entire 20-mL volume. Extraction of 14 mL of atezolizumab solution from a 1200 mg per vial contains an 840-mg dose.

For information on the formulation and handling of atezolizumab, refer to the Atezolizumab Investigator's Brochure and pharmacy manual.

4.3.1.3 Pembrolizumab

Patients in the control arm (Arm B) will receive pembrolizumab. In the countries where pembrolizumab is considered a NIMP, by local regulations, the commercial formulation of pembrolizumab will be provided by the local institution as part of standard of care treatment. It will be provided by the Sponsor where it is considered an IMP or not commercially available.

For information on the formulation, packaging, and handling of pembrolizumab, see the local prescribing information for pembrolizumab.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Cobimetinib

Patients randomized to Arm A will receive cobimetinib 60 mg (three tablets of 20 mg each) by mouth 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.

Guidelines for dosage modification and treatment interruption or discontinuation of cobimetinib are provided in Section 5.1.5.1.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF (see Section 5.4.4).

4.3.2.2 Atezolizumab

Patients randomized to Arm A will receive atezolizumab 840 mg by IV infusion on Day 1 and Day 15 of each 28-day cycle. This 4-week period is considered a treatment cycle.

Atezolizumab will be administered in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

For more detailed information on drug preparation, storage, and administration, refer to the Atezolizumab Investigator's Brochure and pharmacy manual.

Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Infusions of Atezolizumab

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (±5 minutes for all timepoints) during the infusion and at 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Dose modifications to atezolizumab are not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events are provided in Section 5.1.5, Appendix 10 (cobimetinib plus atezolizumab-associated AE management), Appendix 11 (atezolizumab-associated AE management).

For anaphylaxis precautions, see Appendix 7.

See the pharmacy manual for detailed instructions on drug preparation, storage, and administration or guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5.2, Appendix 10, and Appendix 11.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF (see Section 5.4.4).

4.3.2.3 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.

Pembrolizumab will be supplied in the commercially available formulation.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5. For information on the formulation and handling of pembrolizumab, refer to the pembrolizumab prescribing information.

Any overdose or incorrect administration of pembrolizumab should be noted on the Pembrolizumab Administration eCRF. Adverse events associated with an overdose or incorrect administration of pembrolizumab should be recorded on the Adverse Event eCRF (see Section 5.4.4).

4.3.3 Assessment of Compliance

To assess patient compliance with self-administration of cobimetinib, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits (see Appendix 1) for assessments of compliance.

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (cobimetinib and atezolizumab) will be provided by the Sponsor where required by local health authority regulations; pembrolizumab is an approved treatment for melanoma and can be considered standard of care in some countries. Pembrolizumab will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of cobimetinib and atezolizumab, using the IWRS to confirm the shipment condition and content. Any damaged shipments will be replaced. Where pembrolizumab is supplied by the Sponsor, shipment receipt will be documented using the IWRS; otherwise, it will be documented per local practice.

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

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

4.3.5 Continued Access to Cobimetinib and Atezolizumab

The Sponsor will offer post-trial access to Sponsor study drugs (atezolizumab and cobimetinib) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Sponsor study drugs after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Sponsor study drugs after completing the study if any of the following conditions are met:

- The study drugs are commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drugs or data suggest that the study drug is not effective for melanoma
- The Sponsor has reasonable safety concerns regarding the study drugs as treatment for melanoma
- Provision of study drugs is not permitted under the laws and regulations of the patient's country

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

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

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study drug to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

The following therapies are permitted in the study:

- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as low-molecular-weight heparin or warfarin at a stable dose level)

  Although allowable, caution should be used when using concomitant medications that increase the risk of bleeding, including antiplatelet or anticoagulant therapy, because of the risk of hemorrhage with cobimetinib.
- Palliative radiotherapy (e.g., treatment of known bone metastases), provided it does not interfere with assessment of tumor target lesions

  It is not required to withhold atezolizumab during palliative radiotherapy.
- Inactive influenza vaccinations during influenza season **only**
- Megestrol administered as an appetite stimulant
- Inhaled corticosteroids for COPD
- Mineralocorticoids (e.g., fludrocortisone)

Anti-emetic and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drugs. At the discretion of the investigator, prophylactic anti-emetic and anti-diarrheal medication(s) may be used per standard clinical practice before subsequent doses of study drugs. Hematopoietic growth factors should not be administered prophylactically before initial treatment with study drugs. Hematopoietic growth factors may be administered according to local guidelines if indicated during the study.

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

hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

All medications must be recorded on the Concomitant Medications eCRF.

4.4.2 Prohibited Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the anti-cancer agent (see Section 4.1.2.5), and during study treatment until disease progression is documented and patient has discontinued study treatment. This includes, but is not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy.

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2.2), and during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see Section 4.4.1 for details).
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days or 5 half-lives prior to initiation of study treatment and during study treatment.
- Immunomodulatory agents, including, but not limited to, ipilimumab, IFNs or IL-2, are prohibited during the entire study; these agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab and pembrolizumab.
- Immunosuppressive medications, including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide are prohibited during study treatment; these agents could potentially alter the activity and the safety of atezolizumab and pembrolizumab.

    Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab and pembrolizumab. Therefore, in situations where systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered first by the treating physician. If the alternatives are not feasible,

systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the treating physician (see Section 4.4.3).

- For patients randomized to receive cobimetinib and atezolizumab:

  Concomitant use of strong and moderate inhibitors of CYP3A (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) should be avoided as cobimetinib is a sensitive substrate of CYP3A and exposures will be increased in presence of these agents (approximately 7-fold increase in presence of itraconazole in healthy subjects).

  Avoidance of strong and moderate CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's wort) as they increase the metabolism of cobimetinib. Strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4, should be considered.

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication when determining whether a certain medication is metabolized by or strongly inhibits or induces CYP3A. In addition, the investigator should contact the Medical Monitor if questions arise regarding any medications not listed above.

4.4.3 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.3.1 Corticosteroids and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator (see Section 4.4.2).

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to the Appendix 11 for details).

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed

Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

BRAF status will be prescreened prior to beginning the remaining screening evaluations. Standard-of-care screening assessments may be performed concurrently with $BRAF^{V600}$ mutation testing. Locally or centrally tested $BRAF^{V600}$ status must be known prior to performing subsequent study-specific screening assessments.

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

Screening Window Extension

The screening window may be extended for an agreed upon and acceptable period to allow re-evaluation of assessments after discussion and agreement with the Medical Monitor.

Rescreening

Rescreening may be allowed in certain cases (e.g., such as an aberrant laboratory value, washout of a prior medication, unavailability of study drug, or inability to complete screening within the screening window) in which patients have not previously been randomized into the study and have not received study treatment, after discussion and agreement with the Medical Monitor. For these patients, one rescreening will be allowed.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, prior surgeries within 5 years prior to initiation of study treatment, and use of alcohol, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study drug will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity. Baseline disease characteristics data will include melanoma disease status (metastatic or locally advanced and unresectable) at enrollment, ECOG Performance Status, date of diagnosis of first metastatic disease, site of primary disease, *RAS* status, history of melanoma cancer surgery, and location of metastasis at enrollment.

4.5.3 Physical Examinations

A complete physical examination should be performed at screening and should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF (see Section 5.3.5).

Height will be recorded at screening only. Weight will be recorded at screening and at various timepoints indicated in Appendix 1.

In addition, patients randomized to receive cobimetinib plus atezolizumab will be asked specifically about vision-related changes as part of each physical examination in addition to interval medical history. Note: If physical examinations are performed within 7 days of Day 1, Cycle 1, they do not have to be repeated on Day 1 of Cycle 1.

4.5.4 Vital Signs

Vital signs will include temperature (measured in degrees Centigrade), pulse rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position. Blood pressure and pulse rate measurements will be recorded after a 5-minute rest while the patient is in a seated position. Resting oxygen saturation will be measured during screening and at subsequent visits.

Vital signs will be measured and recorded at the following timepoints:

- Within 60 minutes prior to infusion
- During infusion or after infusion per schedule of assessments

For patients who experienced an infusion-related reaction (IRR) during the previous atezolizumab infusion, refer to Section 4.3.2.2. For patients who experienced an IRR during the previous pembrolizumab infusion, refer to the prescribing information for pembrolizumab.

4.5.5 Tumor and Response Evaluations

All measurable and non-measurable lesions must be documented at screening (within 35 days prior to initiation of study treatment). Evaluation of tumor response conforming to RECIST v1.1 must then be documented 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, until investigator-determined disease progression (according to RECIST v1.1 that is confirmed 4–8 weeks after initial documentation of progression), withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first. Thus, tumor assessments are to continue according to schedule for patients who discontinue treatment for reasons other than disease progression. At the investigator's discretion, tumor assessments may be repeated at any time if disease progression is suspected.

Tumor assessments must be performed independently of changes to the study treatment administration schedule (i.e., when treatment is withheld). If a tumor assessment has to be performed early or late, subsequent assessments should be conducted according to the original schedule based on the date of first study treatment administration on Day 1 of Cycle 1. The tumor assessment schedule is identical in both arms to avoid potential bias.

Tumor assessments will include contrast-enhanced CT or MRI scans of the chest, abdomen, and pelvis. Imaging of the neck should be included if clinically indicated. In the event a positron emission tomography (PET)/CT scanner is used for tumor assessments, the CT portion of the PET/CT must meet criteria for diagnostic quality. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. Patients with untreated or actively progressing CNS metastases are not eligible for the study (see Section 4.1.2). Stable brain metastases (as defined in Section 4.1.2) must be evaluated at each tumor assessment using the same radiographic procedure as the baseline study. Patients without brain metastases do not need brain scans for tumor assessment unless clinically warranted. Clinical disease assessments by physical examination should be performed for patients with palpable or superficial lesions. Tumor measurements for each patient should be made by the same investigator or radiologist, if feasible, using the same assessment technique or procedure throughout the study.

Tumor response and progression will be evaluated according to RECIST v1.1 (see Appendix 3) and immune-modified RECIST (see Appendix 4). Objective response (a complete response or partial response) must be confirmed by repeat assessments 4-8 weeks after initial documentation. In the case of stable disease, tumor measurements must meet criteria for stable disease ≥6 weeks after initiation of study treatment.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

4.5.6.1 Local Laboratory Assessments

Study Inclusion Assessment

A sample for the following laboratory test for study inclusion will be sent to the study site's local laboratory for analysis:

- *BRAF*^{V600} status
- If local analysis is not available, the sample is to be sent for central assessment.

Screening Assessments

Samples for the following laboratory tests during screening will be sent to the study site's local laboratory for analysis:

- Hematology: RBC, reticulocytes, hemoglobin, hematocrit, WBC count with differential count (neutrophils, bands, eosinophils, basophils, monocytes, and lymphocytes), and platelet count
- Serum chemistry panel: BUN or urea, creatinine, sodium, potassium, chloride, bicarbonate or total CO_2 (HCO_3 and CO_2 not mandatory if unavailable at site), magnesium, calcium, phosphorus, total bilirubin, direct bilirubin, ALT, AST, ALP, CPK, uric acid, total protein, LDH, and albumin
- Fasting blood glucose (after a minimum 8-hour fast), at screening only
- Fasting lipids: total cholesterol, LDL cholesterol, and triglycerides (after a minimum 8-hour fast), at screening only
- Coagulation: INR and aPTT
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria).
- Serum pregnancy test for women of childbearing potential, including women who have had a tubal ligation

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (defined as 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone permanent surgical sterilization (removal of bilateral ovaries and/or uterus).
- Thyroid-function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- HBV serology: HBsAg, antibodies against HBsAg, 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: HCV antibody (anti-HCV)

  HCV RNA should be obtained prior to randomization if patient tests positive for anti-HCV.
- HIV testing

  All patients will be tested for HIV prior to the inclusion into the study, and HIV-positive patients will be excluded from the study.

Treatment

Samples for the following laboratory tests during study treatment will be sent to the study site's local laboratory for analysis:

- Hematology: RBC, reticulocytes, hemoglobin, hematocrit, WBC count with differential count (neutrophils, bands, eosinophils, basophils, monophils, lymphocytes, and platelet count)
- Serum chemistry panel: glucose, BUN or urea, creatinine, sodium, potassium, chloride, bicarbonate or total CO_2 (HCO_3 and CO_2 not mandatory if unavailable at site), magnesium, calcium, phosphorus, total bilirubin, direct bilirubin, ALT, AST, ALP, CPK, uric acid, LDH, albumin
- Thyroid-function testing: thyroid-stimulating hormone, T3 (or total T3 for sites where free T3 is not performed), and free T4

4.5.6.2 Central Laboratory Assessments

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

- *BRAF*^{V600} testing
- LDH
- PD-L1
- Anti-drug antibody (ADA) assays for patients in Arm A only, provided that it does not cause undue hardship to the patient (e.g., the patient is in hospice care and not able to come in for a visit)

  Serum samples also may be assayed for other anti-atezolizumab antibodies with use of validated immunoassays.
- PK assay, provided that it does not cause undue hardship to the patient (e.g., the patient is in hospice care and not able to come in for a visit)

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

  Plasma samples for cobimetinib concentrations will be measured using validated liquid chromatography combined with tandem mass spectrometry method.
- Plasma samples for exploratory research on biomarkers
- Archival (the most recently obtained and sample collection date <5 years) or fresh tumor tissue sample consistent with the patient's diagnosis, collected at screening for determination of extended *BRAF*^{V600} mutation status and for exploratory research on biomarkers

  A representative 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 randomization.

Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Tumor tissue should be of good quality based on total and viable tumor content. Acceptable samples include those from resections, core-needle biopsies (at least three cores, embedded in a single paraffin block), or excisional, incisional, or forceps biopsies. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

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 unacceptable, a pretreatment tumor biopsy is required.

For archival samples, remaining tumor tissue blocks from randomized patients will be returned to the site upon request, after biomarker testing has been completed. Remaining tumor tissue blocks from patients who are not randomized into the study will be returned to the site no later than 3 months after eligibility determination. Slides will not be returned.

- An optional biopsy during treatment is requested on Day 15 (±5 days) of Cycle 1, provided the patient's disease is easily accessible and tumor biopsies can be performed with minimal risk and discomfort.
- Tumor tissue sample collected at the time of progression, if deemed clinically feasible by the investigator, for exploratory research on biomarkers

  Biopsies should be performed at the time of confirmed disease progression, preferably within 3 days after the last dose of study treatment. Acceptable samples include those from resections, core-needle biopsies (three cores preferred), excisional, incisional, or forceps biopsies.
- Exploratory biomarker research may include, but will not be limited to, analysis of S100, ctDNA, genes or gene signatures associated with tumor immunobiology, tumor immune profiles (e.g., CD8, MHC, and PD-L1), lymphocytes, TCR repertoire, or cytokines associated with T-cell activation and may involve DNA or RNA extraction, analysis of somatic mutations, and use of NGS.

NGS may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator can obtain results from these analyses in the form of an NGS report, which is available upon request directly from Foundation Medicine. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results may not be available for samples that do not meet testing criteria.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biologic samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma and serum samples collected for PK analysis or immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood samples collected for whole genome sequencing will be stored until they are no longer needed or until they are exhausted.
- Blood and tissue samples collected for biomarker analyses will be destroyed no later than 5 years after the final Clinical Study Report has been completed, or earlier depending on local regulations.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.7 Tumor Tissue Samples

A central laboratory will coordinate the sample collection of tissue samples for research-related testing at central laboratories or at the Sponsor. Instruction manuals and supply kits will be provided for all central laboratory assessments.

See the laboratory manual for additional details on tissue sample handling.

4.5.8 Electrocardiograms

A 12-lead ECG will be performed at screening for all patients, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at the same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

4.5.9 Left Ventricular Ejection Fraction

All patients will require evaluation of LVEF at screening, and only patients receiving cobimetinib (Arm A) will require subsequent evaluations of LVEF.

Evaluation of LVEF by ECHO or MUGA must be performed at the following timepoints:

- Screening
- Day 1 of Cycle 2 (±1 week)
- Day 1 of every three treatment cycles and starting at Cycle 5 and thereafter (±2 weeks)
- The treatment discontinuation visit evaluation of LVEF does not need to be performed at the 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.
- All patients restarting treatment with a dose reduction of cobimetinib because of a decrease in LVEF should have LVEF measurements taken after approximately 2 weeks, 4 weeks, 10 weeks, and 16 weeks, and then resume monitoring of LVEF every three treatment cycles.

Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF assessment. Evaluation of LVEF must be performed using the same method (ECHO or MUGA) for each patient. It is strongly encouraged that the same laboratory and operator perform ECHO or MUGA scans for each individual patient. Investigators must be aware of local institution regulations regarding repeat MUGA scans. The repeat administration of radioisotopes is limited in some nuclear medicine laboratories, and some patients in this study could require monitoring on four or more occasions.

4.5.10 Ophthalmologic Examination

All patients will require an ophthalmologic examination at screening, and only patients receiving cobimetinib (Arm A) will require subsequent ophthalmologic examinations.

Ophthalmologic examination must be performed at the following timepoints:

- Screening
- 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: The treatment discontinuation visit evaluation does not need to be performed if an evaluation has been performed within the last 12 weeks and there are no clinically significant findings and/or changes from baseline.

The objective of baseline ophthalmologic examination is to evaluate for evidence of retinal pathology that may be a risk factor for central serous retinopathy or RVO. Ophthalmologic examination must be performed by a qualified ophthalmologist. Risk factors for RVO include uncontrolled serum cholesterol, hypertriglyceridemia, hyperglycemia, hypertension, and glaucoma. See Sections 4.1.2.1 and 4.1.2.3.3 for inclusion and exclusion criteria.

Baseline and serial surveillance ophthalmologic examination will include visual acuity testing, intraocular pressure measurements by tonometry, slitlamp ophthalmoscopy, indirect ophthalmoscopy, and spectral–domain optical coherence tomography. Spectral-domain optical coherence tomography, if not available, may be substituted with time-domain optical coherence tomography.

4.5.11 Patient-Reported Outcomes

To more fully characterize disease burden and clinical benefit of atezolizumab and cobimetinib in patients with advanced melanoma, patient-reported outcome (PRO) data will be obtained through use of the following instruments: EORTC QLQ-C30 and the EQ-5D-5L. The questionnaires will be translated as appropriate into the local language. Reminders will be provided in order to maximize compliance. It is critical to rigorously collect the PRO data as they support the secondary and exploratory efficacy endpoints.

The EORTC QLQ-C30 and EQ-5D-5L will be completed on Day 1 of Cycle 1 and every 4 weeks thereafter, including prior to tumor assessments visits every 8 weeks. In addition, the questionnaires will be completed at the site for the treatment discontinuation visit and at unscheduled visits. All PRO questionnaires must be completed prior to any study assessment(s) that could bias a patient's responses.

Also, the PROs will be collected every 4 weeks for 6 months after the treatment discontinuation visit. PRO data collected post-study treatment will be used as a unique opportunity to quantify patients' post-treatment experience in terms of humanistic outcomes.

Patients will use an electronic device to capture all PRO data. Instructions to use the device and to complete the PRO questionnaires will be provided by site staff once the patient is randomized and before initiation of study treatment. The data will be transmitted to a centralized database maintained by the vendor and will be made available for access by appropriate study personnel at the site. In the event that the device or the Web-based system is not readily available, paper questionnaires formatted for use as backup data collection forms should be used to minimize missing data. Compliance with data collection will be documented throughout the study.

4.5.11.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a validated, reliable self-reported measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) that is commonly used in clinical trials involving patients with metastatic melanoma (Revicki et al. 2012; Schadendorf et al. 2015). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), GHS/QoL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The EORTC QLQ-C30 module takes approximately 10 minutes to complete. A 10-point change is defined as a clinically meaningful difference for the EORTC QLQ-C30 (Osoba et al. 1998) and has been used in other melanoma studies (Long et al. 2016; Shadendorf et al. 2015).

4.5.11.2 EQ-5D-5L

The EQ-5D-5L is a validated, self-reported health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale that measures health state. Published weighting systems allow for creation of a single composite score of a patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be utilized in this study for informing pharmacoeconomic evaluations.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Study termination or site closure
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.2 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Confirmed disease progression or loss of clinical benefit (see Section 3.1.2 for dosing beyond progression)
- Symptomatic deterioration attributed to disease progression, as determined by the investigator, after integrated assessment of radiographic data, biopsy results, and clinical status
- Intolerable toxicity related to any study drug
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Use of another non–protocol-specified anti-cancer therapy (see Section 4.4.2)
- Pregnancy
- Withdrawal of consent
- Investigator of Sponsor determines it is in the best interest of the patient (e.g., unwillingness to comply with study assessments that compromise their safety)
- Any adverse event that requires study treatment discontinuation per the guidelines in Section 5.1, Appendix 10, and Appendix 11.

- In cases where discontinuation of one study drug is required for toxicity, patients may continue on the remaining drug (Arm A only) per the guidelines in Section 5.1 and Appendix 10.

The primary reason for study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced.

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with cobimetinib and atezolizumab in completed and ongoing studies, and published data from similar molecules. The anticipated important safety risks for cobimetinib and atezolizumab are outlined below. Refer to the Cobimetinib Investigator's Brochure and Atezolizumab Investigator's Brochure for a complete summary of safety information.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification, and treatment interruption or discontinuation, are provided below. There are separate guidelines for the two different arms as the toxicities and management guidelines are distinct. Refer to the specific guidelines for each arm individually.

The risks associated with cobimetinib, atezolizumab, and pembrolizumab are detailed in Sections 5.1.1, 5.1.2, and 5.1.4, respectively.

Adverse events will be reported as described in Sections 5.2–5.6. In addition to the oversight provided by the Medical Monitor and drug safety personnel for this trial, an iDMC will monitor and evaluate patient safety throughout the study.

5.1.1 Risks Associated with Cobimetinib

The information related to the risks attributed to cobimetinib is based on safety data from Studies GO28141, NO25395, and MEK4592g. Additional clinical experience has been obtained through postmarketing experience and clinical studies with cobimetinib in combination with other agents. The safety data is also based on postmarketing experience. For further information regarding clinical safety, refer to the current Cobimetinib Investigator's Brochure.

5.1.1.1 Important Identified Risks Associated with Cobimetinib

5.1.1.1.1 Hemorrhage

Hemorrhage, including major hemorrhages, defined as symptomatic bleeding in a critical area or organ, can occur with cobimetinib. In clinical studies with cobimetinib, events of cerebral hemorrhage, gastrointestinal tract hemorrhage, reproductive tract hemorrhage, and hematuria have been reported.

In Study GO28141, Grade 1–4 hemorrhagic events were reported in 13.0% of patients treated with cobimetinib plus vemurafenib and in 7.3% of patients treated with placebo plus vemurafenib. The majority of hemorrhagic events were Grade 1 or 2 and non-serious. Grade 3 and 4 hemorrhage events were reported in 1.2% of patients receiving cobimetinib plus vemurafenib and in 0.8% of patients receiving placebo plus vemurafenib.

Caution should be used in patients with additional risk factors for bleeding, such as brain metastases, and/or in patients that use concomitant medications that increase the risk of bleeding (including antiplatelet or anticoagulant therapy).

Instructions for dose modification for hemorrhagic events are included in Appendix 10.

5.1.1.1.2 Serous Retinopathy

Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in patients treated with MEK-inhibitors, including cobimetinib (Flaherty et al. 2012). Manifestations of serous retinopathy include visual disturbances, findings of retinal detachment, and retinopathy. Serous retinopathy events may also be asymptomatic.

Serous retinopathy has been characterized in Study GO28141. The study incorporated prospective serial ophthalmologic examinations for all enrolled patients. Serous retinopathy was reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (25.5% vs. 2.8%, respectively), and approximately half the events were asymptomatic Grade 1 events. Few patients treated with cobimetinib plus vemurafenib experienced Grade $\geq$ 3 ocular events (2.8%); the majority of these events were managed with dose modification of both cobimetinib and vemurafenib.

To address serous retinopathy with cobimetinib treatment, all patients are required to undergo a baseline ophthalmologic examination to assess for history or evidence of retinal pathology that is considered to be a risk factor for or indicative of neurosensory retinal detachment, central serous chorioretinopathy, neovascular retinopathy, or retinopathy of prematurity. Patients will also undergo ophthalmologic examinations at specified timepoints throughout the study (see Appendix 1). Details regarding baseline and subsequent ophthalmologic examinations are provided in Section 4.5.10.

Guidelines for management of patients who develop Grade $\geq$ 2 visual disorders or retinopathy are provided in Appendix 10.

5.1.1.1.3 Left Ventricular Dysfunction

Decreases in LVEF from baseline have been reported in patients receiving cobimetinib. Left ventricular dysfunction may occur with signs and symptoms of cardiac failure, or reduction in LVEF events may be asymptomatic.

Left ventricular dysfunction has been characterized in Study GO28141. The study incorporated prospective serial LVEF evaluations in all patients. With active surveillance, measured Grade 2 or 3 reductions in LVEF were observed more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (8.5% vs. 3.7%, respectively). Of the patients treated with cobimetinib plus vemurafenib, 2 patients (0.8%) had symptomatic reduction in LVEF and the remaining patients were asymptomatic. Most LVEF reduction events in patients treated with cobimetinib plus vemurafenib (62%) improved or resolved with management according to dose modification guidelines (see Appendix 10).

5.1.1.1.4 Rhabdomyolysis and CPK Elevations

Elevations in CPK have been observed in patients who received cobimetinib monotherapy as well as when administered with other agents. The majority of CPK

elevations reported were asymptomatic, non-serious, and resolved with or without study drug interruption. One event of rhabdomyolysis was reported in the Phase III study GO28141 (cobimetinib plus vemurafenib), and rhabdomyolysis has been reported in the postmarketing experience.

In Study GO28141, elevated CPK was reported as an adverse event more frequently in patients treated with cobimetinib plus vemurafenib (32.4% all grades, 11.3% Grade ≥3 events) than placebo plus vemurafenib (8.1% all grades, 0% Grade ≥3 events).

CPK will be monitored at baseline and monthly during treatment or as clinically indicated. Instructions for Dose Modification for elevated CPK and rhabdomyolysis are included in Appendix 10.

5.1.1.1.5 Pneumonitis

Events of pneumonitis have been reported in cobimetinib clinical studies. Most reported events were considered to be non-serious and of low severity grade. In Study GO28141, pneumonitis events were reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (1.6% vs. 0.4%; all grades). There were no reported Grade ≥3 events in either study arm. Serious events were reported for 2 patients (0.8%) treated with cobimetinib plus vemurafenib. Refer to Appendix 10 for pneumonitis management guidelines.

5.1.1.2 Potential Risks Associated with Cobimetinib

5.1.1.2.1 Liver Laboratory Abnormalities and Severe Hepatoxicity (Grade ≥3)

Liver laboratory test abnormalities, including increases in ALT, AST, and ALP have been reported as adverse events and serious adverse events in patients treated with cobimetinib plus vemurafenib.

In the Phase III study GO28141, liver laboratory test abnormalities reported as Grade ≥3 adverse events occurred more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (20.5% vs. 15.1%, respectively).

Generally, elevations in liver laboratory tests were managed effectively with dose modification guidelines. In both study arms, the majority of Grade ≥ 3 liver laboratory test abnormalities resolved. Refer to Appendix 10 for hepatotoxicity management guidelines.

5.1.1.2.2 Impaired Female Fertility and Developmental Toxicity

There is a potential for effects on fertility and embryo–fetal toxicity based on results from nonclinical studies.

Although no dedicated fertility studies have been conducted with cobimetinib in animals, degenerative changes observed in reproductive tissues included increased apoptosis/necrosis of corpora lutea and seminal vesicle, epididymal and vaginal

epithelial cells in rats, and epididymal epithelial cells in dogs. These changes were reversible upon discontinuation of cobimetinib administration.

5.1.1.2.3 Teratogenicity and Developmental Toxicity

In a dedicated embryo–fetal toxicity study, cobimetinib produced fetal toxicity (resorptions and reductions in fetal weight) and teratogenicity (malformations of the great vessels and skull) at similar systemic exposures to those observed in patients administered the 60-mg dose.

5.1.1.3 Other Risks with Cobimetinib

5.1.1.3.1 Rash

In Study GO28141, combined rash events of all types and grades were reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (71.7% vs. 66.7%, respectively), although Grade ≥3 events (approximately 16% of patients) and types of rash reported were similar between study arms. Specific events in patients treated with cobimetinib plus vemurafenib included rash (39% all grades, 5.9% Grade≥3, and 1.6% serious adverse events) and maculopapular rash (14.6% all grades, 6.3% Grade≥3, and 1.2% serious adverse events).

Generally, Grade≥3 rash events were effectively managed with dose modification guidelines. In Study GO28141, approximately 90% of Grade ≥3 rash events resolved in both arms. Refer to Appendix 10 for rash management guidelines.

5.1.1.3.2 Gastrointestinal Toxicity

A range of gastrointestinal adverse events, including nausea, vomiting, and diarrhea, have been reported in all cobimetinib studies in adult patients with cancer.

In Study GO28141, diarrhea was the most common adverse event reported. Diarrhea events of all severity grades were reported in 59.9% of patients and Grade 3 or 4 events were reported in 6.5% of patients treated with cobimetinib plus vemurafenib versus 30.9% (Grade 3) and 0.8% (Grade 4) in the patients treated with placebo plus vemurafenib. No Grade 5 events of diarrhea have been reported. Serious adverse events of diarrhea were reported for 1.2% of patients treated with cobimetinib plus vemurafenib.

Nausea and vomiting have been reported in association with cobimetinib. Most nausea and vomiting events were considered to be non-serious and of low severity grade. In Study GO28141, nausea and vomiting events were reported more frequently in the active cobimetinib arm than the control arm (nausea, 41.3% vs. 25.2%; vomiting, 24.3% vs. 12.6%). However, of patients treated with cobimetinib plus vemurafenib, few experienced Grade 3 events (nausea, 0.8%; vomiting, 1.2%).

In the Phase I, single-agent study (MEK4592g), all grades of nausea and vomiting were both reported as 33.9%, with 0.9% reported for Grade ≥3 nausea and none reported for vomiting.

The combination of diarrhea, nausea, and vomiting has the potential to contribute to clinically significant volume depletion/dehydration from the combination of fluid losses with decreased oral intake. In the majority of cases, diarrhea has been effectively managed with anti-diarrheal agents and supportive care. Routine anti-emetic prophylaxis is not recommended. Refer to Appendix 10 for gastrointestinal toxicity management guidelines.

5.1.1.3.3 Hypersensitivity

There have been few reports of hypersensitivity and/or anaphylaxis in clinical trials with patients who have been exposed to cobimetinib monotherapy or cobimetinib when used with other agents. These have appeared to be isolated reports, and in some cases, occurred in patients with history of drug allergies. Thus, the relationship of cobimetinib to these events is unclear.

In Study GO28141, Grade 3 hypersensitivity events were reported for 3 patients in the cobimetinib plus vemurafenib arm compared with no such events in the placebo plus vemurafenib arm. All events required hospitalization and treatment with steroids.

Investigators should promptly evaluate and treat patients who are suspected of experiencing a hypersensitivity reaction.

5.1.2 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as IRRs and immune-*mediated* hepatitis, pneumonitis, myocarditis, colitis, pancreatitis, diabetes mellitus, hypophysitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, nephritis*, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab*. Refer to Section 6 of the Atezolizumab Investigator's Brochure and Appendix 11 of the protocol for a detailed description of anticipated safety risks for atezolizumab.

5.1.3 Anticipated Overlapping Adverse Events for Cobimetinib and Atezolizumab

Special consideration is given to areas of potential overlapping toxicity based on data from previous clinical experience with each compound individually or with other molecules. Potential overlapping toxicities of cobimetinib and atezolizumab include dermatologic reactions, ocular toxicity, hepatic toxicity, liver laboratory abnormalities, pneumonitis, and gastrointestinal toxicity. Refer to the Atezolizumab Investigator's Brochure, Cobimetinib Investigator's Brochure, and Appendix 10 for details regarding these adverse events. Patients treated with cobimetinib and atezolizumab should be closely monitored for evidence of overlapping and/or potentiation of these and any other acute toxicities. If any evidence of overlapping and/or potentiation of the below toxicities

is observed, patients should receive maximal supportive care as clinically indicated. Management guidelines for these potential overlapping toxicities are included in Appendix 10.

5.1.4 Risks Associated with Pembrolizumab

The overall safety profile for pembrolizumab is based on data from more than 2300 patients in clinical trials, including Phase III data for 1500 patients with metastatic melanoma. Some of the most serious adverse drug reactions in patients who received pembrolizumab are immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis, immune-mediated skin reactions, other immune-mediated adverse reactions, infusion-related reactions (IRRs), complications of allogeneic hematopoietic stem cell transplantation (HSCT), and embryo–fetal toxicity. The most frequently observed adverse drug reactions (≥20%) in patients who received pembrolizumab are fatigue, musculoskeletal pain, pyrexia, decreased appetite, dyspnea, pruritus, rash, constipation, diarrhea, and nausea.

Of note, this is not an exhaustive list of risks associated with pembrolizumab. Please refer to the pembrolizumab prescribing information for complete information regarding clinical safety.

5.1.5 Management of Patients Who Experience Specific Adverse Events

5.1.5.1 Cobimetinib Dose Modifications

General dose modification for cobimetinib is provided in Table 3. Dose modification for specific adverse events is provided in Appendix 10. After dose reduction, consideration may be given to allow for dose escalation of cobimetinib by a maximum of one dose level (20 mg) increments following resolution of the adverse event that resulted in dose modification, provided there are no safety concerns.

Table 3 Recommended Cobimetinib Dose Modifications

Grade (NCI CTCAE) [a]	Recommended Cobimetinib Dose
Grade 1 or Grade 2 (tolerable)	No dose reduction. Maintain cobimetinib at the same dose of 60 mg QD (3 tablets).
Grade 2 (intolerable) or Grade 3 or 4 (any)	
First appearance	Interrupt treatment until Grade ≤ 1: restart treatment at 40 mg QD (2 tablets).
Second appearance	Interrupt treatment until Grade ≤ 1: restart treatment at 20 mg QD (1 tablet).
Third appearance	Consider permanent discontinuation.

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QD = once a day.

5.1.5.2 Atezolizumab and Pembrolizumab Dose Modifications

There will be no dose reduction for atezolizumab or pembrolizumab in this study.

5.1.5.3 Management of Cobimetinib- and Atezolizumab-Specific Adverse Events (Arm A)

Toxicities associated or possibly associated with cobimetinib plus atezolizumab treatment should be managed according to standard medical practice.

For management of cobimetinib- and atezolizumab-specific toxicities, including IRRs, gastrointestinal toxicity, dermatologic toxicity, hepatotoxicity, pulmonary toxicity, potential eye toxicity, reductions in LVEF from baseline, rhabdomyolysis, elevated CPK, and hemorrhage, see Appendix 10.

Guidelines for management of patients who experience atezolizumab-associated or possibly associated adverse events, including infusion-related reactions and immune-*mediated* reactions (e.g., pulmonary, hepatic, gastrointestinal, endocrine, ocular, myocarditis, pancreatic, dermatologic, neurologic, meningoencephalitis, and renal events) are provided in Appendix 11.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7) and based on the following observations:

  Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)

  Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

  Hepatitis, including AST or ALT $>10\times$ ULN

  Significant liver toxicity

- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Systemic lupus erythematosus

- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine-release syndrome *(CRS)*, influenza-like illness, *HLH, and MAS*
- Nephritis
- Ocular toxicities

  Uveitis or retinitis

  RVO

  Serous retinopathy, including events of retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment, and central serous chorioretinopathy
- Myositis
- Cardiac disorders for the following events

  Grade ≥2 cardiac disorders, including atrial fibrillation, myocarditis, and pericarditis

  Symptomatic heart failure or Grade ≥3 reduction in LVEF
- Vasculitis
- Myopathies, including rhabdomyolysis or Grade ≥3 CPK elevation
- Grade ≥ 3 hemorrhage or any-grade cerebral hemorrhage
- Grade ≥3 rash
- Grade ≥3 diarrhea

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive

procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events, serious adverse events, and adverse events of special interest will be reported until 135 days after the last dose of study drug, or until a new systemic anti-cancer therapy is initiated, whichever occurs first.

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

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation time points. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

Table 5 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions *and Cytokine-Release Syndrome*

There may be significant overlap in signs and symptoms of IRRs and CRS. While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, HLH, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured on the Adverse Event eCRF *as a diagnosis (e.g., "infusion-related reaction" or "cytokine-release syndrome").* Avoid ambiguous terms such as "systemic reaction." *Cases of late-onset CRS should be reported as "cytokine-release syndrome" on the Adverse Event eCRF.* Associated signs and symptoms *of an IRR* should be recorded on the dedicated Infusion-Related Reaction eCRF.

If a patient experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with associated signs and symptoms of an IRR also recorded separately on the dedicated Infusion-Related Reaction eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 11.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5× ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of melanoma should be recorded on the Death during Adverse Event Reporting Period Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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

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

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

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

5.3.5.10 Lack of Efficacy or Worsening of Melanoma

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

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

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

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

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

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

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data (i.e., EORTC QLQ-C30 and EQ-5D-5L) by the Sponsor, and safety analyses will not be performed using PRO data. Although sites are not expected to review the PRO data, it is possible that an investigator could become aware of PRO data that may be indicative of an adverse event. Under these circumstances, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Overdoses, medication errors, drug abuse, or drug misuse (see Section 5.4.4 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board or Ethics Committee (IRB/EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted], M.D., Ph.D.

Telephone No.: [redacted]

Email: [redacted]

24-HOUR MEDICAL COVERAGE (Roche Emergency Medical Call Center Help Desk): To reach the Roche Emergency Medical Call Center Help Desk, please refer to your Regulatory binder for country-specific access numbers.

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide

medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators (see "Protocol Administrative and Contact Information and List of Investigators").

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, all adverse events, serious adverse events, and adverse events of special interest will be reported until 135 days after the last dose of study drug, or until a new systemic anti-cancer therapy is initiated, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur $>$90 days after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab or pembrolizumab or within 3 months after the last dose of cobimetinib. A Clinical Trial Pregnancy Reporting Form should be completed and

submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 3 months after the last dose of cobimetinib. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to cobimetinib. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.}

Special situations are not in themselves adverse events, but may result in adverse events. All special situations associated with cobimetinib and atezolizumab regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

For cobimetinib, atezolizumab, and pembrolizumab, each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For cobimetinib and atezolizumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.

- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 135 days for all adverse events, serious adverse events, and adverse events of special interest after the last dose of study drug, or until a new systemic anti-cancer therapy is initiated, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF or Post-Study Reporting of Death by Public Records eCRF, as appropriate. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior study drug treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious

Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- Cobimetinib Investigator's Brochure
- Atezolizumab Investigator's Brochure
- Local prescribing information for pembrolizumab

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a Phase III, randomized, open-label study designed to evaluate the efficacy and safety of cobimetinib plus atezolizumab compared with pembrolizumab in patients with previously untreated *BRAF*^{V600} wild-type melanoma. Please refer to the Statistical Analysis Plan for additional details.

6.1 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.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, eligibility violations, and patient disposition will be summarized for randomized patients by treatment arm. Study treatment administration will be summarized by treatment arm for all treated patients.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables, stratification factors, and other baseline and disease characteristics will be summarized by treatment group using descriptive statistics.

6.4 EFFICACY ANALYSES

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.

6.4.1 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. 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 (Brookmeyer and Crowley 1982). 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.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are listed in Section 2 (see Table 1).

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. The stratification factors used for analysis will be the same as the randomization stratification factors. 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).

Objective response will be presented as ORR, 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 intent-to-treat population with measurable disease at baseline. Objective response is defined as a complete response or partial response on two consecutive occasions $\geq$ 4 weeks apart, as determined by the IRC and investigator using RECIST v1.1. A 95% Clopper-Pearson CI will be calculated for the ORR. The difference in ORR between treatment arms will be tested using the stratified Cochrane-Mantel-Haenszel test.

PFS, as determined by the investigator according to RECIST v1.1, will be analyzed using the same methods as described for PFS in Section 6.4.1.

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

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 and 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.

The GHS/HRQoL will be scored according to the EORTC scoring manual as listed in Section 6.4.3. The change from baseline in GHS/HRQoL scores at each timepoint by treatment arm during treatment, as measured by the EORTC QLQ-C30 GHS/HRQoL scale, will be analyzed for all randomized patients who had a baseline and one or more post-baseline assessments.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are listed in Section 2 (see Table 1).

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

Summary statistics (mean, standard deviation, median, 25th and 75th percentiles, and range) and the mean change from baseline of linear-transformed scores will be calculated for all subscales of the EORTC QLQ-C30 according to the EORTC scoring manual guideline at each assessment timepoint for each arm, including progression, treatment discontinuation, and post-study treatment. The mean (and 95% CI) and median of the absolute scores and the change from baseline will be reported for interval and continuous variables. Completion and compliance rates will be summarized at each timepoint by treatment arm. Compliance with PRO assessments will be calculated as the number of forms received divided by the number expected at every assessment. Only patients with a non-missing baseline assessment and at least one non-missing post-baseline assessment will be included in the analyses.

All of the scales and single-item measures range in score from 0 to 100. A high score for a functional scale represents a high, healthy level of functioning, a high score for the GHS/QoL represents a high QoL, but a high score for a symptom scale or item represents a high level of symptomatology and problems.

A longitudinal analysis will be conducted to estimate the effect difference on PRO repeated responses over the time on study treatment and between the treatment arms, and mixed models on a set of covariates (baseline domain score, patient demographics, and clinical variables) will be conducted. The change from baseline at subsequent cycles will be presented by treatment arm and will include LS mean, the difference in LS

mean between two treatment arms, and 95% CIs for the differences. The standard error will also be calculated for each LS mean.

Patients' post-baseline PRO scores will be classified as being "improved," "stable," or "worsened" according to a $\geq$10-point change in the GHS/QoL, functional, and symptom scores of the EORTC QLQ-C30. The number and proportion of patients who improve, remain stable, or worsen from baseline will be summarized by treatment group and study visit, at each timepoint, including progression, treatment discontinuation, and post-study treatment.

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

Relevant subgroup and sensitivity analyses will be performed and will be detailed in the Statistical Analysis Plan.

6.5 SAFETY ANALYSES

The safety analyses will include all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs, and study treatment exposure, presented by treatment arm.

Verbatim description of adverse events will be summarized by mapped terms and appropriate thesaurus levels and graded according to NCI CTCAE v4.0. All adverse events 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, severe adverse events (Grade $\geq$3), adverse events of special interest, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. The proportion of patients who experience at least one adverse event will be reported by toxicity term and treatment arm.

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

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

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

6.6 PHARMACOKINETIC 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. In addition, atezolizumab and cobimetinib PK samples will be used to conduct exposure–response analyses for efficacy and safety.

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

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analyses for atezolizumab will include patients from Arm A with any ADA assessment, with patients grouped by disease status (metastatic or locally advanced and unresectable) and arm.

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) and arm. 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, PK, and biomarker endpoints may be analyzed and reported using descriptive statistics.

6.8 BIOMARKER ANALYSES

Efficacy will be explored in biomarker subgroups defined by PD-L1 expression, CD8 T-cell density, and other significant biomarkers at the conclusion of this study.

NGS data will 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.

6.9 INTERIM ANALYSES

6.9.1 Planned Interim Analysis of the Primary Efficacy Endpoint

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

6.9.2 Interim Efficacy Analyses of the Secondary Efficacy Endpoint

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. 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. Table 6 summarizes the assumptions and characteristics of the interim and final analyses for OS.

Table 6 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.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

PRO data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Upon randomization, patients will use an electronic device to capture PRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR, Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure method. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data.

Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format.

In case of electronic device failure or patient refusal to use the electronic device, a paper backup solution will be implemented.

7.4 SOURCE DATA DOCUMENTATION

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

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

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for

the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor’s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child’s Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports

or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This study is sponsored by F. Hoffmann-La Roche Ltd. Approximately 160 study centers will participate in this study globally and enroll a total of approximately 450 patients. The Sponsor will provide clinical operations oversight, data management support, and medical monitoring.

An IWRS will be used to manage site drug supply and to randomize patients to study drug. For patients not previously tested for tumor mutational status, testing will be performed at screening. Plasma and serum will be sent to a central laboratory for analysis and sample storage. Routine sample analysis will be performed by an accredited external vendor or the center's local laboratory; central and local laboratory ranges will be collected.

An iDMC will be employed to monitor and evaluate patient safety throughout the study. Tumor response will be evaluated by an IRC as the primary efficacy endpoint in this study.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

American Cancer Society. Cancer facts & figures 2016. Atlanta: American Cancer Society; 2016.

Ascierto PA. Ipilimumab in the treatment of metastatic melanoma: a summary of recent studies. Tumori 2013;99:302e–5e.

Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199–206.

Bedikian AY, Millward M, Pehamberger H, et al. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. J Clin Oncol 2006;24:4738–45.

Bendell J, Kim TW, Chee CE, et al. LBA-01: Safety and efficacy of cobimetinib and atezolizumab in a phase Ib study of metastatic colorectal cancer [abstract]. Ann Oncol 2016;27(suppl 2):ii140.

Boni A, Cogdill AP, Dang P, et al. Selective BRAFV600E inhibition enhances T-cell recognition of melanoma without affecting lymphocytes function. Cancer Res 2010;70:5213–9.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29–41.

Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.

Cancer Genome Atlas Network. Genomic classification of cutaneous melanoma. Cell 2015;161:1681–96. doi: 10.1016/j.cell.2015.05.044.

Carbognin L, Pilotto S, Milella M, et al. Differential activity of nivolumab, pembrolizumab and MPDL3280A according to the tumor expression of programmed death–ligand-1 (PD-L1): sensitivity analysis of trials in melanoma, lung and genitourinary cancers. PLoS One 2015;10:e0130142.

Chang LH, Pan SL, Lai CY, et al. Activated PAR-2 regulates pancreatic cancer progression through ILK/HIF-α-induced TGF-α expression and MEK/VEGF-A-mediated angiogenesis. Am J Pathol 2013;183:566–75.

Chapman PB, Einhorn LH, Meyers ML, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. J Clin Oncol 1999;17:2745–51.

Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507–16.

Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. Nat Rev Immunol 2013;13:227–42. doi: 10.1038/nri3405. Epub: 8 March 2013. Erratum in: Nat Rev Immunol 2013;13:542.

Ciuffreda L, Del Bufalo D, Desideri M, et al. Growth-inhibitory and antiangiogenic activity of the MEK inhibitor PD0325901 in malignant melanoma with or without BRAF mutations. Neoplasia 2009;11:720–31.

Cornish D, Holterhues C, van de Poll-Franse LV, et al. A systematic review of health-related quality of life in cutaneous melanoma. Ann Oncol 2009;20(Suppl 6):vi51–8.

Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med 2005;353:2135–47.

Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature 2002;417:949–54.

Diem S, Kasenda B, Martin-Liberal J, et al. Prognostic score for patients with advanced melanoma treated with ipilimumab. Eur J Cancer 2015;51:2785–91.

Diepgen TL, Mahler V. The epidemiology of skin cancer. Br J Dermatol 2002;146 (Suppl 61):1–6.

Di Leo A, Bleiberg H, Buyse M. Overall survival is not a realistic end point for clinical trials of new drugs in advanced solid tumors: a critical assessment based on recently reported phase III trials in colorectal and breast cancer. J Clin Oncol 2003;21:2045–7.

Dummer R, Hauschild A, Lindenblatt N, et al., on behalf of the ESMO Guidelines Committee. Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26(Suppl 5):v126–32.

Dummer R, Schadendorf D, Ascierto PA, et al. Results of NEMO: a phase III trial of binimetinib vs dacarbazine in NRAS-mutant cutaneous melanoma [abstract]. J Clin Oncol 2016;34(Suppl 9500);9500.

Ebert PJ, Cheung J, Yang Y, et al. MAP kinase inhibition promotes T cell and anti-tumor activity in combination with PD-L1 checkpoint blockade. Immunity 2016;44:609–21.

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

European Medicines Agency, Oncology Working Group. Guideline on the evaluation of anticancer medicinal products in man [resource on the Internet]. 2012 [cited: 5 April 2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137128.pdf.

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374–403.

Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer 1999;35:939−41.

Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012;367:107–14.

Frederick DT, Piris A, Cogdill AP, et al. BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. Clin Cancer Res 2013;19:1225–31.

Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192:1027–34.

Garbe C, Leiter U. Melanoma epidemiology and trends. Clin Dermatol 2009;27:3–9.

Greenwood M. The natural duration of cancer. Reports on Public Health and Medical Subjects 1926;33:1–26. Her Majesty's Stationery Office, London.

Haass NK, Sproesser K, Nguyen TK, et al. The mitogen-activated protein/extracellular signal-regulated kinase kinase inhibitor AZD6244 (ARRY-142886) induces growth arrest in melanoma cells and tumor regression when combined with docetaxel. Clin Cancer Res 2008;14:230–9.

Hales RK, Banchereau J, Ribas A, et al. Assessing oncologic benefit in clinical trials of immunotherapy agents. Ann Oncol 2010;21:1944–51.

Hauschild A, Chapman PB, Robert C, et al. Impact of key prognostic factors on long-term overall survival in patients with BRAF V600-mutated metastatic melanoma treated with vemurafenib in the BRIM-3 study [abstract]. EADO 2016;P-057.

Hauschild A, Grobb JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358–65.

Hauschild A, Grobb JJ, Demidov LV, et al. 1092PD: An update on overall survival (OS) and follow-on therapies in BREAK-3, a phase III, randomized trial: dabrafenib (D) vs. dacarbazine (DTIC) in patients (PTS) with BRAF V600E mutation-positive metastatic melanoma (MM) [abstract]. Ann Oncol 2014;25 (Suppl 4): iv378.

Hauschild A, Grobb J, Demidov L, et al. An update on overall survival (OS) and follow-on therapies in BREAK, a phase II randomized trial:dabrafenib (D) dacarbazine (DTIC) in patients (PTS) with BRAF V600E [abstract]. Ann Oncol 2015;25 (1 Supp): 1092PD.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.

Hodi FS, Chesney J, Pavlick AC, et al. Combined nivolimuab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol 2016a:17:1558–68.

Hodi FS, Kluger H, Sznol M, et al. Abstract CT001: durable, long-term survival in previously treated patients with advanced melanoma who received nivolumab monotherapy in a phase I trial [abstract]. Cancer Res 2016b:76(Suppl):CT001.

Hodi FS, Lawrence D, Hamid O et al. Clinical activity of the PD-L1 inhibitor MPDL3280A in patients with metastatic melanoma: updated phase 1 data. Pigment Cell Melanoma Res 2014;27:1169–1241.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Hu-Lieskovan S, Mok S, Homet Moreno B, et al. Improved antitumor activity of immunotherapy with BRAF and MEK inhibitors in BRAF(V600E) melanoma. Sci Transl Med 2015;7:279ra41.

Ives NJ, Stowe RL, Lorigan P, et al. Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2621 patients. J Clin Oncol 2007;25:5426–34.

Jakob JA, Bassett RL Jr, Ng CS, et al. *NRAS* mutation status is an independent prognostic factor in metastatic melanoma. Cancer 2012;118:4014–23.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27.

Johnson GL, Lapadat R. Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. Science 2002;298:1911–2.

Kakavand H, Wilmott JS, Menzies AM, et al. PD-L1 expression and tumor-infiltrating lymphocytes define different subsets of MAPK inhibitor-treated melanoma patients. Clin Cancer Res 2015;21:3140–8.

Kelderman S, Heemskerk B, van Tinteren H, et al. Lactate dehydrogenase as a selection criterion for ipilimumab treatment in metastatic melanoma. Cancer Immunol Immunother 2014;63:449–58.

KEYTRUDA® (pembrolizumab) U.S. Package Insert, Merck & Co., Whitehouse Station, New Jersey.

Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.

Lee JH, Choi JW, Kim YS. Frequencies of BRAF and NRAS mutations are different in different histologic subtypes and sites of origins of cutaneous melanoma: a meta-analysis. Br J Dermatol 2011;164:776–84.

Liu I, Mayes PA, Eastman S, et al. The BRAF and MEK inhibitors dabrafenib and trametinib: effects on immune function and combination with immunomodulatory antibodies targeting PD-1, PD-L1, and CTLA-4. Clin Cancer Res 2015;21:1639–51.

Loi S, Dushyanthen S, Beavis PA, et al. RAS/MAPK activation is associated with reduced tumor-infiltrating lymphocytes in triple-negative breast cancer: therapeutic cooperation between MEK and PD-1/PD-L1 immune checkpoint inhibitors. Clin Cancer Res 2016;22:1499–509.

Long GV, Atkinson V, Ascierto PC, et al. Effect of nivolumab on health-related quality of life in patients with treatment-naïve advanced melanoma: results from the phase III CheckMate 066 study. Ann Onco 2016:27:1940–6.

Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014;371:1877–88.

Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet 2015;386:444–51.

McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol 2014; 15:323–32.

Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol 2000;18:158–66.

Miller WH, Kim TM, Lee CB, et al. Atezolizumab plus cobimetinib in metastatic melanoma: updated safety and clinical activity [abstract]. J Clin Oncol 2017;35:suppl;abstr 3057.

Mohan S, Vander Broek R, Shah S, et al. MEK inhibitor PD-0325901 overcomes resistance to PI3K/mTOR inhibitor PF-5212384 and potentiates antitumor effects in human head and neck squamous cell carcinoma. Clin Cancer Res 2015;21:3946–56.

[NCCN] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Melanoma, Version 3 [resource on the Internet]. 2016 [cited 10 April 2017]. Available from: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

OPDIVO® (nivolumab) U.S. Package Insert, Bristol-Meyers Squibb, Princeton, New Jersey.

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

Phan VT, Wu X, Cheng JH, et al. Oncogenic RAS pathway activation promotes resistance to anti-VEGF therapy through G-CSF-induced neutrophil recruitment. Proc Natl Acad Sci USA 2013;110:6079–84.

Revicki DA, van den Eertwegh AJ, Lorigan P, et al. Health related quality of life outcomes for unresectable stage III or IV melanoma patients receiving ipilimumab treatment. Health Qual Life Outcomes 2012;10:66.

Richman J, Martin-Liberal J, Diem S, et al. BRAF and MEK inhibition for the treatment of advanced BRAF mutant melanoma. Expert Opin Pharmacother 2015;16:1285–97.

Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015a;372:320–30.

Robert C, Ribas A, Hamid O, et al. Three-year overall survival for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001 [abstract]. J Clin Oncol 2016;34(Suppl):9503.

Robert C, Schachter J, Long G, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015b;372:2521–32.

Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517–26.

Roberts PJ, Der CJ. Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. Oncogene 2007;26:3291–310.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Schachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival analysis of KEYNOTE-006 [abstract]. J Clin Oncol 2016;34(Suppl):9504.

Schadendorf D, Amonkar MM, Stroyakovskiy D, et al. Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma. Eur J Cancer 2015;51:833–40.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30.

Solit DB, Garraway LA, Pratilas CA, et al. BRAF mutation predicts sensitivity to MEK inhibition. Nature 2006;439:358–62.

Wang X, Teng F, Kong L, et al. PD-L1 expression in human cancers and its association with clinical outcomes. Onco Targets Ther 2016;9:5023–39.

Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015;16: 375–84.

Wilmott JS, Long GV, Howle JR, et al. Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma. Clin Cancer Res 2012;18:1386–94.

Zhu Z, Liu W, Gotlieb V. The rapidly evolving therapies for advanced melanoma–towards immunotherapy, molecular targeted therapy, and beyond. Crit Rev Oncol Hematol 2016;99:91–9.

Appendix 1
Schedule of Activities

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 2								
PK sample and ADA sample for atezolizumab		See Appendix 2								
Chemistry panel [k]	x	x		x		x		x		

Appendix 1
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 2						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 1
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 1
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 1
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 1
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 1
Schedule of Activities (cont.)

Table 2 Arm B: Pembrolizumab Schedule of Activities (21-Day Cycles) (cont.)

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 1
Schedule of Activities (cont.)

Table 2 Arm B: Pembrolizumab Schedule of Activities (21-Day Cycles) (cont.)

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 2						
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).

Appendix 1
Schedule of Activities (cont.)

Table 2 Arm B: Pembrolizumab Schedule of Activities (21-Day Cycles) (cont.)

[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 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).

Appendix 1
Schedule of Activities (cont.)

Table 2 Arm B: Pembrolizumab Schedule of Activities (21-Day Cycles) (cont.)

[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.

Appendix 1
Schedule of Activities (cont.)

Table 2 Arm B: Pembrolizumab Schedule of Activities (21-Day Cycles) (cont.)

[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 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 2
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 3
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 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 $\leq$ 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 $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 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.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (cont.)

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.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (cont.)

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

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (cont.)

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.

Appendix 4
Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immune-modified response criteria have been developed to incorporate new lesions into the assessment of total tumor burden and allow radiographic progression to be confirmed at a subsequent assessment. Immune-modified Response Evaluation Criteria in Solid Tumors (RECIST), as described within this appendix, were adapted from RECIST, Version 1.1 (v1.1) (Eisenhauer et al. 2009), in the same manner that immune-related response criteria were adapted from WHO criteria (Wolchok et al. 2009) and RECIST v1.0 (Nishino et al. 2014). When not otherwise specified, RECIST v1.1 conventions will apply. Differences between immune-modified RECIST and RECIST v1.1 are summarized in Table 1.

Table 1 Comparison of RECIST v1.1 and Immune-Modified RECIST

	RECIST v1.1	Immune-Modified RECIST
Measurable new lesions	Always represent progression	Incorporated into the total tumor burden [a] and followed
Non-measurable new lesions	Always represent progression	Do not represent progression, but preclude CR
Non-target lesions	Contribute to defining CR, PR, SD, and PD	Contribute to defining CR only
CR	Disappearance of all lesions	Disappearance of all lesions
PR	≥30% decrease in sum of diameters of target lesions, in the absence of CR, new lesions, and unequivocal progression in non-target lesions	≥30% decrease in tumor burden, [a] in the absence of CR
PD	≥20% increase in sum of diameters of target lesions, unequivocal progression in non-target lesions, and/or appearance of new lesions	≥20% increase in tumor burden [a]
SD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Tumor burden is the sum of diameters of target lesions and measurable new lesions.

Appendix 4
Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST) (cont.)

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 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 $\leq$ 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 $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 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," "New Lesions," and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with short axis $\geq$ 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.

Appendix 4
Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST) (cont.)

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 $\geq$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.

Appendix 4
Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST) (cont.)

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.

<u>ASSESSMENT OF TUMOR BURDEN</u>

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.

Appendix 4
Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST) (cont.)

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").

Appendix 4
Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST) (cont.)

NEW LESIONS

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST (e.g., non–lymph node lesions must be ≥ 10 mm on the longest diameter; new lymph nodes must be ≥ 15 mm on the short axis [see note below]). All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden that is performed as part of the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the calculation of tumor burden and thus will not affect overall tumor response evaluation. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint can be included in the tumor response evaluation from that point on, if the maximum number of measurable new lesions has not been reached.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is ≥ 15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is ≥ 10 mm and < 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is < 10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is ≥ 15 mm.

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 as a measure of tumor burden. At each subsequent tumor assessment, 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 plus measurable new lesions (up to five new lesions, with a maximum of two new lesions per organ) that have emerged after baseline. Hence, each net percentage change in tumor burden per assessment accounts for the size and growth kinetics of both old lesions and new lesions as they appear.

Measuring Lymph Nodes

If at first appearance the short axis of a new lymph node lesion is ≥ 15 mm, it will be considered a measurable new lesion and may be included in the sum of the diameters. If the new lymph node lesion is included in the sum of diameters, it will continue to be

measured and included in the sum of diameters at subsequent timepoints, even if the short axis decreases to < 15 mm (or even < 10 mm). However, if it subsequently decreases to < 10 mm and all other lesions are no longer detectable or have also decreased to a short axis of < 10 mm (if lymph nodes), a response assessment of complete response may be assigned.

Lymph nodes 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 in the sum of diameters, the sum 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 and up to five measurable new lesions (lymph node and non–lymph node) should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes 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 AND NON-MEASURABLE NEW LESIONS

Measurements are not required for non-target lesions or non-measurable new lesions. Non-target lesions should be noted at baseline, and non-measurable new lesions should be noted at the time of identification. At subsequent evaluations, non-target lesions and non-measurable new lesions will be categorized as "present" or "absent."

After baseline, changes in non-target lesions or non-measurable new lesions (or measurable new lesions in excess of five total or two per organ) will contribute only in the assessment of complete response (i.e., a complete response is attained only with the complete disappearance of all tumor lesions, including non-target lesions and non-measurable new lesions) and will not be used to assess progressive disease.

RESPONSE CRITERIA

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

- Complete response (CR): Disappearance of all 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 plus measurable new lesions (up to a maximum of five total or two per organ), 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 all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), 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.

  New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is factored into the sum of the diameters, which is used to determine the overall immune-modified RECIST tumor response.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 2 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Appendix 4
Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST) (cont.)

Table 2 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions and Measurable New Lesions [a]	Non-Target Lesions and Non-Measurable New Lesions [b]	Overall Response
CR	Absent	CR
CR	Present or not all evaluated	PR
PR	Any	PR
SD	Any	SD
Not all evaluated	Any	NE
PD	Any	PD

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

[a] Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden, in addition to the target lesions identified at baseline.

[b] Also includes measurable new lesions in excess of five total or two per organ.

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 or measurable new 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 well as new lesions, as shown in Table 2.

Appendix 4
Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST) (cont.)

REFERENCES

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.

Nishino M, Gargano M, Suda M, et al. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab? J Immunother Can 2014;2:17.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res 2009;15:7412–20.

Appendix 5
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited self-care; confined to a bed or chair >50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 6
Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias for whom the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty about autoimmune exclusions. *Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent.*

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus, Type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cirrhosis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix 7
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Maintain an adequate airway.
3. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.

Continue to observe the patient and document observations.

Appendix 8
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|

Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|

Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4

Please go on to the next page

Appendix 8
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (cont.)

During the past week:	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 9
EuroQol 5-Dimension, 5-Level Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

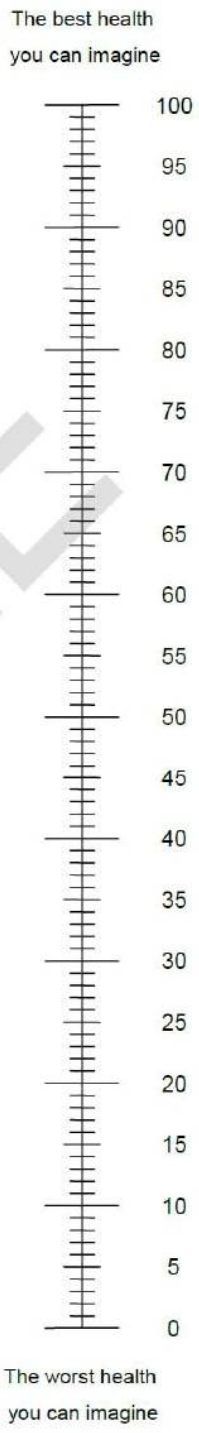
ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

Appendix 9
EuroQol 5-Dimension, 5-Level Questionnaire (cont.)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A)

Note: For information regarding management of atezolizumab-associated adverse events, please refer to Appendix 11.

Guidelines for Management of Cobimetinib plus Atezolizumab Adverse Events

Event	Action to Be Taken
General guidance for dose modifications and treatment delays and discontinuation	• There will be no dose modifications for atezolizumab. • If atezolizumab is withheld and corticosteroids are initiated for an atezolizumab-related toxicity, corticosteroids must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. [a, b, c] The dose of cobimetinib can be reduced by 20 mg (one dose level) up to two times (i.e., from 60 mg to 40 mg and then from 40 mg to 20 mg). If further dose reduction is indicated after two dose reductions, the patient must discontinue cobimetinib but may continue treatment with atezolizumab at the investigator's discretion. • If cobimetinib is withheld for > 28 days because of toxicity, the patient should be discontinued from cobimetinib, unless resumption of treatment is approved by the Medical Monitor after discussion with the investigator. • After dose reduction, consideration may be given to allow for dose escalation of cobimetinib by a maximum of one dose level following resolution of the adverse event that resulted in dose modification, provided there are no safety concerns. • If atezolizumab is withheld for >12 weeks because of toxicity, the patient should be discontinued from atezolizumab, unless resumption of treatment is approved by the Medical Monitor after discussion with the investigator.
IRRs, *CRS,* anaphylaxis, and hypersensitivity reaction	• Guidelines for management of IRRs *and CRS* are provided in the Atezolizumab Investigator's Brochure and. Appendix 11 • For anaphylaxis precautions, see Appendix 7. • For severe hypersensitivity reactions, permanently discontinue all study treatment.

CRS = cytokine-release syndrome; IRR = infusion-related reaction.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 105 days to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A) (cont.)

GASTROINTESTINAL TOXICITY

Diarrhea and colitis have been associated with the administration of cobimetinib plus atezolizumab (see Section 5.1.1.3.2).

See Table 1 for guidelines on how to manage gastrointestinal toxicity in patients treated with cobimetinib plus atezolizumab.

Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A) (cont.)

Table 1 Guidelines for Managing Atezolizumab- and Cobimetinib-Associated Gastrointestinal Toxicity

Event	Action to Be Taken
Gastrointestinal toxicity	
Gastrointestinal events: general guidance	• All events of diarrhea or colitis should be thoroughly evaluated for more common etiologies other than drug-induced effects. • For events of significant duration or severity or associated with signs of systemic inflammation or acute-phase reactants, check for immune-*mediated* colitis. • Administer anti-diarrheal agents and other maximal supportive care per institutional guidelines, such as at the first report of watery diarrhea or loose stool, initiate maximal anti-diarrheal supportive care (Lomotil® and loperamide). • Suggested regimen: – Loperamide: Initiate dose with 4 mg, then 4 mg/6 hr around the clock, alternating with Lomotil.® – Lomotil® (diphenoxylate and atropine): Dispense 2 tablets (diphenoxylate 5 mg, atropine 0.05 mg) every 6 hours around the clock. – Continue Lomotil® and loperamide until no loose stools for 24 hours. – If Grade ≤2 diarrhea persists after 48 hours of total treatment with Lomotil® and loperamide, consider second-line agents (e.g., octreotide, budesonide, tincture of opium). • Oral supplementation: – Initiate oral supplementation of potassium and/or magnesium if serum levels are < LLN. – Consider oral rehydration therapy (e.g., Pedialyte®) for Grade ≥1 diarrhea or vomiting. • Dietary modifications: – Stop all lactose-containing products and instruct patient to eat small meals. – Suggest the BRAT diet (banana, rice, apples, toast) diet, without fiber (other vegetables and fruits). – Encourage adequate hydration with salt-containing liquids, such as broth or Gatorade®.
Diarrhea, Grade 1 or Grade 2 (tolerable)	• Continue atezolizumab and cobimetinib. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis if appropriate. • Initiate supportive care and monitor patient closely.

Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A) (cont.)

Table 1 Guidelines for Managing Atezolizumab- and Cobimetinib-Associated Gastrointestinal Toxicity (cont.)

Event	Action to Be Taken
Diarrhea, Grade 2 (intolerable) or Grade 3	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Investigate etiology and refer patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with the dose reduced by one level. If not, permanently discontinue cobimetinib.
Diarrhea, Grade 4	• Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor. [c] • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Rule out bowel perforation. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.
Colitis, Grade 1	• Continue atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy if symptoms persist for > 7 days.
Colitis, Grade 2	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with the dose reduced by one level. If not, permanently discontinue cobimetinib.

Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A) (cont.)

Table 1 Guidelines for Managing Atezolizumab- and Cobimetinib-Associated Gastrointestinal Toxicity (cont.)

Event	Action to Be Taken
Colitis, Grade 3	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.
Colitis, Grade 4	• Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor. [c] • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 105 days to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A) (cont.)

HEPATOTOXICITY

Hepatoxicity has been associated with the administration of atezolizumab and cobimetinib (see Section 5.1.1.2.1)

Patients with LFT abnormalities should be managed according to the guidelines in Table 2.

Table 2 Guidelines for Managing Atezolizumab and Cobimetinib–Associated Hepatotoxicity

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin	
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin < 2 × ULN	• Continue atezolizumab and cobimetinib. • Continue with the standard monitoring plan (i.e., LFTs Q4W before dosing).
AST/ALT > 3 × ULN to < 5 × ULN with total bilirubin < 2 × ULN	• Continue all study treatment. • Monitor LFTs at least weekly. • Consider referral to a hepatologist and liver biopsy. • For suspected immune-*mediated* events of > 5 days duration – Consider withholding atezolizumab [c] – Consider administering 1–2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper – Restart atezolizumab if event resolves to Grade 1 or better within 12 weeks [a, b] – Permanently discontinue atezolizumab and cobimetinib if event does not resolve to Grade 1 or better within 12 weeks [a, b, c]
AST/ALT > 5 × ULN to < 10 × ULN with total bilirubin < 2 × ULN	• Continue all study treatment. • Monitor LFTs at least weekly. • Consider referral to a hepatologist and liver biopsy. • For suspected immune-*mediated* events: – Withhold atezolizumab – Consider administering 1–2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper – If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. – Permanently discontinue atezolizumab and cobimetinib if event does not resolve to Grade 1 or better within 12 weeks [a, b, c]

Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A) (cont.)

Table 2 Guidelines for Managing Atezolizumab and Cobimetinib–Associated Hepatotoxicity (cont.)

Event	Action to Be Taken
AST/ALT > 3 × ULN with bilirubin > 2 × ULN	• Withhold atezolizumab and cobimetinib. • Consult hepatologist and consider liver biopsy. • Consider administering 1–2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper (for possible autoimmune hepatitis). • If LFTs do not decrease within 48 hours after initiation of systemic steroids, consider adding an immunosuppressive agent (e.g., mycophenolate mofetil or TNF-α antagonist). • Monitor LFTs every 48–72 hours until decreasing and then follow weekly. • Restart atezolizumab at fixed dose and cobimetinib at 1 dose reduction after discussion with medical monitor if AST/ALT < 3 × ULN with bilirubin < 2 × ULN and steroid dose < 10 mg oral prednisone equivalent per day. [a, b, c] • Permanently discontinue atezolizumab and cobimetinib for life-threatening hepatic events, and contact the Medical Monitor.
AST/ALT > 10 × ULN	• Permanently discontinue atezolizumab and cobimetinib. [c] • Consult hepatologist and consider liver biopsy. • Consider administering 1–2 mg/kg/day oral prednisone or equivalent (for possible autoimmune hepatitis). If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. • If LFTs do not decrease within 48 hr after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate mofetil or TNF-α antagonist) or dose escalation of corticosteroids may be considered. • Monitor LFTs every 48–72 hours until decreasing and then follow weekly.

LFT = liver function test; Q4W = every 4 weeks; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 105 days to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A) (cont.)

DERMATOLOGIC TOXICITY

Dermatologic toxicity and rash is associated with cobimetinib and atezolizumab (see Section 5.1.1.3.1) and should be managed according to the guidelines in Table 3. *Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab.*

Table 3 Guidelines for Managing Atezolizumab and Cobimetinib Rash

Event	Action to Be Taken
Dermatologic toxicity	
General guidance	• A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.
Dermatologic event, Grade 1 or 2	• Continue atezolizumab and cobimetinib. • Initiate supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve, consider treatment with higher-potency topical corticosteroids. • For Grade 2 rash, consider referral to dermatologist *for evaluation and, if indicated, biopsy*. **Acneiform rash:** • Consider topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) as clinically indicated.

Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A) (cont.)

Table 3 Guidelines for Managing Atezolizumab and Cobimetinib Rash (cont.)

Event	Action to Be Taken
Dermatologic event, Grade 3	• Withhold atezolizumab and cobimetinib. • Refer patient to dermatologist *for evaluation and, if indicated, biopsy*. • Consider initiating treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 2 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib. [a, b] • Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c] • If event resolves to Grade 2 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. **Acneiform rash:** • Consider continuation of topical corticosteroids (e.g., 2.5% alclometasone) and oral antibiotics (e.g., minocycline, doxycycline or antibiotics covering skin flora) when restarting cobimetinib.
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• *Follow guidelines for atezolizumab in Appendix 11.* • *Withhold cobimetinib.* • *If event resolves to Grade 1 or better, resume cobimetinib.* *Permanently discontinue cobimetinib if withheld for >4 weeks or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed.*

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 105 days to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A) (cont.)

PULMONARY EVENTS

Pneumonitis is associated with atezolizumab and cobimetinib (see Section Section 5.1.1.1.5 and should be managed according to the guidelines in Table 4.

Table 4 Guidelines for Managing Atezolizumab– and Cobimetinib–Associated Pulmonary Toxicity

Event	Action to Be Taken
Pulmonary events	
General guidance	• Mild-to-moderate events of pneumonitis have been reported with atezolizumab and cobimetinib. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. • For events concerning for pneumonitis, consider comprehensive infectious evaluation including viral etiologies.
Pneumonitis, Grade 1 (asymptomatic)	• Continue atezolizumab and cobimetinib. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Pneumonitis, Grade 2	• Withhold atezolizumab and cobimetinib. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-*mediated* etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • Resume atezolizumab and cobimetinib if event resolves to Grade 1 or better within 12 weeks. [a, b] • Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c] • For recurrent events, treat as a Grade 3 or 4 event.
Pneumonitis, Grade 3 or 4	• Permanently discontinue atezolizumab and cobimetinib. [c] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-*mediated* etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If pulmonary event does not improve within 48 hours or worsens, consider adding an immunosuppressive agent (e.g., infliximab, cyclophosphamide, IVIg, or mycophenolate). • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A) (cont.)

Table 4 Guidelines for Managing Atezolizumab– and Cobimetinib–Associated Pulmonary Toxicity (cont.)

BAL = bronchoscopic alveolar lavage; IVIg = intravenous immunoglobulin.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 105 days to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

OCULAR EVENTS

Serous retinopathy and retinal vein occlusion is associated with cobimetinib (see Section 5.1.1.1.2) and should be managed according to the guidelines in Table 5.

Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A) (cont.)

Table 5 Guidelines for Managing Cobimetinib-Associated Serous Retinopathy and Retinal Vein Occlusion

Description	Management
General guidance	• An ophthalmologist should evaluate visual complaints. • Uveitis or episcleritis and other immune–mediated ocular disease may be associated with atezolizumab and may be treated with topical corticosteroid eye drops. Atezolizumab should be permanently discontinued for immune-*mediated* ocular event that is unresponsive to local immunosuppressive therapy. • Serous retinopathy is associated with cobimetinib. In clinical trials, most events were Grade 1 (asymptomatic) or 2 (symptomatic). Most events in clinical trials resolved or improved to asymptomatic Grade 1 following dose interruption or reduction. If serous retinopathy is diagnosed, cobimetinib should be withheld until visual symptoms improve to Grade 1 or better. Serous retinopathy can be managed with treatment interruption, dose reduction, or with treatment discontinuation. • RVO has been reported in patients treated with MEK inhibitors other than cobimetinib.
Serous retinopathy Severity grade assessment based on NCI CTCAE v4 "Eye Disorders – Other" scale [a-d]	**Serous retinopathy, Grade 1 [a] or 2 [b] (tolerable):** • Continue cobimetinib and atezolizumab without dose change. • Continue ophthalmology follow-up as clinically indicated. **Serous retinopathy, Grade 2 [b] (intolerable) or 3/4 [c/d]:** • Interrupt cobimetinib until Grade ≤ 1. • Continue atezolizumab as clinically indicated. • Consult ophthalmology and undergo complete ophthalmologic examination, which includes visual acuity testing, intra-ocular pressure measurements, slit lamp ophthalmoscopy, indirect ophthalmoscopy, visual field, and OCT. Consider a fluorescein angiogram and/or indocyanine green angiogram, if clinically indicated. • Cobimetinib should be dose reduced by 1 dose level when restarting. • Consider permanent discontinuation of cobimetinib if serous retinopathy recurs despite 2 dose level reductions
Retinal vein occlusion Any grade	• If RVO (any grade) is diagnosed, cobimetinib dosing should be permanently discontinued and RVO treated per institutional guidelines. • Continue atezolizumab.

Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A) (cont.)

Table 5 Guidelines for Managing Cobimetinib-Associated Serous Retinopathy and Retinal Vein Occlusion (cont.)

Description	Management
Potential immune-*mediated* ocular toxicity (e.g., uveitis, iritis, episcleritis, or retinal events)	• For atezolizumab, Follow guidelines provided in the Appendix 11. • Continue cobimetinib as clinically indicated.

ADL = activities of daily living; RVO = retinal vein occlusion.

[a] Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

[b] Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.

[c] Grade 3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL.

[d] Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye.

GUIDELINES FOR MANAGEMENT OF PATIENTS WHO EXPERIENCE DECREASED LEFT VENTRICULAR EJECTION FRACTION

Decreased left ventricular ejection fraction (LVEF) has been seen with cobimetinib (see Section 5.1.1.1.3) and should be managed according to the guidelines in Table 6.

Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A) (cont.)

Table 6 Recommended Dose Modifications for Cobimetinib in Patients with Left Ventricular Ejection Fraction Decrease from Baseline

Left Ventricular Ejection Fraction (LVEF) Decrease from Baseline				
Patient	LVEF Value	Recommended Action with Cobimetinib and Atezolizumab	LVEF Value following Treatment Break	Recommended Cobimetinib Daily Dose
Asymptomatic	≥ 50% (or 40%–49% and < 10% absolute decrease from baseline)	Continue atezolizumab and cobimetinib at current dose	NA	NA
	< 40% (or 40%–49% and ≥ 10% absolute decrease from baseline)	Interrupt cobimetinib treatment for 2 weeks Continue atezolizumab as clinically indicated	< 10% absolute decrease from baseline	First occurrence: 40 mg
				Second occurrence: 20 mg
				Third occurrence: permanent discontinuation
			< 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
Symptomatic	NA	Interrupt cobimetinib treatment for 4 weeks	Asymptomatic and < 10% absolute decrease from baseline	First occurrence: 40 mg
				Second occurrence: 20 mg
				Third occurrence: permanent discontinuation
		Consider withholding atezolizumab. Discuss with Medical Monitor regarding resumption of atezolizumab.	Asymptomatic and < 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
		Cardiology consultation is strongly recommended.	Symptomatic regardless of LVEF	Permanent discontinuation

LVEF = left ventricular ejection fraction; NA = not applicable.

Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A) (cont.)

GUIDELINES FOR MANAGEMENT OF PATIENTS WHO EXPERIENCE ELEVATED CPK AND RHABDOMYOLYSIS

Elevated CPK has been reported with cobimetinib (see Section 5.1.1.1.4) and should be managed according to the guidelines in Table 7.

Table 7 Recommended Dose Modifications for Cobimetinib and Atezolizumab in Patients with CPK Elevations and Rhabdomyolysis

Event	Action to Be Taken
Rhabdomyolysis or CPK elevation	
General guidance	• Rule out cardiac cause (check ECG, serum cardiac troponin, and CPK-isoforms M and B fraction) and rule out rhabdomyolysis (clinical examination; serum creatinine, potassium, calcium, phosphorus, uric acid, and albumin; and urine myoglobin). • Assess patient for any history of strenuous physical activity, blunt trauma, or recent intramuscular injections.
For Grade ≤3 CPK elevations that are asymptomatic and deemed not clinically significant	• Cobimetinib and atezolizumab dosing does not need to be modified or interrupted to manage asymptomatic Grade ≤3 CPK elevations. • Recheck CPK at least once a week.
For Grade 4 CPK elevations that are asymptomatic and deemed not clinically significant	• Interrupt cobimetinib and atezolizumab treatment. • If improved to Grade ≤3 within 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. • If CPK elevations do not improve to Grade ≤3 within 4 weeks following dose interruption, permanently discontinue cobimetinib treatment. • Resumption of atezolizumab may be considered in patients who are deriving benefit.
Rhabdomyolysis or symptomatic CPK elevations	• Interrupt cobimetinib and atezolizumab treatment. • If severity is improved by at least one grade and symptoms resolve within 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. • If rhabdomyolysis or symptomatic CPK elevations do not improve within 4 weeks, permanently discontinue cobimetinib treatment • Resumption of atezolizumab may be considered in patients who are deriving benefit after discussion with the Medical Monitor.

Appendix 10
Management of Cobimetinib plus Atezolizumab-Associated Adverse Events (Arm A) (cont.)

GUIDELINES FOR MANAGEMENT OF PATIENTS WHO EXPERIENCE HEMORRHAGE

Hemorrhage has been reported with cobimetinib (see Section 5.1.1.1.1) and should be managed according to the guidelines in Table 8.

Table 8 Recommended Dose Modifications in Patients with Hemorrhage

Event	Action to Be Taken
Hemorrhage	
Grade 3 hemorrhage	• Interrupt cobimetinib treatment. There are no data on the effectiveness of cobimetinib dose modification for hemorrhage events. Clinical judgment should be applied when considering restarting cobimetinib treatment. • Continue atezolizumab treatment.
Grade 4 hemorrhage or any grade cerebral hemorrhage	• Interrupt cobimetinib treatment. Permanently discontinue cobimetinib for hemorrhage events attributed to cobimetinib. • Continue atezolizumab treatment.
Grade 3 or 4 or intolerable Grade 2 treatment-related toxicities not described above and Table 3 (dose modifications for cobimetinib)	• Withhold all study treatment. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 105 days to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology, *when clinically indicated*.

Although most immune-*mediated* adverse events observed with *atezolizumab* have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-*mediated* toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit–risk balance *for* a given patient prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

DOSE MODIFICATIONS

There will be no dose modifications for atezolizumab in this study.

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the Medical Monitor agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 1.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

HEPATIC EVENTS

Immune-*mediated* hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	All events: • Monitor LFTs more frequently until return to baseline values. Events of > 5 days' duration: • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

GASTROINTESTINAL EVENTS

Immune-*mediated* colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 3.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist $>$ 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	TSH $\geq$ 0.1 mU/L and $<$ 0.5 mU/L: • Continue atezolizumab. • Monitor TSH every 4 weeks. TSH $<$ 0.1 mU/L: • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-*mediated* hyperthyroidism. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., $>$ 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to $\leq$ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over $\geq$ 1 month to $\leq$ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 5.

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-*MEDIATED* MYOCARDITIS

Immune-*mediated* myocarditis has been associated with the administration of atezolizumab. Immune-*mediated* myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, *laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities,* dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-*mediated* myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 6 Management Guidelines for Immune-*Mediated* Myocarditis

Event	Management
Immune-*mediated* myocarditis, Grade 1	• Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.
Immune-*mediated* myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-*mediated* myocarditis, Grade 3-4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

INFUSION-RELATED REACTIONS *AND CYTOKINE-RELEASE SYNDROME*

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) *or cytokine-release syndrome (CRS)* with atezolizumab may receive premedication with antihistamines*,* anti-pyretics*, and/or* analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs *and CRS* are provided in Table 7.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 [a] *Fever [b] with or without constitutional symptoms*	• *Immediately interrupt* infusion. • *Upon symptom resolution, wait for 30 minutes and then restart infusion at* half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • *If symptoms recur, discontinue infusion of this dose.* • *Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration.* • *In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2.* • *For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.*
Grade 2 [a] *Fever [b] with hypotension not requiring vasopressors* ***and/or*** *Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by*	• *Immediately interrupt* infusion. • *Upon symptom resolution, wait for 30 minutes and then restart* infusion at half the rate being given at the time of event onset. • *If symptoms recur, discontinue infusion of this dose.* • *Administer symptomatic treatment. [c]* • *For hypotension, administer IV fluid bolus as needed.* • *Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.* • *Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix.* • *Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).* • *Consider anti-cytokine therapy.* • *Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor. [e]* • *If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS.* • *If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

Event	Management
Grade 3 [a] *Fever* [b] *with hypotension requiring a vasopressor (with or without vasopressin)* ***and/or*** *Hypoxia requiring high-flow oxygen* [d] *by nasal cannula, face mask, non-rebreather mask, or Venturi mask*	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [e] • *Administer symptomatic treatment.* [c] • *For hypotension, administer IV fluid bolus and vasopressor as needed.* • *Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.* • *Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix.* • *Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).* • *Consider anti-cytokine therapy.* • *Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.*
Grade 4 [a] *Fever* [b] *with hypotension requiring multiple vasopressors (excluding vasopressin)* ***and/or*** *Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)*	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [e] • *Administer symptomatic treatment.* [c] • *Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice.* • *Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix.* • *Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).* • *Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments* [f] *may be considered at the discretion of the investigator and in consultation with the Medical Monitor.* • *Hospitalize patient until complete resolution of symptoms.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

ASTCT =American Society for Transplantation and Cellular Therapy; BiPAP =bi-level positive airway pressure; CAR =chimeric antigen receptor; CPAP =continuous positive airway pressure; CRS =cytokine-release syndrome; CTCAE =Common Terminology Criteria for Adverse Events; eCRF =electronic Case Report Form; HLH =hemophagocytic lymphohistiocytosis; ICU =intensive care unit; IRR =infusion-related reaction; MAS =macrophage activation syndrome; NCCN =National Cancer Comprehensive Network; NCI =National Cancer Institute.

Note: These management guidelines have been adapted from NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] *Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.*

[b] *Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.*

[c] *Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.*

[d] *Low flow is defined as oxygen delivered at ≤6 L/min, and high flow is defined as oxygen delivered at >6 L/min.*

[e] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after consulting the Medical Monitor and considering the benefit–risk ratio.*

[f] *Refer to Riegler et al. (2019).*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	• Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-*mediated* pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-*mediated* pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. *Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab.* A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist *for evaluation and, if indicated, biopsy*. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist *for evaluation and, if indicated, biopsy*. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 9 Management Guidelines for Dermatologic Events (cont.)

Event	Management
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	***Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:*** • *Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis.* • *Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy.* • *Follow the applicable treatment and management guidelines above.* *If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.*

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-*mediated* neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-*mediated* neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-*mediated* neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-*MEDIATED* MENINGOENCEPHALITIS

Immune-*mediated* meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-*mediated* meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from

potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for Immune-*Mediated* Meningoencephalitis

Event	Management
Immune-*mediated* meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Refer patient to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

RENAL EVENTS

Immune-*mediated* nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. *Renal* function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-*mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among

the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13 Management Guidelines for Immune-Mediated Myositis

Event	*Management*
Immune-mediated myositis, Grade 1	• *Continue atezolizumab.* • *Refer patient to rheumatologist or neurologist.* • *Initiate treatment as per institutional guidelines.*
Immune-mediated myositis, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset* [a] *and contact Medical Monitor.* • *Refer patient to rheumatologist or neurologist.* • *Initiate treatment as per institutional guidelines.* • *Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

Table 13 Management Guidelines for Immune-Mediated Myositis (cont.)

Immune-mediated myositis, Grade 3	• *Withhold atezolizumab for up to 12 weeks after event onset* [a] *and contact Medical Monitor.* • *Refer patient to rheumatologist or neurologist.* • *Initiate treatment as per institutional guidelines.* • *Respiratory support may be required in more severe cases.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *For recurrent events, treat as a Grade 4 event.*

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[c] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab.

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- *Fever ≥38.5°C*
- *Splenomegaly*
- *Peripheral blood cytopenia consisting of at least two of the following:*
  - *Hemoglobin <90 g/L (9 g/dL) (<100 g/L [10 g/dL] for infants <4 weeks old)*
  - *Platelet count <100 ×10^9/L (100,000/μL)*
  - *ANC <1.0 ×10^9/L (1000/μL)*
- *Fasting triglycerides >2.992 mmol/L (265 mg/dL) and/or fibrinogen <1.5 g/L (150 mg/dL)*
- *Hemophagocytosis in bone marrow, spleen, lymph node, or liver*
- *Low or absent natural killer cell activity*
- *Ferritin >500 mg/L (500 ng/mL)*
- *Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥2 standard deviations above age-adjusted laboratory-specific norms*

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- *Ferritin >684 mg/L (684 ng/mL)*
- *At least two of the following:*
  - *Platelet count ≤181 ×10^9/L (181,000/μL)*
  - *AST ≥48 U/L*
  - *Triglycerides >1.761 mmol/L (156 mg/dL)*
  - *Fibrinogen ≤3.6 g/L (360 mg/dL)*

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	*Management*
Suspected HLH or MAS	• *Permanently discontinue atezolizumab and contact Medical Monitor.* • *Consider patient referral to hematologist.* • *Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines.* • *Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy.* • *If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019).* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

HLH =hemophagocytic lymphohistiocytosis; MAS =macrophage activation syndrome.

REFERENCES

Adashek ML, Feldman M. Cytokine release syndrome resulting from anti–programmed death-1 antibody: raising awareness among community oncologist. J Oncol Practice 2019;15:502–4.

La Rosée P. Treatment of hemophagocytic lymphohistiocytosis in adults. Hematology Am Soc Hematol Educ Protram 2015;1:190–6.

La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465–77.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625–38.

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481–9.

Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323–35.

Rotz SJ, Leino D, Szabo S, et al. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. Pediatr Blood Cancer 2017;64:e26642.

Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908–14.