Official Title: A Phase Ib Study Evaluating Cobimetinib Plus Atezolizumab in Patients With Advanced BRAF V600 Wild-Type Melanoma Who Have Progressed During or After Treatment With Anti−PD-1 Therapy and Atezolizumab Monotherapy in Patients With Previously Untreated Advanced BRAF V600 Wild-Type Melanoma

NCT Number: NCT03178851

Document Date: Protocol Version 5: 26-October-2018

PROTOCOL

TITLE:	**A PHASE IB STUDY EVALUATING COBIMETINIB PLUS ATEZOLIZUMAB IN PATIENTS WITH ADVANCED *BRAF*^{V600} WILD-TYPE MELANOMA WHO HAVE PROGRESSED DURING OR AFTER TREATMENT WITH ANTI–PD-1 THERAPY AND ATEZOLIZUMAB MONOTHERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED *BRAF*^{V600} WILD-TYPE MELANOMA**
PROTOCOL NUMBER:	CO39721
VERSION NUMBER:	5
EUDRACT NUMBER:	2016-004402-34
IND NUMBER:	*135,717*
TEST PRODUCTS:	Cobimetinib (RO5514041) Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	14 December 2016
DATES AMENDED:	Version 2: 23 June 2017 Version 3: 19 September 2017 Version 4: 3 February 2018 Version 5: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	26-Oct-2018 10:19:14

PROTOCOL AMENDMENT, VERSION 5
RATIONALE

Protocol CO39721 has been amended primarily to update the primary analysis timelines and to align with current atezolizumab risk language.

- The primary analysis will be conducted in Cohorts A and B approximately 24 weeks after the last patient is enrolled in Cohort A. At this time, Cohorts A and B will have a minimum follow up of approximately 24 weeks. The primary analysis for Cohort C may be analysed independently, with a minimum of 24 weeks follow up for patients in Cohort C (Section 6).
- The list of risks associated with atezolizumab has been revised to align with current atezolizumab risk language (Section 5.1.2).
- Guidelines for managing patients who experience atezolizumab-associated adverse events have been revised to include nephritis (Appendix 8).

Additional changes to the protocol are summarized below:

- Independent review committee (IRC)-assessed objective response rate (ORR), duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) have been added as secondary efficacy endpoints for Cohort C (Table 1 in Section 2 and Sections 3.1 and 6.4.2).
- Text has been added to clarify that the patient numbers for each cohort are approximate (Sections 3.1, 3.3.2.2, and 6.1).
- The inclusion criterion that addresses female contraception has been modified to specify when women must refrain from donating eggs (Section 4.1.1.4).
- The exclusion criterion related to treatment with immunosuppressive medication for patients who have received acute, low-dose systemic immunosuppressant medication ($\leq$10 mg/day oral prednisone or equivalent) or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) has been revised, specifying that such patients are eligible for the study after Medical Monitor approval has been obtained (Section 4.1.2.6).
- Denosumab has been removed from the list of prohibited therapies (Section 4.3.2).
- Text stating that ophthalmologic examinations should be performed prior to dosing has been added, and the frequency of the examinations has been clarified (Table 3 in Section 4.4.7).
- Text stating recurrent Grade 1 pneumonitis should be treated as a Grade 3 or 4 event has been removed (Table 6 in Section 5.1.3.3).
- The Medical Monitor has been changed and updated contact information has been provided (Section 5.4.1).
- Language has been added for consistency with Roche's current data retention policy and to accommodate more stringent local requirements (if applicable) (Section 7.5).

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.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IB STUDY EVALUATING COBIMETINIB PLUS ATEZOLIZUMAB IN PATIENTS WITH ADVANCED *BRAF*^{V600} WILD-TYPE MELANOMA WHO HAVE PROGRESSED DURING OR AFTER TREATMENT WITH ANTI–PD-1 THERAPY AND ATEZOLIZUMAB MONOTHERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED *BRAF*^{V600} WILD-TYPE MELANOMA**
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MEDICAL MONITOR:	[redacted] M.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 retain the signed original of this form for your study files. Please return a copy as instructed by the contract research organization.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IB STUDY EVALUATING COBIMETINIB PLUS ATEZOLIZUMAB IN PATIENTS WITH ADVANCED *BRAF*^{V600} WILD-TYPE MELANOMA WHO HAVE PROGRESSED DURING OR AFTER TREATMENT WITH ANTI–PD-1 THERAPY AND ATEZOLIZUMAB MONOTHERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED *BRAF*^{V600} WILD-TYPE MELANOMA**
PROTOCOL NUMBER:	CO39721
VERSION NUMBER:	5
EUDRACT NUMBER:	2016-004402-34
IND NUMBER:	135,717
TEST PRODUCTS:	Cobimetinib (RO5514041) Atezolizumab (RO5541267)
PHASE:	Phase Ib
INDICATION:	Advanced *BRAF*^{V600} wild-type melanoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the preliminary efficacy, safety, and pharmacokinetics of cobimetinib and atezolizumab in patients with advanced *BRAF*^{V600} wild-type (WT), metastatic, or unresectable locally advanced melanoma who have progressed on prior anti–programmed death (PD)-1 therapy and atezolizumab monotherapy in patients with previously untreated advanced BRAF^{V600} WT melanoma. Specific objectives and corresponding endpoints for the study are outlined below.

Objectives	Corresponding Endpoints
Primary Efficacy Objectives	
• To evaluate the preliminary efficacy of cobimetinib and atezolizumab in patients with advanced *BRAF*^{V600} WT melanoma who have progressed on prior anti–PD-1 therapy • To evaluate the efficacy of atezolizumab monotherapy in patients with advanced BRAF^{V600} WT melanoma who have not been previously treated	Co-primary endpoints: • Objective response rate (ORR), defined as the proportion of patients who had a confirmed overall response. Confirmed overall response is defined as a complete response (CR) or a partial response (PR) on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1. • Disease control rate (DCR), defined as the proportion of patients with a CR, a PR, or stable disease at 16 weeks

Objectives	Corresponding Endpoints
Secondary Efficacy Objectives	
• To evaluate the efficacy of cobimetinib and atezolizumab in patients with advanced *BRAF*^{V600} WT melanoma who have progressed on prior anti–PD-1 therapy • To evaluate the efficacy of atezolizumab monotherapy in patients with advanced *BRAF*^{V600} WT melanoma who have not been previously treated	• Duration of response (DOR), defined as the time from the first occurrence of a documented overall response to disease progression, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), or death from any cause, whichever occurs first • Overall survival (OS), defined as the time from Cycle 1, Day 1 to death from any cause • Progression-free survival (PFS), defined as the time from Cycle 1, Day 1, to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first • *ORR, DCR, DOR, and PFS, as determined by an independent review committee (IRC) according to RECIST v1.1, in Cohort C*
Exploratory Efficacy Objectives	
• To evaluate the efficacy of cobimetinib and atezolizumab in patients with advanced *BRAF*^{V600} WT melanoma who have progressed on prior anti–PD-1 therapy • To evaluate the efficacy of atezolizumab monotherapy in patients with advanced BRAF^{V600} WT melanoma who have not been previously treated	• ORR response *as determined by the investigator* according to immune-modified RECIST • DOR *as determined by the investigator* according to immune-modified RECIST • PFS *as determined by the investigator* according to immune-modified RECIST
Safety Objectives	
• To evaluate the safety of cobimetinib and atezolizumab in patients with advanced *BRAF*^{V600} WT melanoma who have progressed on prior anti–PD-1 therapy • To evaluate the safety of atezolizumab monotherapy in patients with advanced BRAF^{V600} WT melanoma who have not been previously treated	• Occurrence, frequency, and severity of adverse events, with severity determined through use of National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v4.0) • Change from baseline in targeted vital signs during and following treatment • Change from baseline in targeted clinical laboratory test results during and following treatment • Incidence, severity, and time course of serous retinopathy (for Cohorts A and B)
Pharmacokinetic Objective	
• To characterize the pharmacokinetics of atezolizumab monotherapy in Cohort C • To characterize the pharmacokinetics of cobimetinib and atezolizumab when administered in combination in Cohorts A and B	• Serum concentration of atezolizumab at specified timepoints • Plasma concentration of cobimetinib at specified timepoints

Objectives	Corresponding Endpoints
Exploratory Pharmacokinetic Objectives	
• To investigate the relationship between cobimetinib exposure and efficacy or safety outcomes using population approaches • To investigate the relationship between atezolizumab exposure and efficacy or safety outcomes using population approaches	• Relationship between cobimetinib plasma concentration and efficacy or safety endpoints • Relationship between atezolizumab serum concentration and efficacy or safety endpoints
Immunogenicity Objective	
• To evaluate the immune response to atezolizumab in previously untreated patients and in patients who have progressed on previous anti-PD-1 therapy	• Incidence of anti-drug antibodies (ADAs) to atezolizumab 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 pharmacokinetic (PK) endpoints
Exploratory Biomarker Objectives	
• Mechanisms of resistance to anti-PD-1 in Cohorts A and B or anti-PD-L1 in Cohort C • Cobimetinib effect on tumor immune contexture	• Tumor-infiltrating lymphocyte distribution, CD8, PD-L1, and stromal markers (TBD) by immunohistochemistry • Immune-signatures and stromal signature by RNA sequencing • *RAS*, *NF1* mutations, tumor mutation burden, and T-cell receptor repertoires by DNA sequencing

ADA =anti-drug antibody; anti–PD-1 =anti–programmed death-1; CR =complete response; DOR =duration of response; DCR =disease control rate; IHC =immunohistochemistry; IRC =independent review committee; NCI CTCAE =National Cancer Institute Common Terminology Adverse Events; OR =objective response; ORR =objective response rate; OS =overall survival; PD-L1 = programmed death–ligand 1; PK = pharmacokinetic; PFS =progression-free survival; PR =partial response; RECIST =Response Evaluation Criteria in Solid Tumors; SD =stable disease; TBD =to be determined; TIL =tumor-infiltrating lymphocyte; TCR =T-cell receptor; tMB =tumor mutation burden; WT =wild type.

Study Design

Description of Study

Study CO39721 is a Phase Ib, open-label, multicenter, global study designed to evaluate the preliminary efficacy, safety, and pharmacokinetics of cobimetinib and atezolizumab when given to patients with *BRAF*^{V600} WT metastatic or unresectable locally advanced melanoma who have progressed on a prior anti-PD-1 therapy. It is also designed to evaluate efficacy, safety, and pharmacokinetics of atezolizumab monotherapy in patients with BRAF^{V600} WT metastatic or unresectable locally advanced melanoma who have not been previously treated.

Number of Patients

Approximately 102 patients with *BRAF*^{V600} WT advanced melanoma who have progressed on a prior anti–PD-1 therapy will be enrolled in Cohorts A and B of this study.

- Cohort A: Approximately 90 patients who have progressed on or after treatment with an anti-PD-1 agent will be enrolled.

- Cohort B (biopsy cohort): *Approximately* 12 patients will be enrolled in a mandatory biopsy cohort

Approximately 50 patients who have not *received any prior anti-cancer treatment in the metastatic setting* will be enrolled in Cohort C.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

Disease-Specific Inclusion Criteria: Cohorts A and B

- Histologically confirmed Stage IV (metastatic) or unresectable Stage IIIc *BRAF*^{V600} WT (locally advanced) melanoma
- Documentation of *BRAF*^{V600} mutation–negative status in melanoma tumor tissue (archival [< 5 years old] 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, CE-marked [European conformity] in vitro diagnostic in E.U. countries, CLIA-certified NGS test, or equivalent)
- Measurable disease according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)
- Disease progression during or after treatment with a PD-1 inhibitor either as monotherapy or in combination with other agent(s)

Additional Disease-Specific Inclusion Criteria in Cohort B (Biopsy Cohort)

- Patients in this cohort must have progressed during or after anti–PD-1 therapy within 12 weeks before study start.
- Patients in this cohort must have received a minimum of two cycles of anti–PD-1 therapy.
- Patients in this cohort must meet criteria for primary (n = 6) or secondary (n = 6) resistance to an anti–PD-1 agent as outlined below:

  Primary resistance is defined as progressive disease, according to RECIST v1.1, as best response.

  Secondary resistance is defined as progressive disease after initial confirmed response according to RECIST v1.1,
- Patients in this cohort must consent to undergo tumor biopsies of accessible lesions before and during treatment and at radiographic progression for biomarker analyses.
- Patients in this cohort must have at least two accessible lesions that are amenable to excisional or core-needle (minimum three cores and minimum diameter 18 gauge; however, 16 gauge is desirable) biopsy with acceptable risk of a major procedural complication. Exceptions may be made if patient has only one lesion that allows multiple biopsies following discussion with Medical Monitor.

Disease-Specific Inclusion Criteria: Cohort C

- Histologically confirmed Stage IV (metastatic) or unresectable Stage IIIc BRAFV600 WT (locally advanced) 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 $BRAF^{V600}$ mutation–negative status in melanoma tumor tissue (archival [< 5 years old] 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, CE-marked [European conformity] in vitro diagnostic in E.U. countries, CLIA-certified next-generation sequencing [NGS] test 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.
- Measureable disease according to RECIST v1.1

General Inclusion Criteria

- Signed Informed Consent Form
- Age ≥ 18 years
- Ability to comply with the study protocol, in the investigator's judgment
- Eastern Cooperative Oncology Group Performance Status of 0 or 1
- Available and adequate baseline tumor tissue sample (archival [< 5 years old] or newly obtained biopsy)
- Life expectancy ≥ 18 weeks
- Adequate hematologic and end-organ function, defined using the following laboratory test results, obtained within 14 days before initiation of study treatment:

  Neutrophils (ANC ≥ 1500 cells/μL without granulocyte-colony stimulating factor support within 2 weeks before Cycle 1, Day 1)

  WBC counts > 2500 cells /μL and < 15,000 cells /μL

  Lymphocyte count ≥ 500 cells/μL

  Platelet count ≥ 100,000 cells /μL (without transfusion within 2 weeks before Cycle 1, Day 1)

  Hemoglobin ≥ 9.0 g/dL (without transfusion)

  Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CrCl) ≥ 40 mL/min on the basis of measured CrCl from a 24-hour urine collection or Cockcroft-Gault glomerular filtration rate estimation:

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

  AST, ALT, and alkaline phosphatase ≤ 2.5 × upper limit of normal (ULN), with the following exceptions.

    Patients with documented liver metastases: AST and/or ALT ≤ 5 × ULN. Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 × ULN

  Serum albumin ≥ 25 g/L

  Total bilirubin ≤ 1.5 × ULN; patients with known Gilbert's disease may have a bilirubin ≤ 3.0 × ULN

  For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 × ULN within 28 days before initiation of study treatment

  For patients receiving therapeutic anticoagulation: stable anticoagulant regimen and stable INR during the 28 days immediately preceding initiation of study treatment

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the last dose of atezolizumab within 3 months after the last dose of cobimetinib. *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 (≥ 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 a condom, and agreement to refrain from donating sperm, as defined below:

  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.

<u>Exclusion Criteria</u>

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

Cancer-Related Exclusion Criteria

- Prior treatment with a MAPK inhibitor
- Ocular melanoma
- Major surgical procedure other than for diagnosis within 4 weeks before initiation of study treatment, or anticipation of need for a major surgical procedure during the course of the study
- Traumatic injury within 2 weeks before initiation of study treatment
- Palliative radiotherapy within 14 days before initiation of study treatment
- Active malignancy (other than $BRAF^{V600}$ mutation–negative melanoma) or malignancy within 3 years before screening, with the exception of resected melanoma, resected basal cell carcinoma, resected cutaneous squamous cell carcinoma, resected carcinoma in situ of the cervix, resected carcinoma in situ of the breast, in situ prostate cancer, limited-stage bladder cancer, or other curatively treated malignancies from which the patient has been disease-free for at least 3 years

  Patients with a history of isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer are eligible for the study.
- Treatment with any anti-cancer agent 14 days prior to Cycle, Day 1 other than aPD-1 based therapy
- Adverse events from prior anti-cancer therapy that have not resolved to Grade ≤ 1

  Clinically stable patients with manageable immune-related adverse events resulting from prior cancer immunotherapy may be eligible for the study after discussion with and approval by the Medical Monitor.

- For Cohort C, specific exclusion criteria include any prior anti-cancer therapy for advanced melanoma

Ocular Exclusion Criteria (Cohorts A and B)

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

Cardiac Exclusion Criteria (Cohorts A and B)

- History of clinically significant cardiac dysfunction, including the following:

  Unstable angina, or new-onset angina within 3 months before initiation of study treatment

  Symptomatic congestive heart failure, defined as New York Heart Association Class II or higher

  Myocardial infarction within 6 months before initiation of study treatment

  Unstable arrhythmia

  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

  Left ventricular ejection fraction below the institutional lower limit of normal or below 50%, whichever is lower

Central Nervous System Exclusion Criteria

- Untreated or actively progressing central nervous system (CNS) lesions (carcinomatous meningitis)

  Patients with stable and asymptomatic CNS metastases are eligible, if they meet all of the following:

  Measurable disease, per RECIST v1.1, must be present outside the CNS.

  All known CNS lesions are clinically stable.

  CNS lesions have not been treated with whole-brain radiotherapy, except in patients who underwent definitive resection of or stereotactic therapy for all radiologically detectable parenchymal brain lesions.

  Absence of interim progression must be confirmed by radiographic study within 4 weeks before initiation of study treatment. If new CNS metastases are suspected during the screening period, a confirmatory radiographic study is required before initiation of study treatment.

  Any radiotherapy or surgery must be completed $\geq$ 4 weeks before initiation of study treatment.

  There is no ongoing requirement for corticosteroids, and any prior corticosteroid treatment must be discontinued $\geq$ 2 weeks before initiation of study treatment. Treatment with an anticonvulsant at a stable dose is allowed.
- History of metastases to brain stem, midbrain, pons, or medulla, or within 10 mm of the optic apparatus (optic nerves and chiasm)
- History of leptomeningeal metastatic disease

Exclusions Related to Infections

- 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 chronic obstructive pulmonary disease) are eligible.
- Active or chronic viral hepatitis B or C infection

  Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study if quantitative HBV DNA $<$ 500 IU/mL at screening.

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

Exclusion Criteria Related to Autoimmune Conditions and Immunomodulatory Drugs

- 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 a stable dose of thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study.

  Patients with a history of manageable immune-related adverse events resulting from prior immunotherapy may be eligible for the study after discussion with and approval by the Medical Monitor.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

    Rash must cover less than 10% of body surface area.

    Disease is well controlled at baseline and requires only low–potency topical corticosteroids

    No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Treatment with systemic immunosuppressive medication (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor–alpha [TNF-α] agents) within 2 weeks before initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study *with the following exceptions:*

  Patients who have received acute, low-dose systemic immunosuppressant medication ($\leq$ 10 mg/day oral prednisone or equivalent) or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study *after Medical Monitor approval has been obtained.*

  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

Additional Exclusion Criteria

- Current severe, uncontrolled systemic disease (including, but not limited to, clinically significant cardiovascular, pulmonary, or renal disease) other than cancer
- 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
- Any psychological, familial, sociological, or geographic condition that may hamper compliance with the protocol and follow-up after treatment discontinuation
- Inability or unwillingness to swallow pills
- History of malabsorption or other clinically significant metabolic dysfunction that may interfere with absorption of oral study treatment
- Pregnant or breastfeeding, or intending to become pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days before initiation of study treatment.
- Known clinically significant liver disease, including alcoholism, cirrhosis, fatty liver, and other inherited liver disease as well as active viral disease, including positive HIV test at screening
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Treatment with a live, attenuated vaccine within 4 weeks before initiation of study treatment or anticipation of need for such a vaccine during the course of the study
- Known hypersensitivity to biopharmaceutical agents produced in Chinese hamster ovary cells
- Known hypersensitivity to any component of the atezolizumab or cobimetinib formulations
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent
- Requirement for concomitant therapy or food that is prohibited during the study

End of Study

The study will end when all patients enrolled have been followed until death, have withdrawn consent, have been lost to follow-up, or when the Sponsor decides to end the trial, whichever occurs first.

Length of Study

The total length of the study, from first patient in until the end of follow-up, is expected to be approximately 4 years.

Investigational Medicinal Products

Test Products (Investigational Drugs)

Cobimetinib tablets will be supplied by the Sponsor. The 20-mg cobimetinib drug product is a film-coated, white, round, immediate-release tablet. Patients in Cohorts A and B will receive 60 mg (three tablets of 20 mg each) orally QD for Days 1–21 of each 28-day cycle. This 4-week period is considered a treatment cycle.

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

Cohort A: Patients will initiate dosing with atezolizumab concurrently with cobimetinib and will receive atezolizumab 840 mg intravenously Q2W on Days 1 and 15 of all cycles.

Cohort B: Patients will receive the first dose of atezolizumab at 840 mg intravenously on Day 15 of Cycle 1. Thereafter, they will receive atezolizumab 840 mg intravenously Q2W on Days 1 and 15 of Cycle 2 and all subsequent cycles.

Cohort C: Patients will receive atezolizumab 1200 mg intravenously Q3W as monotherapy.

Statistical Methods

Primary Analysis

The primary analysis will be conducted *in Cohorts A and B approximately 24 weeks after the last patient is enrolled in Cohort A. At this time, Cohorts A and B will have a minimum follow up of approximately 24 weeks. The primary analysis for Cohort C may be analyzed independently, with a minimum of 24 weeks follow up for patients in Cohort C.* Both separate and pooled efficacy and safety analyses will be performed on Cohorts A and B given their similar patient populations. Additional tumor immunology and biomarker analyses will also be conducted on Cohort B. Study data will be described and summarized for Cohort C separately.

Determination of Sample Size

This study is designed for hypothesis generation with the intention to provide an informative evaluation on the selected efficacy endpoints. No formal inferential testing is planned. Approximately 152 patients are anticipated to be enrolled, with *approximately* 90 patients in Cohort A, 12 patients in Cohort B, and 50 patients in Cohort C.

A combined 102 patients in Cohorts A and B allows for a robust comparison against historical control of ipilumumab and chemotherapy in patients who have previously progressed on anti-PD1 therapy, which generally have response rates of less than 17%. For example, with 102 patients in Cohorts A and B, observing 26 patients with objective response corresponds to ORR (95% CI) of 25.5% (17.4%, 35.1%) and observing 60 patients with disease control corresponds to a DCR (95% CI) of 58.8% (48.6%, 68.5%).

Enrolling 50 patients in Cohort C provides reasonably reliable estimates of the ORR and DCR in patients who have not been previously treated to allow for an accurate understanding of the achievable magnitude of efficacy in this population.

For example, observing 17 patients with objective response corresponds to ORR (95% CI) of 34.0% (21.1%, 48.8%) and observing 32 patients with disease control corresponds to DCR (95% CI) of 64% (49.2%, 77.1%). Enrolling 50 patients in Cohort C also provides an opportunity to explore the preliminary efficacy in relevant patient subgroups including biomarker subgroups defined by PD-L1 expression.

Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody (anti-therapeutic antibody)
anti–PD-1	anti–programmed death-1
anti–PD-L1	anti–programmed death ligand-1
CE	European conformity
CNS	central nervous system
CPK	increased creatine phosphokinase
CR	complete response
CRC	colorectal cancer
CT	computed tomography
DCR	disease control rate
DOR	duration of response
EC	Ethics Committee
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
Fc	fragment crystallizable
FDA	Food and Drug Administration
G-CSF	granulocyte-colony stimulating factor
GWAS	genome-wide association studies
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
IC	immune cell
IFN	interferon
IL-2	interleukin-2
IMP	investigational medicinal product
IND	Investigational New Drug (Application)

Abbreviation	Definition
IOP	intraocular pressure
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
IxRS	interactive voice- or web-based response system
LVEF	left ventricular ejection function
MAPK	mitogen activated–protein kinase
MHC	major histocompatibility complex
MHCI	major histocompatibility complex class I
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NRAS	neuroblastoma *RAS*
NSCLC	non–small cell lung cancer
OCT	optical coherence tomography
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
RECIST	Response Evaluation Criteria in Solid Tumors
RVO	retinal vein occlusion
QD	once daily
QW	every week
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
SD	stable disease

Abbreviation	Definition
T3	triiodothyronine
TCR	T-cell receptor
TNF-α	tumor necrosis factor alpha
ULN	upper limit of normal
VF	visual field
WT	wild type

1. BACKGROUND

1.1 BACKGROUND ON MELANOMA

1.1.1 Incidence and Pathogenesis

Melanoma is a potentially deadly form of skin cancer that originates from melanocytes. The clinical outcome of patients with melanoma is highly dependent on the stage of disease at presentation. Although the outcome for promptly diagnosed superficial tumors is good and despite recent therapeutic advances, melanoma is associated with high rates of mortality and disease-related morbidity in the metastatic setting (see Section 1.1.2).

In 2012, there were about 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, an estimated 76,380 new cases of melanoma will be diagnosed and approximately 10,130 patients are expected to die of the disease in 2016 (American Cancer Society 2016). Moreover, the number of melanoma cases worldwide is increasing faster than any other cancer, especially in fair-skinned, Caucasian populations (Diepgen and Mahler 2002); estimates suggest a doubling of melanoma incidence every 10–20 years (Garbe and Leiter 2009). The incidence 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).

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 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; CGAN 2015). Approximately 14% harbor mutations of NF1, an inhibitory protein of the MAPK pathway (CGAN 2015). Thus, the MAPK pathway is an important driver of pathogenesis in $BRAF^{V600}$ wild-type (WT) melanoma, as well as $BRAF^{V600}$-mutated melanoma.

1.1.2 Treatment Options for Melanoma

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

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 (Richman et al. 2015).

Treatment options for *BRAF*^{V600} WT 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). T-cell activation is an essential component of cell-mediated immunity, which has led to the development of immunomodulation as a strategy for anti-cancer therapy. The two-signal model of T-cell activation 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). Co-inhibitory receptors, or "immune checkpoints", including CTLA-4 and programmed death−1 (PD-1) receptor can prevent T-cell overactivation and downregulate the immune system, protecting against autoimmunity (Freeman et al. 2000). Targeting of these checkpoints can render cancer cells susceptible to immune attack and has been applied in the treatment of melanoma.

Immunotherapeutic agents currently available for advanced melanoma include the following:

- The anti−CTLA-4 antibody, ipilimumab
- Two anti−PD-1 antibodies, nivolumab and pembrolizumab
- Nivolumab and ipilimumab combination therapy

Although responses to anti−PD-1 agents can be prolonged, they are limited to 30%−40% of patients across several clinical trials. Median PFS for these agents is 5−6 months (Robert et al. 2015a; Robert et al. 2015b; Weber et al. 2015), and OS is approximately 20−24 months (Hodi et al 2016; Robert et al. 2016). Reported response rates for ipilimumab monotherapy are 10%−15% and OS 10−11 months (Hodi et al. 2010; Robert et al. 2011). In Phase III studies in previously untreated patients with advanced melanoma, the combination of ipilimumab and nivolumab showed an increased objective response rate (ORR) and improved PFS relative to either agent as monotherapy, but it resulted in challenging toxicity, with more than 50% of patients experiencing Grade $\geq$3 adverse events. The OS benefit for this combination is not yet known (Larkin et al. 2015).

Thus, despite the therapeutic advance with the development of these agents, there still exists a high unmet need for all patients with advanced *BRAF*^{V600} WT melanoma.

For *BRAF*^{V600} WT patients whose disease relapsed or is refractory to anti−PD-1 agents, treatment options are currently limited to ipilimumab (if they have not previously received this agent), chemotherapy, or rechallenge with anti−PD-1 therapy. Consequently, there is an urgent need to develop new therapies for this population.

1.2 BACKGROUND ON THE STUDY TREATMENTS

1.2.1 Cobimetinib

Cobimetinib is a potent and highly selective inhibitor of MEK1 and MEK2, central components 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, suggesting a potentially important role for MEK inhibitors in melanoma and other tumors that harbor the *BRAF*^{V600} mutation (Solit et al. 2006).

Cobimetinib (Cotellic®) is approved for use with vemurafenib for the treatment of advanced *BRAF*^{V600}-mutated melanoma in the European Union, United States, and Switzerland as well as a number of other countries across the world.

Cobimetinib shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies, 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 immunoglobulin G1 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 fragment crystallizable (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 cancer patients 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 (Tecentriq®) is approved in the United States for the treatment of patients with locally advanced or metastatic urothelial bladder carcinoma and metastatic non–small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy and are currently in clinical development for other indications.

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 for Advanced *BRAF*^{V600} Wild-Type Melanoma after Progression on Anti-PD-1 Therapy

The rationale for combining cobimetinib, a MEK inhibitor, with atezolizumab, an anti–PD-L1 antibody, in treatment of patients with advanced *BRAF*^{V600} WT melanoma is based on the complementary mechanisms of action of these agents, as well as on observations that the effects of MAPK pathway inhibition on tumor microenvironment may enhance anti-tumor T cell–mediated immunity. This rationale is supported by nonclinical and clinical data as summarized in this section.

As detailed in Sections 1.1.2 and Section 1.3.2, only 30%–40% of patients with metastatic melanoma respond to anti–PD-1 monotherapies, and many of those who respond initially eventually progress. Patients who do not respond or attain disease stabilization are defined as having refractory disease or primary resistance, whereas those whose tumors progress after initial response or stabilization are defined as having relapsed disease or secondary resistance. The molecular mechanisms of primary and secondary resistance to immunotherapy are poorly understood. However, the known effects of MAPK inhibitors, including cobimetinib, on tumor microenvironment (see Section 1.3.4) include effects that may enable conversion to an immuno-responsive phenotype, sensitize refractory tumors to anti–PD-1/PD-L1 agents, and/or resensitize relapsed tumors to these agents, leading researchers to the hypothesis that combining MEK inhibition with anti–PD-1/PD-L1 therapy may lead to improved efficacy. This hypothesis is supported by clinical data from Study GP28363 (see Section 1.3.5), which has shown that combination therapy with cobimetinib and atezolizumab in advanced melanoma results in improved ORR and PFS relative to either PD-1/PD-L1 or MEK inhibitor monotherapy.

1.3.1.1 Rationale for Atezolizumab Monotherapy for Previously Untreated Patients with Advanced *BRAF*^{V600}-Wild-Type Melanoma

While evidence of efficacy of atezolizumab monotherapy in melanoma has also been demonstrated in Study PCD4989g, as described below, the patient population was heterogeneous with respect to line of therapy and *BRAF*^{V600} status. Enrolling a cohort of previously untreated patients with advanced *BRAF*^{V600} WT melanoma in a separate

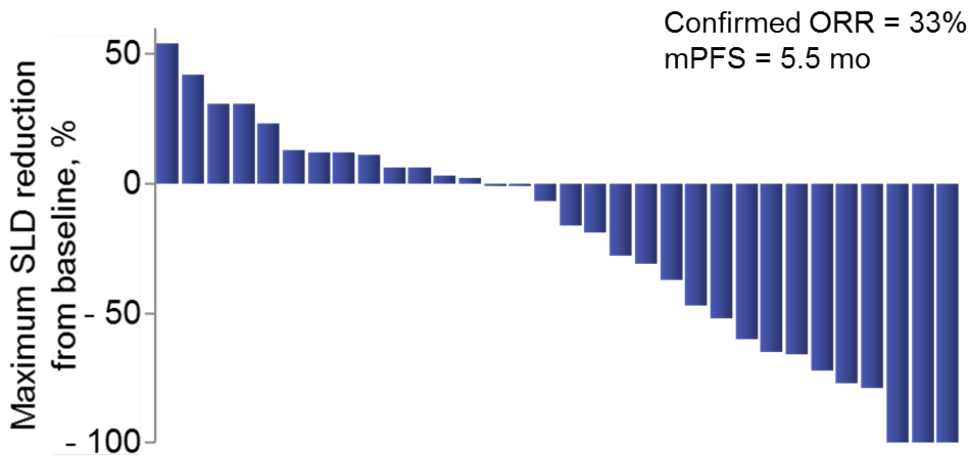
atezolizumab monotherapy cohort will allow a more accurate evaluation of the magnitude of efficacy achievable, pharmacokinetics, and safety profile in this patient population. In addition, it will allow comparison of the potential molecular mechanisms of resistance to checkpoint inhibitor therapy between patients in Cohort C and those previously treated patients enrolled in Cohorts A and B.

1.3.2 Activity of Atezolizumab in Advanced Melanoma

1.3.2.1 Study PCD4989g: Atezolizumab Monotherapy

In the Phase Ia setting (Study PCD4989g), atezolizumab monotherapy has shown anti-tumor efficacy in melanoma efficacy parameters comparable to those documented reported for two PD-1 inhibitors that are currently approved for the treatment of melanoma (pembrolizumab and nivolumab; Hodi et al. 2014; see Figure 1). In patients with metastatic non-ocular melanoma enrolled in Study PCD4989g who received doses of at least 10 mg/kg every 3 weeks (Q3W; N = 37), ORR by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) was 33% and median PFS was 5.5 months as of the 15 December 2015 data cut. In addition, atezolizumab monotherapy was well tolerated by patients with metastatic melanoma.

Figure 1 Phase I Study of Atezolizumab Monotherapy in Cutaneous Melanoma



mPFS = median progression-free survival; ORR = objective response rate; SLD = sum longest diameter.
Note: n = 37.

Please see the current Atezolizumab Investigator's Brochure for the most current safety and efficacy data from atezolizumab studies.

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

MEK inhibitors, as monotherapy and in combination with *BRAF* inhibitors, have proven efficacy in advanced *BRAF*^{V600}-mutated melanoma (Chapman et al. 2011; Flaherty et al. 2012; Larkin et al. 2014; Long et al. 2014; Robert et al. 2015a), and cobimetinib in combination with vemurafenib is approved in this indication.

As described in Section 1.1.1, the MAPK pathway is also implicated in *BRAF*^{V600} WT melanoma. Clinical evidence for modest anti-tumor activity of MEK inhibition in a subset of patients with *BRAF*^{V600} WT melanoma has recently been provided by the Phase III Study NCT01763164 (NEMO), which showed improved PFS for single-agent binimetinib, a small molecule MEK inhibitor, in patients with *BRAF*^{V600} WT, *NRAS*-mutated, advanced melanoma when compared with dacarbazine (hazard ratio = 0.62; Dummer et al. 2016).

1.3.4 Effect of MAPK Inhibition on Tumor-Immune Contexture

The MAPK pathway has also 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). Further, in tumor biopsies from melanoma patients, *BRAF* and MEK inhibitors, alone or in combination, have been shown to increase melanoma antigen expression, major histocompatibility complex **(**MHC) expression, T-cell infiltration, and PD-L1 expression (Wilmott et al. 2012; Frederick et al. 2013; Kakavand et al. 2015; Liu et al. 2015; Hu-Lieskovan et al. 2015). MEK inhibition has also been shown to increase tumor 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 $CD8^+$ and $CD4^+$ T cells and reduced secretion of granulocyte colony-stimulating factor (G-CSF) with reduced mobilization and activity of CD11-positive GRL^+ myeloid–derived suppressor cells (Phan et al. 2013; Ebert et al. 2016), as well as reduced expression of angiogenesis factors with altered tumor vascular support (Ciuffreda et al. 2009; Chang et al. 2013; Mohan et al. 2015).

In addition, 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).

The nonclinical and clinical data described above show that inhibition of the MAPK pathway leads to an increase in immune effector cells in the tumor, thereby priming the microenvironment to enable the immune system to attack the tumor.

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 WT metastatic colorectal cancer (CRC), and NSCLC.

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.

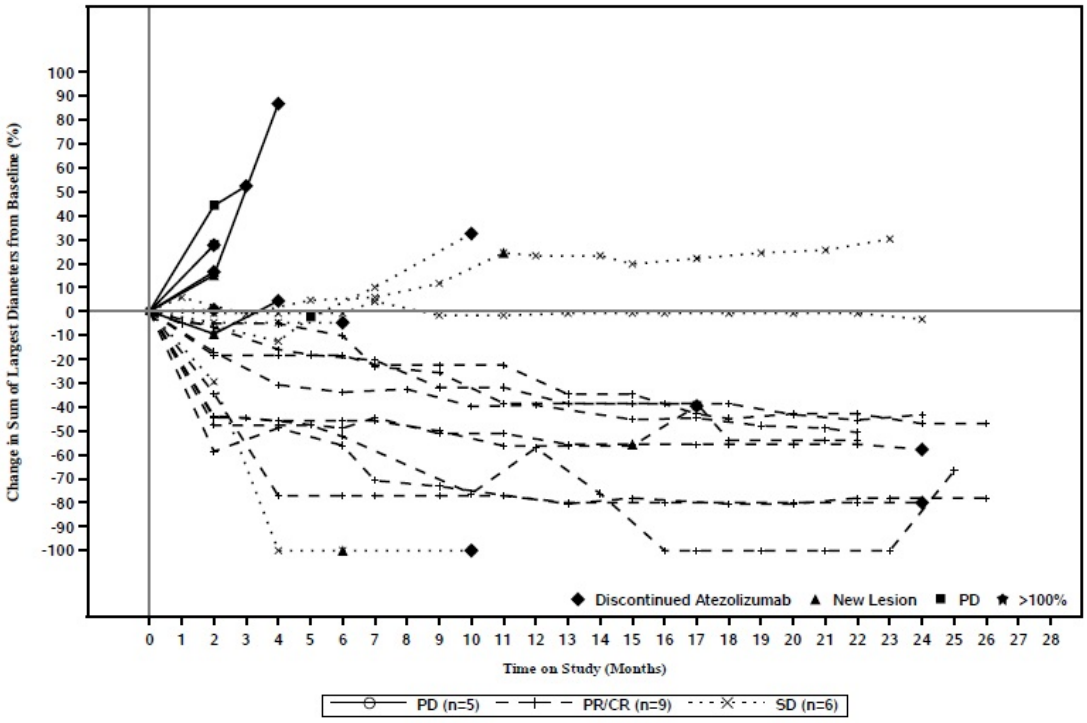
During the Stage 1 dose-escalation phase, there were no dose-limiting toxicities, and 60 mg of cobimetinib on a 21 days on/7 days off schedule with 800 mg of atezolizumab every 2 weeks (Q2W) was determined to be the recommended Phase II dose (Miller et al. 2017).

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 $BRAF^{V600}$ WT disease who had received no prior anti–PD-1 or anti–PD-L1 therapy, were evaluable for efficacy. The data were comparable in both $BRAF^{V600}$-mutant and $BRAF^{V600}$ WT 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 2 and Figure 3 show the RECIST v1.1 responses for all melanoma patients and $BRAF^{V600}$ WT melanoma patients, 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 [CR], a partial response [PR], or stable disease [SD]) was 75%, and median PFS was 15.7 months (95% CI: 2.8, not evaluable). Patients with metastatic melanoma had durability of response, as shown over time in Figure 2 (Miller et al. 2017).

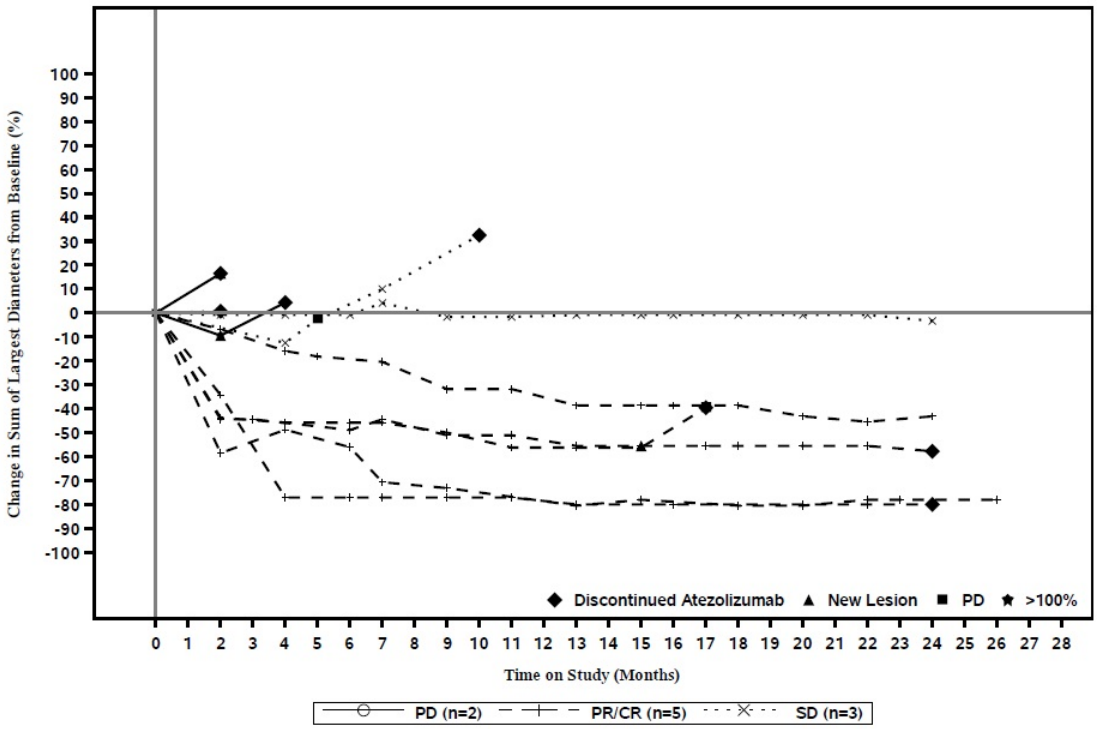
Figure 2 Tumor Burden over Time by Investigator-Confirmed Response per RECIST v1.1 in All Melanoma Patients: Study GP28363



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} WT 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, not evaluable). Patients with *BRAF*^{V600} WT metastatic melanoma had durability of response (confirmed response per RECIST v1.1), as shown in Figure 3.

Figure 3 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 (major histocompatibility complex class 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 Non-Ocular Melanoma

At the time of the data cutoff (17 January 2017), 22 patients with melanoma, including 20 with non-ocular melanoma and 2 patients with ocular melanoma, were evaluated for safety. The median safety follow-up in these patients (n = 22) was 19.4 months (range, 1.4–26.3 months). All grade adverse events occurred in 100% of patients; study treatment–related Grades 3 and 4 adverse events were reported for 59.1% of patients, with diarrhea and dermatitis acneiform being the most common (reported for 3 patients [13.6%] and 2 patients [9.1%], respectively). All adverse events were manageable. Although no cobimetinib-related Grade 5 adverse events occurred, 14% of patients had

study treatment–related serious adverse events, 82% of patients had an adverse event leading to study treatment dose modification and/or interruption, and 27% of patients had discontinued at least one treatment because of adverse events.

Safety in All Patients

As of 17 January 2017, 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 atezolizumab. All patients who received atezolizumab also received cobimetinib. The mean duration of safety follow-up was 3.3 months (0.0–31.3 months). Safety follow-up is defined as the number of days from date of first dose to the minimum of date of last dose + 30 days, discontinuation date, initiation date of anti-cancer therapy, cutoff date, or death date.

Overall, 98.7% of patients experienced at least one adverse event regardless of attribution; 64.0% experienced a Grade ≥ 3 adverse event; and 44. 7 % experienced a serious adverse event. There were 7 (4.0%) Grade 5 (fatal) adverse events in the study, of which 6 were 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.

The most common adverse events (occurring in ≥ 20% of patients) were diarrhea (70.7%), fatigue (56.0%), rash (48.0%), vomiting (42.0%), nausea (36.0%), pruritus (35.3%), decreased appetite (34.7%), constipation (29.3%), peripheral edema (26.0%), pyrexia (23.3%), acneiform dermatitis (23.3%), increased creatine phosphokinase (CPK) (22.7%), dyspnea (20.0%), and anemia (20.0%). The most common Grade ≥ 3 events (occurring in ≥ 5% of patients) were fatigue (10.0%), anemia 9.3%, and diarrhea (8.0%).

In the 17 Jan 2017 data cut for melanoma, the safety data were generally similar. The mean duration of safety follow-up was 19.4 months (range: 1.4–26.3 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 and included pulmonary embolism, bacterial infection, and pain management. There was one (treatment-unrelated) Grade 5 (fatal) adverse event in the melanoma cohort.

The most common treatment-related adverse events (occurring in ≥ 20% of melanoma patients), as of 17 Jan 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%).

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 Risk-Benefit Statement

This Phase Ib 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 in order to enhance the safety of patients in this trial. Oversight will be provided by the Medical Monitor and drug safety personnel.

Treatment options are extremely limited for patients with advanced *BRAF*^{V600} WT melanoma whose disease has progressed on or after treatment with an anti–PD-1 therapy. Given 1) the observed efficacy and safety data for cobimetinib and atezolizumab as single agents and in combination in the Phase Ib study GP28363, 2) biomarker data from Study GP28363, suggesting that the effects of cobimetinib on tumor immune contexture may sensitize refractory tumors or re-sensitize relapsed tumors to anti–PD-1/PD-L1 agents, and 3) the extent of safety monitoring proposed, the potential benefits for patients receiving this combination treatment for advanced melanoma outweigh the potential risks.

The observed efficacy data for atezolizumab as a single agent in Study PCD4989g suggests comparable efficacy to the currently available anti-PD-1 therapies. Based on the known safety profile of atezolizumab, the potential benefit for patients outweigh the potential risks

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the preliminary efficacy, safety, and pharmacokinetics of cobimetinib and atezolizumab in patients with advanced *BRAF*^{V600} WT, metastatic, or unresectable locally advanced melanoma who have progressed on prior anti–PD-1 therapy and atezolizumab monotherapy in patients with previously untreated advanced *BRAF*^{V600} WT melanoma. Specific objectives and corresponding endpoints are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objectives	
• To evaluate the preliminary efficacy of cobimetinib and atezolizumab in patients with advanced *BRAF*^{V600} WT melanoma who have progressed on prior anti–PD-1 therapy • To evaluate the efficacy of atezolizumab monotherapy in patients with advanced *BRAF*^{V600} WT melanoma who have not been previously treated	Co-primary endpoints: • ORR, defined as the proportion of patients who had a confirmed OR. Confirmed OR is defined as a CR or a PR on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1. • DCR, defined as the proportion of patients with a CR, PR, or SD at 16 weeks
Secondary Efficacy Objectives	
• To evaluate the efficacy of cobimetinib and atezolizumab in patients with advanced *BRAF*^{V600} WT melanoma who have progressed on prior anti–PD-1 therapy • To evaluate the efficacy of atezolizumab monotherapy in patients with advanced *BRAF*^{V600} WT melanoma who have not been previously treated	• DOR, defined as the time from the first occurrence of a documented OR to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first • OS, defined as the time from Cycle 1, Day 1 to death from any cause • PFS, defined as the time from Cycle 1, Day 1 to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first • *ORR, DCR, DOR, and PFS, as determined by an independent review committee (IRC) according to RECIST v1.1, in Cohort C*
Exploratory Efficacy Objectives	
• To evaluate the efficacy of cobimetinib and atezolizumab in patients with advanced *BRAF*^{V600} WT melanoma who have progressed on prior anti–PD-1 therapy • To evaluate the efficacy of atezolizumab monotherapy in patients with advanced *BRAF*^{V600} WT melanoma who have not been previously treated	• ORR *as determined by the investigator* according to immune-modified RECIST • DOR *as determined by the investigator* according to immune-modified RECIST • PFS *as determined by the investigator* according to immune-modified RECIST
Safety Objectives	
• To evaluate the safety of cobimetinib and atezolizumab in patients with advanced *BRAF*^{V600} WT melanoma who have progressed on prior anti–PD-1 therapy • To evaluate the safety of atezolizumab monotherapy in patients with advanced *BRAF*^{V600} WT melanoma who have not been previously treated	• Occurrence, frequency, and severity of adverse events, with severity determined through use of NCI CTCAE v4.0 • Change from baseline in targeted vital signs during and following treatment • Change from baseline in targeted clinical laboratory test results during and following treatment • Incidence, severity and time course of serous retinopathy (for Cohorts A and B)

Table 1 Objectives and Corresponding Endpoints (cont.)

Pharmacokinetic Objectives	
• To characterize the pharmacokinetics of atezolizumab monotherapy in Cohort C • To characterize the pharmacokinetics of cobimetinib and atezolizumab when administered in combination in Cohorts A and B	• Serum concentration of atezolizumab at specified timepoints • Plasma concentration of cobimetinib at specified timepoints
Exploratory Pharmacokinetic Objectives	
• To investigate the relationship between cobimetinib exposure and efficacy or safety outcomes using population approaches • To investigate the relationship between atezolizumab exposure and efficacy or safety outcomes using population approaches	• Relationship between cobimetinib plasma concentration and efficacy or safety endpoints • Relationship between atezolizumab serum concentration and efficacy or safety endpoints
Immunogenicity Objective	
• To evaluate the immune response to atezolizumab in previously untreated patients and in patients who have progressed on previous anti-PD-1 therapy	• Incidence of ADAs to atezolizumab 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 Objectives	
• Mechanisms of resistance to anti–PD-1 in Cohorts A and B or anti-PD-L1 in Cohort C • Cobimetinib effect on tumor immune contexture	• TIL distribution, CD8, PD-L1, and stromal markers (TBD) by IHC • Immune-signatures and stromal signature by RNA sequencing • *RAS*, *NF1* mutations, tMB and TCR repertoires by DNA sequencing

ADA=anti-drug antibody; anti–PD-1=anti–programmed death-1; CR=complete response; DOR=duration of response; DCR=disease control rate; IHC= immunohistochemistry; *IRC=independent review committee;* NCI CTCAE=National Cancer Institute Common Terminology Adverse Events; OR=objective response; ORR=objective response rate; OS=overall survival; PD-L1= programmed death–ligand 1; PK= pharmacokinetic; PFS=progression-free survival; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; TBD=to be determined; TIL =tumor-infiltrating lymphocyte; TCR=T-cell receptor; tMB=tumor mutation burden; WT=wild type.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study CO39721 is a Phase Ib, open-label, multicenter, global study designed to evaluate the preliminary efficacy, safety, and pharmacokinetics of cobimetinib and atezolizumab when given to patients with *BRAF*^{V600} WT metastatic or unresectable locally advanced melanoma who have progressed on a prior anti–PD-1 therapy. It is also designed to evaluate efficacy, safety, and pharmacokinetics of atezolizumab monotherapy in patients with *BRAF*^{V600} WT metastatic or unresectable locally advanced melanoma who have not been previously treated. The co-primary endpoints of the study are ORR and DCR.

Approximately 102 patients with *BRAF*^{V600} WT advanced melanoma who have progressed on a prior anti–PD-1 therapy will be enrolled in Cohorts A and B of this study (see Figure 4).

- Cohort A: Approximately 90 patients who have progressed on or after treatment with an anti-PD-1 agent will be enrolled.
- Cohort B (biopsy cohort): *Approximately* 12 patients will be enrolled in a mandatory biopsy cohort with inclusion according to the eligibility criteria specified in Section 4.1.

Approximately 50 patients who have not *received any prior anti-cancer treatment in the metastatic setting* will be enrolled in Cohort C.

Cohort A and B

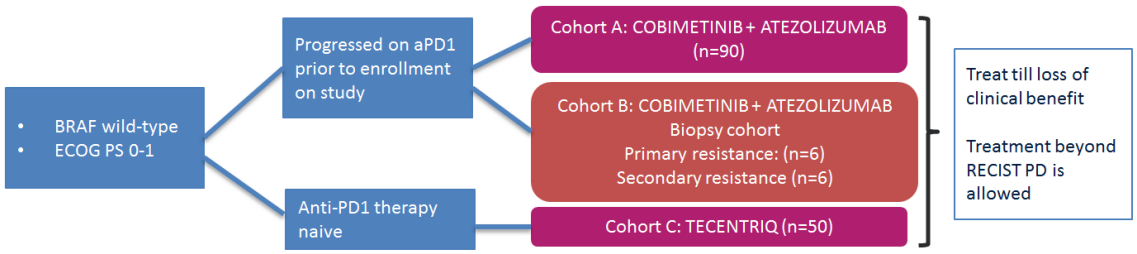
All cycles will be 28 days in length for Cohorts A and B. Patients in Cohort A will begin dosing with cobimetinib and atezolizumab concurrently and will receive in all cycles 840 mg atezolizumab intravenous (IV) Q2W and 60 mg cobimetinib QD 21/7 (see Figure 5).

Patients in Cohort B (biopsy cohort) will also receive 60 mg cobimetinib QD 21/7 in all cycles. However, patients in this cohort will begin dosing with cobimetinib before atezolizumab and will receive 60 mg cobimetinib alone QD for the first 14 days of Cycle 1. Atezolizumab dosing (840 mg IV) will begin on Day 15, Cycle 1, and will continue thereafter at 840 mg IV Q2W. In Cycle 2 and all subsequent cycles, patients in this cohort will receive 60 mg cobimetinib QD 21/7 and 840 mg atezolizumab IV Q2W (see Figure 6).

Cohort C

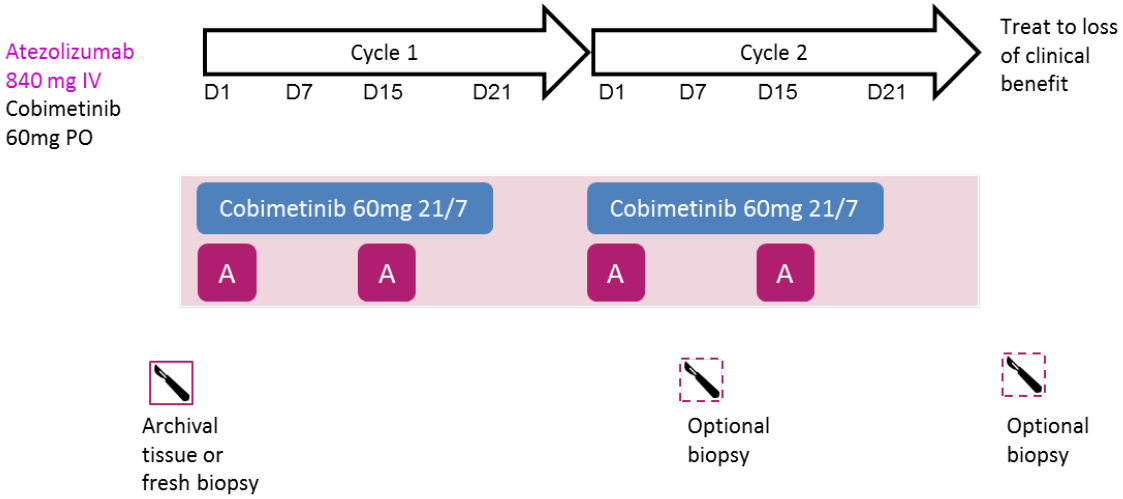
All cycles in Cohort C will be 21 days in length. Patients in Cohort C will receive atezolizumab (1200 mg) Q3W (see Figure 6).

Figure 4 Study Schema



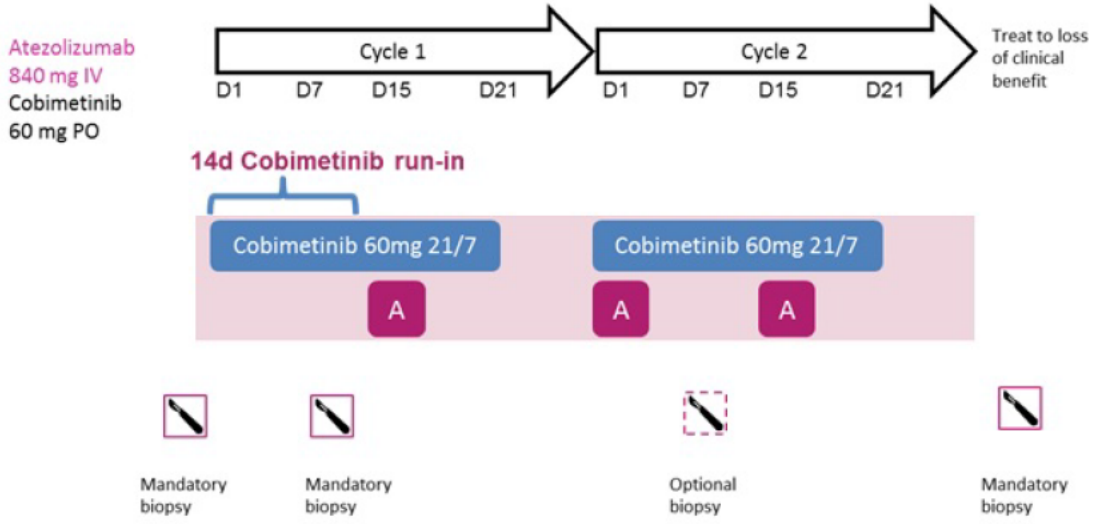
aPD-1 = anti–programmed cell death 1; ECOG = Eastern Cooperative Oncology Group; PD = progressive disease; PS = performance score; RECIST = Response Evaluation Criteria in Solid Tumors.

Figure 5 Treatment and Biopsy Schedule (Cohort A)



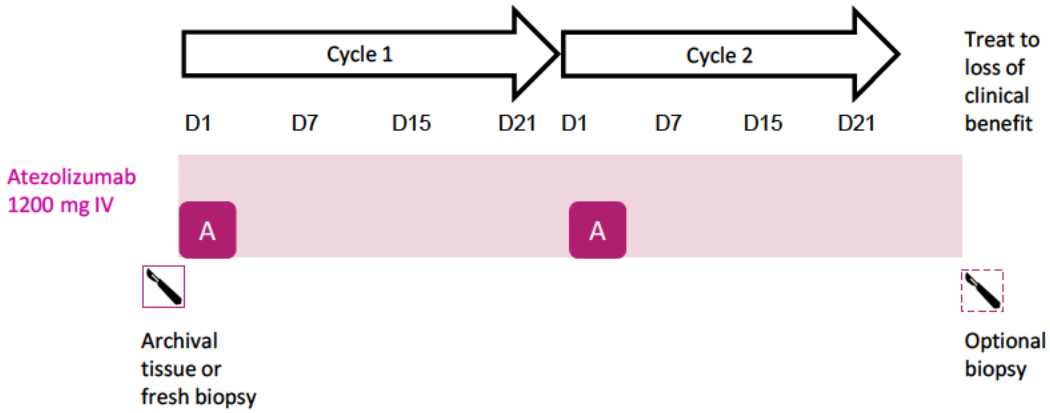
D = day; IV = intravenous; PO = by mouth.

Figure 6 Treatment and Biopsy Schedule (Cohort B)



D = day; IV = intravenous; PO = by mouth.

Figure 7 Treatment and Biopsy Schedule (Cohort C)



D = day; IV = intravenous.

After signing informed consent, eligible patients will undergo screening procedures that include testing for the *BRAF*^{V600} mutation; laboratory tests; 12-lead ECGs; left ventricular function evaluation (LVEF; echocardiogram [ECHO] or multiple-gated acquisition [MUGA] scan); contrast-enhanced brain computed tomography (CT) scan or magnetic resonance imaging (MRI); contrast-enhanced CT or MRI scan of the chest, abdomen, and pelvis; and ophthalmologic (for Cohorts A and B) and dermatologic assessments.

All patients will be closely monitored for safety and tolerability throughout the study. 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 the study treatments for all patients. The protocol includes a detailed risk management plan for monitoring and managing molecule-specific and potential combination toxicities (see Section 5).

For all cohorts, tumor response will be evaluated by the investigator according to RECIST v1.1 (see Appendix 3); immune-modified RECIST v1.1 (see Appendix 4) will also be assessed by the investigator. *For Cohort C, tumor response will also be determined by the independent review committee (IRC) according to RECIST v1.1.* All measurable and non-measurable lesions will be documented at screening. Response will be assessed at 8-week intervals until investigator-determined disease progression (according to RECIST v1.1), death, or initiation of subsequent anti-cancer therapy, whichever occurs first. Patients who experience disease progression must have scans repeated 4 weeks after initial documentation of progression to confirm disease progression. Tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than confirmed disease progression, unless subsequent anti-cancer therapy is initiated.

Study treatment will continue for all patients until investigator-determined disease progression (confirmed 4 weeks later, for clinically stable patients with a favorable benefit-risk assessment), death, unacceptable toxicity, or pregnancy, whichever occurs first. Patients in Cohorts A and B who discontinue one study drug may be able to continue the remaining study drug per guidelines for management of specific adverse events provided in Table 5.

Clinically stable patients who have a favorable benefit-risk assessment may continue on study treatment following radiographic progression per RECIST v1.1. Approval from study medical monitor must be obtained prior to continuing treatment. Patients who continue treatment beyond radiographic disease progression will be closely monitored.

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.

3.1.1 Biopsies and Archival Tissue

Biomarker assessments on tumor biopsy tissue are an important part of this study and will be used to elucidate mechanisms of resistance to anti–PD-1/anti–PDL-1 therapy as well as to evaluate the effects of atezolizumab monotherapy and cobimetinib-atezolizumab combination therapy on tumor immune contexture. All patients must provide archival (< 5 years old) tissue or a fresh biopsy before treatment start.

3.1.1.1 Optional Biopsies (Cohort A)

Patients in Cohort A will be requested, via separate optional consent, to provide biopsies (core needle [minimum three cores and minimum diameter 18 gauge; 16 gauge is preferable] or excisional biopsy) for the study of pharmacodynamic changes related to the activity of cobimetinib and atezolizumab. For patients who consent to biopsies, a predose specimen will be obtained after eligibility criteria have been fulfilled before Cycle 1, Day 1, only if archival tissue (< 5 years old) was provided for the *BRAF* WT testing. Predose specimens are not required for patients who provide a fresh biopsy before treatment start. A subsequent biopsy will be performed 4–6 weeks after the first atezolizumab dose. An additional biopsy may be collected per investigator discretion, preferably at the time of radiographic progression or response.

3.1.1.2 Mandatory Biopsies (Cohort B)

Patients enrolled in Cohort B, the biopsy cohort, must have at least two (preferably three) accessible lesions that meet the requirements specified in the eligibility criteria. Exceptions may be made if patient has only one lesion that allows multiple biopsies following discussion with Medical Monitor. One pretreatment, up to two on-treatment biopsies, and one post-progression biopsy will be performed. If more than one biopsy will be obtained from one lesion, the lesion should be large enough to permit successive biopsies $\geq$1 cm apart. Investigators are strongly encouraged to obtain two on-treatment biopsies as described below; at a minimum, the Day 10–14 biopsy should be obtained to test for possible immunologic effects of cobimetinib alone.

Patients in the biopsy cohort will undergo biopsies according to the following schedule:

- A predose biopsy will be taken before Day 1, Cycle 1. (The predose biopsy is not required if a fresh biopsy was provided during screening).
- On Day 1, Cycle 1, patients will start treatment with cobimetinib alone.
- A mandatory on-treatment biopsy will be obtained between Days 10 and 14 of Cycle 1.
- Patients will receive their first atezolizumab dose on Day 15 of Cycle 1.
- A second, optional, on-treatment biopsy will be obtained during Cycle 2, 4–6 weeks after the first dose of atezolizumab to assess the combined effects of cobimetinib and atezolizumab.
- A mandatory, post-treatment biopsy will be obtained at the time of radiographic progression.

Patients in tumor biopsy cohorts whose tissue sample is not evaluable may receive study treatment, but these patients may be replaced for the purpose of serial biopsy assessment.

If a patient undergoes a medically indicated procedure at any time during the study that has the likelihood of yielding tumor tissue, any remaining samples or a portion of the tumor sample not necessary for medical diagnosis may be obtained for exploratory analysis. Patients must have provided specific consent in order for discarded samples from routine care to be obtained.

3.1.1.3 Optional Biopsies (Cohort C)

Patients in Cohort C are required to provide archival tissue or fresh biopsy during screening. They will be requested to provide optional fresh biopsies (core needle [minimum three cores and minimum diameter 18 gauge; 16 gauge is preferable] or excisional biopsy) for the study of tumor immune contextures related to activity or resistance of atezolizumab. For patients who consent to biopsies, a predose specimen will be obtained after eligibility criteria have been fulfilled before Cycle 1, Day 1, unless a fresh biopsy was provided during screening. An additional biopsy is requested to be collected at the time of radiographic progression.

A schedule of activities is provided in Appendix 1.

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.

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg Q2W (Cohorts A and B) and 1200 mg IV Q3W (Cohort C) 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). Due to the possibility of an initial increase in tumor burden caused by IC infiltration in the setting of a T-cell response (termed pseudoprogression) with atezolizumab 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 atezolizumab will be permitted to continue atezolizumab 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

- Patient's written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial disease progression
- Approval by the Medical Monitor

3.2 END OF STUDY AND LENGTH OF STUDY

The study will end when all patients enrolled have been followed until death, have withdrawn consent, have been lost to follow-up, or when the Sponsor decides to end the trial, whichever occurs first. The total length of the study, from first patient in until end of follow-up, is expected to be approximately 4 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Cobimetinib plus Atezolizumab Dose and Schedule

Concomitant administration of cobimetinib and atezolizumab was studied in Phase Ib Study GP28363 (Section 1.3.5). Cobimetinib and atezolizumab in combination were found to be safe and tolerable with an atezolizumab dose of 800 mg IV Q2W (equivalent to the approved dose and schedule for treatment of bladder cancer of 1200 mg IV Q3W) and cobimetinib on the approved dose and schedule of 60 mg QD 21/7.

Atezolizumab was administered as a single agent in Study PCD4989g with encouraging efficacy and safety outcomes at doses equivalent to the approved dose and schedule for treatment of bladder cancer of 1200 mg IV Q3W (Section 1.3.2). Simulations using a population PK model for atezolizumab demonstrate that at the dose of 840 mg IV Q2W (atezolizumab dose schedule in Arm A and Arm B) provides an exposure within the range typically seen for the 1200 mg IV Q3W dose (Arm C atezolizumab dose schedule). Observed Phase 1 data after Q2W administration was consistent with popPK simulated profiles providing confidence in the predictability of the simulations. Based on the data available, the two dose schedules are expected to be comparable in safety and efficacy.

3.3.1.1 Cohort A (Cobimetinib plus Atezolizumab with Concurrent Start)

Cobimetinib will be given at the approved dose and schedule of 60 mg QD 21/7. For administration with cobimetinib on this 28-day cycle, a dose of 840 mg atezolizumab will be given Q2W. The 840-mg dose is expected to be similar to the 800-mg dose of atezolizumab and was selected in this study to simplify dose administration. Atezolizumab is formulated at a concentration of 60 mg/mL; thus, 800 mg corresponds to a volume of 13.33 mL. To ensure consistent, precise, and clinically feasible administration in this study, the volume was rounded up to 14 mL, corresponding to a dose of 840 mg. The 840-mg dose is not expected to result in meaningfully different exposures compared with an 800-mg dose.

In addition, the atezolizumab dose of 840 mg Q2W is equivalent to an average body weight–based dose of 15 mg/kg Q3W, the Phase II dose for atezolizumab derived from nonclinical and clinical studies. It has been used in multiple atezolizumab Phase III studies in other indications.

3.3.1.2 Cohort B (Biopsy Cohort)

Cohort B is designed to allow assessment of the effects of cobimetinib on immune therapy. In this cohort, in Cycle 1 only, cobimetinib will be given for 14 days before initiation of atezolizumab treatment as described in Section 3.1. Biopsies obtained before treatment start and at the end of the 14-day cobimetinib monotherapy period will allow elucidation of the effects of cobimetinib on tumor immune contexture. Additional biopsies taken during the combination treatment period and at radiographic progression will support evaluation of the effects of combination treatment on the tumor micro-environment and the identification of potential mechanisms of resistance to combination therapy.

During Cycle 2 and all subsequent cycles, patients in Cohort B will receive cobimetinib 60 mg QD 21/7 and atezolizumab 840 mg IV Q2W, the same dose and schedule as in Cohort A.

3.3.1.3 Cohort C (Atezolizumab Monotherapy Cohort)

Atezolizumab will be administered at a dose of 1200 mg IV Q3W. As detailed in Section 3.3.1, this approved dose schedule based on average body weight results in similar atezolizumab exposure after the 840 mg Q2W dose schedule.

3.3.2 Rationale for Patient Population and Cohorts

3.3.2.1 Cohort A (Cobimetinib plus Atezolizumab with Concurrent Start)

Cohort A will enroll patients with advanced *BRAF*^{V600} *WT* melanoma whose disease has progressed on or after treatment with an anti–PD-1 agent. This patient population has limited treatment options and high unmet need. The known effects of MAPK inhibitors, including cobimetinib, on tumor microenvironment (see Section 1.3.4), include effects that may enable conversion to an immunoresponsive phenotype, sensitize refractory tumors to anti–PD-1/PD-L1 agents, and/or re-sensitize relapsed tumors to these 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) which indicate that combination therapy with cobimetinib and atezolizumab in advanced melanoma results in improved ORR and PFS relative to either PD-1/PD-L1 or MEK inhibitor monotherapy.

3.3.2.2 Cohort B (Biopsy Cohort)

The molecular mechanisms of primary and secondary resistance to anti–PD-1/PD-L1 therapies and effects of cobimetinib on the tumor microenvironment in patients with post–PD-1 progression require further elucidation to inform optimal development of combination therapy. In order to ensure that biomarker data collected from biopsies are

optimally informative, patients enrolled in Cohort B are required to fulfill additional eligibility criteria that define their disease as true primary or secondary resistant.

In order to ensure that patients have received sufficient anti–PD-1 therapy to adequately assess the tumor's sensitivity, and that the tumor's current molecular profile represents the molecular profile at progression, all patients in this cohort must have received a minimum of two cycles of the anti–PD-1 agent and must have progressed on or after this therapy within 12 weeks before study start.

The cohort will enroll *approximately* 6 patients with primary resistance, defined as progressive disease (PD) as best response, according to RECIST v1.1, and *approximately* 6 patients with secondary resistance, defined as PD following initial confirmed response according to RECIST v1.1.

3.3.2.3 Cohort C (Atezolizumab Monotherapy)

Cohort C will enroll approximately 50 patients with advanced *BRAF*^{V600} WT melanoma, who have not received previous treatment, to receive atezolizumab monotherapy.

Data from Study PCD4989g indicate that atezolizumab monotherapy provides efficacy benefit in advanced melanoma comparable with that reported for approved aPD-1 monotherapies and has a comparable safety profile (Section 1.1.2). However, since the patient population in this study was heterogeneous with respect to line of therapy and *BRAF* ^{V600} status, evaluation of atezolizumab monotherapy in previously untreated, *BRAF* WT melanoma, will allow more accurate understanding of the achievable magnitude of efficacy in this population. In addition, this cohort will allow comparison of the potential molecular mechanisms of resistance between the 3 cohorts.

In all Cohorts A, B and C, inclusion criteria require that *BRAF*^{V600} WT status has been confirmed using an approved clinical test.

In order to ensure that the ORR, DCR, duration of response (DOR), and PFS can be adequately assessed, patients must have measureable disease (per RECIST v1.1.) and locally advanced, unresectable or metastatic melanoma, as defined by the American Joint Committee on Cancer classification, Version 7 (Balch et al. 2009).

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

3.3.3 Rationale for Primary Endpoint Selection

This study is designed to gain preliminary information on the potential for efficacy of atezolizumab in combination with cobimetinib in *BRAF*^{V600} WT melanoma that has

progressed on or after treatment with an anti−PD-1 therapy and will initially enroll a limited number of patients (n = 42). Compelling evidence of anti-tumor activity in these patients will result in further evaluation of the combination's activity in this indication

The study will also enroll an additional cohort of patients with *BRAF*^{V600} WT melanoma who have not been previously treated to obtain additional efficacy and safety data for atezolizumab as monotherapy. This will extend the efficacy data seen in melanoma in Study PCD4989g and clarify the magnitude of benefit achievable in previously untreated *BRAF*^{V600} WT patients.

The co-primary endpoints for this study are ORR and DCR at 16 weeks.

ORR is recognized as a correlate of survival in advanced melanoma and has been used as a primary endpoint in a pivotal study in this indication (Weber et al. 2015). DCR at 16 weeks is included as a co-primary efficacy endpoint because clinical experience in Study GP28363 indicates that early evaluations of ORR may underestimate the percentage of patients who benefit from the combination. In Study GP28363, of the 9 melanoma patients with a PR, 3 patients had prolonged SD and converted from SD to a PR after > 12 months of therapy. Further, in a recent retrospective study that included 172 metastatic melanoma patients treated with high-dose IL-2, SD and DCR were found to correlate well with survival (Hughes et al. 2015). Early compelling evidence of anti-tumor activity, based on a high DCR rate, will allow timely initiation of further evaluation of the combination.

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

In this study, all patients will have confirmatory scans performed 4 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 burden caused by IC infiltration in the setting of a TCR 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 assessment may continue on study treatment following radiographic progression per RECIST v1.1. Approval from the study medical monitor must be obtained prior to continuing treatment. Patients who continue treatment beyond radiographic disease progression will be closely monitored. Treatment may be discontinued if clinical deterioration occurs due to disease progression.

3.3.5 Rationale for Biomarker Assessments

Tumor tissue samples will be collected at baseline for genetic and histopathologic assessments at DNA, RNA, protein, and cellular levels to add to researchers' understanding of disease pathobiology. Genetic alterations, immune contextures, and microenvironment of *BRAF*^{V600} WT melanoma may have profound effects on the efficacy of this combination. Biomarker data from archival/baseline tumor will be analyzed together with the treatment outcomes to explore potential factors associated with favorable response or treatment escape. Because these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

Tumor biopsies are scheduled during treatment and at progression to further elucidate the possible mechanism of action or mechanisms of treatment escape (innate or acquired) of this regimen and may include evaluation of $CD8^+$ T-cell or other IC infiltrate, PD-L1 expression, TCR repertoires, MAPK activation, and others involved in apoptosis or inflammation.

3.3.6 Rationale for Blood Sampling for Biomarker Assessments

An exploratory objective of this study is to evaluate biomarkers (including, but not limited to, whole genome sequencing (WGS), mutations in circulating-tumor DNA), and TCR repertoires in blood samples. The evaluation of blood biomarkers may provide evidence for biologic activity of atezolizumab plus cobimetinib in patients who have been previously treated with anti−PD-1 and of atezolizumab monotherapy in patients who have not been treated with anti-PD-1, respectively, and may allow for exploration of a relationship of these biomarkers with the activity of cobimetinib and atezolizumab.

3.3.7 Rationale for Ophthalmologic Assessments (Cohorts A and B)

Serous retinopathy has been observed in patients treated with MEK-inhibitors, including cobimetinib (Flaherty et al. 2012). Manifestations of serous retinopathy include retinal detachment (i.e., fluid accumulation between the neurosensory retina and the retinal pigment epithelium) and retinopathy. Although serous retinopathy can lead to visual disturbances, in some circumstances it may also be asymptomatic.

Serous retinopathy was prospectively monitored in Study GO28141 in all 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. Most events of serous retinopathy occurred early in treatment with a median onset of 1 month (De la Cruz-Merino et al. 2015).

In order to further characterize the nature and time course of this adverse event, and its impact to patients, additional ophthalmologic investigations have been incorporated in this study. All patients are required to undergo a baseline ophthalmologic examination to assess for history or evidence of retinal abnormalities. Thereafter, patients will have comprehensive ophthalmologic testing every 2 weeks during the first two cycles of treatment, and then every 4 weeks until Day 1 of Cycle 7 (Cohorts A and B). If serous retinopathy is detected at any of these visits, monitoring will be continued at increased frequency (see Section 4.4.7) until the adverse event resolves or 6 months have elapsed, whichever occurs first.

3.3.7.1 Rationale for Optional Whole Genome Sequencing

Genomics is increasingly informing understanding of disease pathobiology and rationale for the development of new therapeutic approaches. WGS provides comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for making these discoveries.

Relevant literature on genomic analyses shows ample examples of genetic variations and their implications in immune responses. For instance, a recent report identified 20 genes linked to variability of the immune response to seasonal influenza vaccination, 7 of which were shown to be involved in intracellular antigen transport, processing, and presentation (Franco et al. 2013). Similarly, genome–wide association studies (GWAS) have identified specific genetic variants that are associated with differences in WBC, neutrophil, and monocyte counts among individuals (Knight 2013). Furthermore, GWAS in autoimmune diseases have led to novel insights. One example is the role of autophagy in Crohn disease, which was elucidated based on variation at two loci and has now become a major therapeutic target in this disease (Hu and Daly 2012).

It is also established that genetic variants of drug-metabolizing enzymes and transporters can affect the pharmacokinetics of drugs, which affects safety and efficacy. For example, patients who carry defective alleles of the gene encoding uridine diphosphate glucuronosyltransferase 1A1, which facilitates the metabolism and excretion of SN-38 (the active metabolite of irinotecan), are at a higher risk for adverse effects associated with the use of standard doses of irinotecan (O'Dwyer and Catalano 2006).

In addition to the link between genetic variation in drug-metabolizing enzymes and transporters and pharmacokinetics, recent studies have also identified genetic variants that increase the likelihood of (or are protective of) developing drug–induced adverse events. For example, *HLA* has been demonstrated to play an important role in the development of drug-induced rash for some drugs (carbamazepine, abacavir, and allopurinol; Michels and Ostrov 2015; Shirzadi et al. 2015; Stamp et al. 2015). In addition, mutations in *GSTP1*, *CTLA4*, and *FDG4* have been associated with development of drug–induced peripheral neuropathy of various small molecules (Lecomte et al. 2006; Ruzzo et al 2007; Favis et al. 2011; Baldwin et al. 2012).

Therefore, determining host genetic variation by performing WGS on patient samples collected in this study and assessing the relationship with response to treatment and observed adverse events may enable a further understanding of efficacy and safety for cancer immunotherapy and other therapeutic approaches. To this end, a blood sample may be collected from patients enrolled in this study for DNA extraction to enable WGS analysis. The WGS testing is an optional component of this study; patients can decline this sample collection and test.

WGS is contingent upon the review and approval by each site's Institutional Review Board/Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS, this assessment will not be applicable at that site.

3.3.8 Rationale for Pharmacokinetic Assessments

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 potential drug interactions between the two molecules by comparing the PK data from this study with single-agent data from previous studies. In addition, single-agent atezolizumab data from Cohort C will be compared to atezolizumab PK collected in the combination cohorts (Cohort A and Cohort B).

Atezolizumab is primarily eliminated by catabolism to inactive metabolites and, therefore, it 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. Because of the differences in metabolism, no drug–drug interaction is anticipated between cobimetinib and atezolizumab.

A sparse sampling strategy will be applied in this study. Samples for pharmacokinetic (PK) characterization of cobimetinib and atezolizumab will be collected as outlined in Appendix 2. The pharmacokinetics of each compound each drug will be compared with single-agent data for each molecule from previous studies or previously developed population PK models.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 102 patients with advanced melanoma who have progressed on or after prior treatment with an anti–PD-1 therapy will be enrolled in Cohorts A and B.

An additional 50 patients with advanced melanoma who have not received previous treatment will be enrolled in Cohort C.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry.

4.1.1.1 Disease-Specific Inclusion Criteria: Cohorts A and B

- Histologically confirmed Stage IV (metastatic) or unresectable Stage IIIc *BRAF*^{V600} WT (locally advanced) melanoma
- Documentation of *BRAF*^{V600} mutation–negative status in melanoma tumor tissue (archival [< 5 years old] 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, CE-marked [European conformity] in vitro diagnostic in E.U. countries, CLIA-certified next-generation sequencing (NGS) test or equivalent)
- Measurable disease according to RECIST v1.1 (see Appendix 3)
- Disease progression on or after treatment with a PD-1 inhibitor either as monotherapy or in combination with other agent(s)

4.1.1.2 Additional Disease-Specific Inclusion Criteria in Cohort B (Biopsy Cohort)

- Patients in this cohort must have progressed on or after anti–PD-1 therapy within 12 weeks before study start.
- Patients in this cohort must have received a minimum of two cycles of anti–PD-1 therapy.
- Patients in this cohort must meet criteria for primary (n = 6) or secondary (n = 6) resistance to an anti-PD-1 agent as outlined below:

  Primary resistance is defined as PD as best response according to RECIST v1.1.

  Secondary resistance is defined as PD after initial response according to RECIST v1.1.
- Patients in this cohort must consent to undergo tumor biopsies of accessible lesions, before and during treatment and at radiographic progression, for biomarker analyses.
- Patients in this cohort must have at least two accessible lesions that are amenable to excisional or core-needle (minimum three cores and minimum diameter 18 gauge; however, 16 gauge is desirable) biopsy with acceptable risk of a major procedural complication. Exceptions may be made if patient has only one lesion that allows multiple biopsies following discussion with Medical Monitor.

4.1.1.3 Disease-Specific Inclusion Criteria: Cohort C

- Histologically confirmed Stage IV (metastatic) or unresectable Stage IIIc *BRAF*^{V600} WT (locally advanced) 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} mutation–negative status in melanoma tumor tissue (archival [< 5 years old] 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, CE-marked [European conformity] in vitro diagnostic in E.U. countries, CLIA-certified next-generation sequencing [NGS] test 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)

4.1.1.4 General Inclusion Criteria

- Signed Informed Consent Form
- Age ≥ 18 years
- Ability to comply with the study protocol, in the investigator's judgment
- ECOG performance status of 0 or 1 (see Appendix 5)
- Available and adequate baseline tumor tissue sample (archival [< 5 years old] or newly obtained biopsy; see Section 3.1.1)
- Life expectancy ≥ 18 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days before initiation of study treatment:

  Neutrophils (ANC ≥ 1500 cells/μL without G-CSF support within 2 weeks before Cycle 1, Day 1)

  WBC counts > 2500 cells /μL and < 15,000 cells /μL

  Lymphocyte count ≥ 500 cells/μL

  Platelet count ≥ 100,000 cells /μL (without transfusion within 2 weeks before Cycle 1, Day 1)

  Hemoglobin ≥ 9.0 g/dL (without transfusion)

Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance (CrCl) ≥ 40 mL/min on the basis of measured CrCl from a 24-hour urine collection or Cockcroft-Gault glomerular filtration rate estimation:

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

AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ upper limit of normal (ULN), with the following exceptions:

- Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN
- Patients with documented liver or bone metastases: alkaline phosphatase $\leq 5 \times$ ULN

Serum albumin $\geq$ 25 g/L

Total bilirubin $\leq$ 1.5 $\times$ ULN; patients with known Gilbert's disease may have a bilirubin $\leq$ 3.0 $\times$ ULN

For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq$ 1.5 $\times$ ULN within 28 days before initiation of study treatment

For patients receiving therapeutic anticoagulation: stable anticoagulant regimen and stable INR during the 28 days immediately preceding initiation of study treatment

For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period, within 5 months after the last dose of atezolizumab, and within 3 months after the last dose of cobimetinib. *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 (≥ 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 a condom, and agreement to refrain from donating sperm, as defined below:

  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.

4.1.2 Exclusion Criteria

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

4.1.2.1 Cancer-Related Exclusion Criteria

- Prior treatment with a MAPK inhibitor
- Ocular melanoma
- Major surgical procedure other than for diagnosis within 4 weeks before initiation of study treatment, or anticipation of need for a major surgical procedure during the course of the study
- Traumatic injury within 2 weeks before initiation of study treatment
- Palliative radiotherapy within 14 days before initiation of study treatment
- Active malignancy (other than *BRAF*^{V600} mutation–negative melanoma) or malignancy within 3 years before screening, with the exception of resected melanoma, resected basal cell carcinoma, resected cutaneous squamous cell carcinoma, resected carcinoma in situ of the cervix, resected carcinoma in situ of the breast, in situ prostate cancer, limited-stage bladder cancer, or other curatively treated malignancies from which the patient has been disease-free for at least 3 years

  Patients with a history of isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer are eligible for the study.
- Treatment with any anti-cancer agent 14 days prior to Cycle, Day 1 other than a PD-1 based therapy
- Adverse events from prior anti-cancer therapy that have not resolved to Grade ≤ 1

  Clinically stable patients with manageable immune-related adverse events resulting from prior cancer immunotherapy may be eligible for the study after discussion with and approval by the Medical Monitor.
- For Cohort C, specific exclusion criteria include any prior anti-cancer therapy for advanced melanoma

4.1.2.2 Ocular Exclusion Criteria (Cohorts A and B)

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

4.1.2.3 Cardiac Exclusion Criteria (Cohorts A and B)

- History of clinically significant cardiac dysfunction, including the following:

  Unstable angina, or new-onset angina within 3 months before initiation of study treatment

  Symptomatic congestive heart failure, defined as New York Heart Association Class II or higher

  Myocardial infarction within 6 months before initiation of study treatment

  Unstable arrhythmia

  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

  LVEF below the institutional lower limit of normal or below 50%, whichever is lower

4.1.2.4 Central Nervous System Exclusion Criteria

- Untreated or actively progressing central nervous system (CNS) lesions (carcinomatous meningitis)

  Patients with stable and asymptomatic CNS metastases are eligible, if they meet all of the following:

  - Measurable disease, per RECIST v1.1, must be present outside the CNS.
  - All known CNS lesions are clinically stable.
  - CNS lesions have not been treated with whole-brain radiotherapy, except in patients who underwent definitive resection of or stereotactic therapy for all radiologically detectable parenchymal brain lesions.
  - Absence of interim progression must be confirmed by radiographic study within 4 weeks before initiation of study treatment. If new CNS metastases are suspected during the screening period, a confirmatory radiographic study is required before initiation of study treatment.
  - Any radiotherapy or surgery must be completed $\geq$4 weeks before initiation of study treatment.
  - There is no ongoing requirement for corticosteroids, and any prior corticosteroid treatment must be discontinued $\geq$2 weeks before initiation of study treatment. Treatment with an anticonvulsant at a stable dose is allowed.

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

4.1.2.5 Exclusions Related to Infections

- 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 chronic obstructive pulmonary disease) are eligible.
- Active or chronic viral hepatitis B or C infection

  Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study if quantitative HBV DNA $<$ 500 IU/mL at screening.

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

4.1.2.6 Exclusion Criteria Related to Autoimmune Conditions and Immunomodulatory Drugs

- 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 a stable dose of thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study.

  Patients with a history of manageable immune-related adverse events resulting from prior immunotherapy may be eligible for the study after discussion with and approval by the Medical Monitor

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  – Rash must cover $<$10% of body surface area.

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

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

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Treatment with systemic immunosuppressive medication (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor alpha [TNF-α] agents) within 2 weeks before initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study *with the following exceptions:*

  Patients who have received acute, low-dose systemic immunosuppressant medication ($\leq$10 mg/day oral prednisone or equivalent) or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study *after Medical Monitor approval has been obtained*.

  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.

4.1.2.7 Additional Exclusion Criteria

- Current severe, uncontrolled systemic disease (including, but not limited to, clinically significant cardiovascular, pulmonary, or renal disease) other than cancer
- 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
- Any psychological, familial, sociological, or geographic condition that may hamper compliance with the protocol and follow-up after treatment discontinuation
- Inability or unwillingness to swallow pills
- History of malabsorption or other clinically significant metabolic dysfunction that may interfere with absorption of oral study treatment
- Pregnant or breastfeeding, or intending to become pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days before initiation of study treatment.

- Known clinically significant liver disease, including alcoholism, cirrhosis, fatty liver, and other inherited liver disease as well as active viral disease, including positive HIV test at screening.
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Treatment with a live, attenuated vaccine within 4 weeks before initiation of study treatment, or anticipation of need for such a vaccine during the course of the study
- Known hypersensitivity to biopharmaceutical agents produced in Chinese hamster ovary cells
- Known hypersensitivity to any component of the atezolizumab or cobimetinib formulations
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent
- Requirement for concomitant therapy or food that is prohibited during the study, as described in Section 4.3, respectively

4.2 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are cobimetinib and atezolizumab.

4.2.1 Formulation, Packaging, and Handling

4.2.1.1 Cobimetinib

Cobimetinib tablets will be supplied by the Sponsor. The 20-mg cobimetinib drug product is a film-coated, white, round, immediate-release tablet. Cobimetinib will be packaged in blister packs. The inactive ingredients in cobimetinib are as follows: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate for the tablet core. The tablet coating consists of polyvinyl alcohol, part hydrolyzed, titanium dioxide, polyethylene glycol 3350, and talc. Cobimetinib should not be stored above 25°C (77°F). If the study drug is stored outside of the permitted temperature ranges, quarantine the affected supply and contact the monitor.

For further details, see the Cobimetinib Investigator's Brochure.

4.2.1.2 Atezolizumab

Atezolizumab will be supplied by the Sponsor as sterile liquid in 20-mL glass vials. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20-mL volume. For Cohorts A and B, extraction of 14 mL of atezolizumab solution from a 1200 mg 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.

4.2.2 Dosage, Administration, and Compliance

4.2.2.1 Cobimetinib

Patients in Cohorts A and B will receive 60 mg (3 tablets of 20 mg each) orally QD for 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 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 are provided in Section 5.1.3.

Any overdose or incorrect administration of cobimetinib should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of cobimetinib should be recorded on the Adverse Event eCRF (see Section 5.3.5.12).

4.2.2.2 Atezolizumab

Cohort A: Patients will initiate dosing with atezolizumab concurrently with cobimetinib and will receive atezolizumab 840 mg IV Q2W on Days 1 and 15 of all cycles.

Cohort B: Patients will receive the first dose of atezolizumab at 840 mg IV on Day 15 of Cycle 1. Thereafter, they will receive atezolizumab 840 mg IV Q2W on Days 1 and 15 of Cycle 2 and all subsequent cycles.

Cohort C: Patients will receive atezolizumab 1200 mg IV Q3W as monotherapy.

All dosing schedules will be given in a monitored setting where there is immediate access to trained personnel and adequate equipment/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 given per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Infusions of Atezolizumab

First Infusion	Subsequent Infusions
Premedication is allowed.	If patient experienced IRR during any previous infusion, premedication with antihistamines may be administered for Cycles ≥ 2 at the discretion of the treating physician.
Record vital signs (HR, RR, BP, and T) within 60 minutes before starting infusion.	Record vital signs (HR, RR, BP, and T) within 60 minutes before starting infusion.
Infuse atezolizumab (one vial in 250 mL NaCl) over 60 (± 15) minutes	If the patient tolerated the first infusion without infusion-associated AEs, the second infusion may be delivered over 30 (± 10) minutes.
Record vital signs (HR, RR, BP, and T) during the infusion or after the infusion if clinically indicated	If the patient had an IRR during the previous infusion, the subsequent infusion must be delivered over 60 (± 15) minutes.
	Record patient's vital signs (HR, RR, BP, and T) during the infusion or after the infusion if clinically indicated or patient experienced symptoms during the previous infusion.
Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	
	If no reaction occurs, continue subsequent infusions over 30 (± 10) minutes with same schedule for recording vital signs.

AE = adverse event; BP = blood pressure; HR = heart rate; IRR = infusion-related reaction; NaCl = sodium chloride; RR = respiratory rate; T = temperature.

Dose reductions of atezolizumab are not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events related to the combination of cobimetinib and atezolizumab are provided in Sections 5.1.3 (see Table 6). Guidelines for treatment interruption or discontinuation and the management of atezolizumab-specific adverse events are provided in Section 5.1.2 and Appendix 8, as well as the Atezolizumab Investigator's Brochure. For anaphylaxis precautions, see Appendix 7.

See the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

Any overdose or incorrect administration of atezolizumab should be noted on the atezolizumab administration eCRF. Adverse events associated with an overdose or incorrect administration of atezolizumab should be recorded on the Adverse Event eCRF (see Section 5.3.5.12).

4.2.3 Investigational Medicinal Product Accountability

Both IMPs required for completion of this study, cobimetinib and atezolizumab, will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs, using an interactive voice- or Web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

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.

4.2.4 Post-Trial Access to Cobimetinib and Atezolizumab

The Sponsor will offer post-trial access to the study drugs (cobimetinib and atezolizumab) 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 study drug 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 study drug after completing the study if any of the following conditions are met:

- The study drug is 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 drug or data suggest that the study drug is not effective for advanced melanoma that has progressed on or after treatment with an anti–PD-1 therapy.
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for advanced melanoma that has progressed on or after treatment with an anti–PD-1 therapy.
- Provision of study drug 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 website:

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

4.3 CONCOMITANT THERAPY

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 before initiation of study drug to treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.3.1 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 given as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)

Anti-emetic and anti-diarrheal medications should not be given 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 given prophylactically before initial treatment with study drugs. Hematopoietic growth factors may be given 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.

4.3.2 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*)* and during study treatment until disease progression is documented and patient has discontinued study treatment.

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, 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.
- Any live, attenuated vaccine (e.g., FluMist®) within 4 weeks before study start or at any time during the study or within 5 months following the last infusion of atezolizumab.
- Prohibited therapies applicable to patients receiving atezolizumab:

  Immunomodulatory agents, including, but not limited to, IFNs or IL-2, during the entire study; these agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab.

  Immunosuppressive medications, including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab.

  Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations where systemic corticosteroids or TNF-α inhibitors would be routinely given, 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 4.3.2).

- For patients receiving cobimetinib:

  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).

  Avoid 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 medications not listed above.

4.3.3 Cautionary Therapy for Atezolizumab-Treated Patients

4.3.3.1 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 4.3.2).

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 8 for details).

4.4 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of activities to be performed during the study.

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. Safety assessments specified in this section are for the purposes of monitoring and management of toxicities known to be associated with study drugs included in this study (see Section 5 for further information).

4.4.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific procedures. Informed Consent Forms for enrolled patients will be maintained at the study site.

BRAF^{V600} WT status must be known before beginning the remaining screening evaluations. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before study start. 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 and Re-screening

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.

Patients may be eligible for re-screening up to two additional times, with all inclusion and exclusion criteria being re-assessed.

4.4.2 Medical History and Demographic Data

Medical history, including clinically significant diseases and surgeries within 5 years before initiation of study treatment, cancer history (including prior cancer therapies, surgeries, and procedures), and use of alcohol, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days before initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

4.4.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat (HEENT), neck, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. HEENT examination should include visual inspection and/or palpation of the oral cavity and oropharynx, and palpation of the draining lymph nodes of the neck. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations, consisting of an evaluation of the oral cavity, oropharynx, head and neck (including lymph nodes), lungs, heart, abdomen, and skin, should be performed at specified post-baseline visits and as clinically indicated.

Patients should be asked specifically about skin and vision changes as part of each physical examination. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Patients should be asked specifically about skin and vision changes as part of each physical examination.

As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

4.4.4 Vital Signs

Vital signs include measurements of heart rate, respiratory rate, and systolic and diastolic blood pressures while the patient is in a seated position, as well as oral or tympanic temperature. Blood pressure and heart rate measurements will be recorded after a 5-minute rest while the patient is in a seated position. Resting oxygen saturation will be measured during screening.

Vital signs should be measured within 60 minutes before each atezolizumab infusion and, if clinically indicated, during or after the infusion. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

For patients in the atezolizumab arm who experienced an infusion-related reaction (IRR) during the previous atezolizumab infusion, refer to Section 5.3.5.1).

4.4.5 Tumor and Response Evaluations

All measurable and non-measurable lesions must be documented at screening (within 28 days before initiation of study treatment). Evaluation of tumor response conforming to RECIST v1.1 must then be documented every 8 weeks ($\pm$1 week); from the date of first study drug administration until investigator-determined disease progression (according to RECIST v1.1 that is confirmed 4 weeks after initial documentation of progression) 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.

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 scanner 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 Appendix 1) must be evaluated at each tumor assessment with the same radiographic procedure as the baseline study. Patients without brain metastases do not need brain scans for tumor assessment unless clinically warranted. Clinical disease assessments by physical examination should be performed for patients with palpable/superficial lesions. Tumor measurements for each patient should be made by the same investigator or radiologist, if feasible, using the same assessment technique or procedure throughout the study.

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

4.4.6 Left Ventricular Ejection Fraction

All patients will require evaluation of LVEF at screening and Cohorts A and B will require subsequent evaluations of LVEF.

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

- Screening
- Cycle 2, Day 1 $\pm$1 week
- Day 1 of every three treatment cycles thereafter, starting at Cycle 5 ($\pm$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, 4, 10, and 16 weeks, and then resume monitoring 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 by the same method (ECHO or MUGA scan) for each patient. It is strongly encouraged that the same laboratory and operator perform ECHO/MUGA scans for each 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.

4.4.7 Ophthalmologic Examination (Cohorts A and B)

All patients in Cohorts A and B will require an ophthalmologic examination at screening and subsequent ophthalmologic examinations. The objective of a baseline ophthalmologic examination is to evaluate for evidence of retinal abnormalities. An ophthalmologic examination must be performed by a qualified ophthalmologist.

Baseline and serial surveillance ophthalmologic examinations will include visual acuity testing using a standard Snellen chart, intraocular pressure measurement by tonometry, slit-lamp biomicroscopy, indirect ophthalmoscopy, spectral–domain optical coherence tomography (OCT), and automatic visual field testing. Spectral-domain OCT, if not available, may be substituted with time-domain OCT. Ophthalmologic examinations must be performed according to the schedule in Table 3.

Table 3 Ophthalmologic Examination Schedule

	Frequency	Assessments
Screening	One time	Visual acuity test, VF 24-2, slit-lamp biomicroscopy, IOP measurement, OCT, indirect ophthalmoscopy
Cycles 1 and 2	Q2W (±1) day *of the scheduled visit*, if serous retinopathy is not detected	Visual acuity test, OCT, indirect ophthalmoscopy [a]
	Increase to QW (±1) day, if serous retinopathy is detected, until resolution or until Cycle 2, Day 28, whichever occurs first	Visual acuity test, VF [b], OCT, indirect ophthalmoscopy
Cycles 3 to 6	Q4W ±1 day *of the scheduled visit*, if serous retinopathy is not diagnosed	Visual acuity test, OCT, indirect ophthalmoscopy [a]
	Increase to Q2W ±1 day, if serous retinopathy is detected, until resolution or until Cycle 6, Day 28, whichever occurs first	Visual acuity test, VF [b], OCT, indirect ophthalmoscopy

Table 3 Ophthalmologic Examination Schedule (cont.)

From Cycle 7	Every 3 cycles (±2 weeks)	Visual acuity test, indirect ophthalmoscopy [c]
Treatment discontinuation [d]	One time	Visual acuity test, VF [b], slit-lamp biomicroscopy, IOP measurement, OCT, indirect ophthalmoscopy

IOP = intraocular pressure; OCT = optical coherence tomography; Q2W = every two weeks; Q4W = every 4 weeks; VF = visual field.

Note: Examinations should be performed prior to dosing.

[a] If serous retinopathy is diagnosed at any visit, patients must also have visual field testing if not already performed at this visit.

[b] Perform Swedish Interactive Threshold Algorithm Fast strategy (or equivalent):

- 10-2 threshold test if serous retinopathy is detected only within the macula
- 24-2 threshold test if serous retinopathy is extramacular or if extends beyond the macula

[c] Per ophthalmologist discretion, may perform other clinically indicated tests. Also refer to management guidelines in Table 6.

[d] Does not need to be performed if an evaluation has been performed within the last 12 weeks and no signs of serous retinopathy were detected.

4.5 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.5.1 Patient Discontinuation

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
- 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, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

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.

4.5.2 Laboratory, Biomarker, and Other Biologic Samples

4.5.2.1 Local Laboratory Assessments

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, reticulocyte count, and differential count (neutrophils, bands, eosinophils, basophils, monocytes, and lymphocytes)
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate (or total carbon dioxide), BUN or urea, creatinine, albumin, phosphorus, calcium, direct and total bilirubin, ALP, ALT, AST, LDH, CPK, and glucose (non-fasting), total protein, and uric acid
- 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, aPTT
- Thyroid-function testing: thyroid-stimulating hormone, free triiodothyronine (T3; or total T3 for sites where free T3 is not performed), and free thyroxine
- Urinalysis (specific gravity, pH, glucose, protein, ketones, blood and microscopic examination)
- HIV serology
- HBV serology: HBsAg, and total HBcAb and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening, within 7 days before initiation of study treatment. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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

4.5.2.2 Central Laboratory Assessments

The following samples will be sent to one or several central laboratories or to the Sponsor for analysis:

- Serum samples for atezolizumab PK analysis through use of a validated assay
- PBMC and plasma samples for cobimetinib PK analysis through use of a validated assay
- Serum samples for assessment of anti-drug antibodies (ADAs) to atezolizumab through use of a validated assay
- Plasma and blood samples for exploratory research on biomarkers
- Archival (most recently obtained [< 5 years old]) or fresh tumor tissue sample consistent with the patient's diagnosis, collected at baseline for determination of *BRAF*^{V600}-mutation status and for exploratory research on biomarkers

  A representative formalin-fixed paraffin-embedded 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 start.

  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 (< 5 years old), remaining tumor tissue blocks for enrolled patients will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first. Remaining tumor tissue blocks for patients who are not enrolled in the study will be returned to the site no later than 3 months after eligibility determination. Slides will not be returned.
- For patients in Cohorts A and C, optional tumor tissue samples 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 progression, preferably within 3 days after the last does of study treatment. Acceptable samples include those from resections, core-needle biopsies (three cores preferred), or excisional, incisional, or forceps biopsies.

- For Cohort A patients, an optional biopsy can also be collected 4–6 weeks after the first atezolizumab dose.
- For patients enrolled in Cohort B, the biopsy cohort will undergo biopsies according to the following schedule:

  A mandatory predose biopsy will be obtained before Cycle 1, Day 1.

  A mandatory on-treatment biopsy will be obtained between Days 10 and 14 of Cycle 1.

  A second, optional, on-treatment biopsy will be obtained during Cycle 2, after the second dose of atezolizumab, to assess the combined effects of cobimetinib and atezolizumab.

  A mandatory biopsy at the time of progression

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, or TCR repertoire and may involve DNA or RNA extraction, analysis of somatic mutations, and use of NGS (see Table 4). An optional blood sample for WGS may also be obtained.

Table 4 Proposed Biomarkers for Exploratory Research

Sample Type	Timing	Proposed Biomarker(s)
Plasma	Predose on Day 1 of Cycles 1, 2, at time of subsequent radiologic tumor assessments, and at disease progression	• S100 • ctDNA
PBMC	Predose on Day 1 of Cycles 1, 2, and at time of subsequent radiologic tumor assessments, and at disease progression	• TCR repertoires
Tumor tissues	Prior to study: archival (< 5 years old) or at baseline (required)	• Tumor mutations • Tumor-immune contexture, such as PD-L1, MHCI, and $CD8^+$ T cells
Tumor biopsy	On-treatment (optional) and time of disease progression (required if clinically feasible)	• Tumor-immune contexture, such as PD-L1, MHCI, and $CD8^+$ T cells
DNA and RNA extracted from tumor tissues, plasma and PBMC	Same as tumor tissue and biopsy	• Mutation load/profiles in DNA • TCR profiles in DNA • Immuno-signatures by RNA expression

ctDNA = circulating tumor DNA; MHCI = major histocompatibility complex class I; PBMC = peripheral blood mononuclear cell; PD-L1 = programmed death–ligand 1; TCR = T-cell receptor.

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. 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.

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 WGS 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 before 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.

4.5.3 Study Treatment Discontinuation

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

- Clinical deterioration due to disease progression
- Any adverse event that requires study treatment discontinuation per the guidelines in Appendix 7.
- Use of a non–protocol-specified anti-cancer therapy
- Intolerance of study treatment despite undergoing protocol-defined dose reduction
- Pregnancy
- Withdrawal of consent
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment

- Investigator or Sponsor determines it is in the best interest of the patient (e.g., unwillingness to comply with study assessments that compromise their safety)

Patients who discontinue study drug for any reason will be asked to return to the clinic for a treatment discontinuation visit 30 (±3) days after the last dose of study drug. The visit at which response assessment shows disease progression may be used as the treatment discontinuation visit, provided all required assessments have been performed and it is 30 (±3) days after the last dose of study drug. The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced.

After treatment discontinuation, information on survival follow-up and subsequent anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 12 weeks until death (unless the Sponsor terminates the study). If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only as is permissible per local laws and regulations.

4.5.4 Study and Site 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.

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 on 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 three different arms as the toxicities and management guidelines are distinct. Refer to the specific guidelines for each arm individually.

The risks associated with cobimetinib and atezolizumab are detailed in Section 5.1.1 and 5.1.2, respectively. Additional information on the risks of atezolizumab and management of atezolizumab-related adverse events are outlined in Appendix 8

Adverse events will be reported as described in Sections 5.2–5.4. Oversight will be provided by the Medical Monitor and drug safety personnel.

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 are 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 Section 5.1.3.3.

5.1.1.1.2 Serous Retinopathy

Serous retinopathy is a known adverse effect of cobimetinib and has also been observed with other MEK inhibitors (refer to Section 3.3.7 for details).

To address serous retinopathy with cobimetinib treatment, all patients are required to undergo ophthalmologic examination at baseline and at specified timepoints throughout the study. Details regarding baseline and subsequent ophthalmologic examinations are provided in Section 4.4.7.

Guidelines for management of patients who develop Grade $\geq$2 visual disorders or retinopathy are provided in Section 5.1.3.3.

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 on cobimetinib plus vemurafenib (62%) improved or resolved with management according to dose modification guidelines (see in Section 5.1.3.3).

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 was 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.

5.1.1.1.5 Liver Laboratory Abnormalities

Liver laboratory abnormalities can occur when cobimetinib is used with vemurafenib.

Liver laboratory abnormalities, specifically increases in ALT, AST, and ALP, have been observed in patients treated with cobimetinib and vemurafenib.

Liver laboratory tests should be monitored before initiation of treatment and monthly during treatment, or more frequently as clinically indicated.

Grade 3 and 4 liver laboratory abnormalities should be managed with dose interruption, reduction, or discontinuation of cobimetinib.

5.1.1.1.6 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.

5.1.1.2 Potential Risks Associated with Cobimetinib

5.1.1.2.1 Severe Hepatotoxicity (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.

Generally, elevations in liver laboratory tests were managed effectively with dose modification guidelines and the majority of Grade ≥ 3 liver laboratory test abnormalities resolved.

One case of drug-induced liver injury and one case of concurrent elevations of AST/ALT and total bilirubin in Study GO28141 were reported. However, the causality assessment for cobimetinib was confounded by the known liver toxicity of vemurafenib and/or the presence of liver metastases. Therefore, severe hepatotoxicity is a potential risk for cobimetinib.

5.1.1.2.2 Impaired Female Fertility and Developmental Toxicity

There is a potential for effects on fertility and embryofetal 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 embryofetal 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 $\geq$3 events (approximately 16% of patients) and types of rash reported were similar between study arms. Specific events in patients treated with cobimetinib plus vemurafenib included rash (39% all grades, 5.9% Grade$\geq$3, and 1.6% serious adverse events) and maculopapular rash (14.6% all grades, 6.3% Grade$\geq$3, and 1.2% serious adverse events).

Generally, Grade$\geq$3 rash events were effectively managed with dose modification guidelines. In Study GO28141, approximately 90% of Grade $\geq$3 rash events resolved in both arms.

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 cancer patients.

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.

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 *the following:* IRRs and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, hypophysitis, *and* nephritis. In addition, systemic immune activation is a potential risk associated *when* atezolizumab *is given in combination with other immunomodulating agents*. Refer to Appendix 8 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when administered in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations. See Appendix 8 for additional information on the diagnosis and management of systemic immune activation.

5.1.3 Management of Patients Who Experience Specific Adverse Events

5.1.3.1 Cobimetinib Dose Modifications

General dose modifications for cobimetinib are provided in Table 5. Dose modifications for specific adverse events are provided in Table 6.

Table 5 Recommended Cobimetinib Dose Modifications

Grade (NCI CTCAE)	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 daily.

5.1.3.2 Atezolizumab Dose Modifications

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

5.1.3.3 Management of Cobimetinib- and Atezolizumab-Specific Adverse Events

Toxicities associated or possibly associated with cobimetinib plus atezolizumab treatment should be managed according to standard medical practice. See Appendix 8 for management of adverse events related to atezolizumab.

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 Table 6.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab)

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 atezolizumab is discontinued, treatment with cobimetinib may be continued at the investigator's discretion and after discussion with the Medical Monitor. • 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. • If atezolizumab is withheld for > 105 days 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, anaphylaxis, and hypersensitivity reaction	• Guidelines for management of IRRs are provided in Appendix 8. • For anaphylaxis precautions, see Appendix 7. • For severe hypersensitivity reactions, permanently discontinue all study treatment.

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-related 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.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

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-related 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). • <u>Suggested regimen:</u> – Loperamide: Initiate dose with 4 mg and then 4 mg/6 hr around the clock, alternating with Lomotil. ® – Lomotil® (diphenoxylate and atropine): 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 $\leq$2 diarrhea persists after 48 hours of total treatment with Lomotil® and loperamide, consider second-line agents (e.g., octreotide, budesonide, tincture of opium). • <u>Oral supplementation:</u> – Initiate oral supplementation of potassium and/or magnesium if serum levels are $<$LLN. – Consider oral rehydration therapy (e.g., Pedialyte®) for Grade $\geq$1 diarrhea or vomiting. • <u>Dietary modifications:</u> – Stop all lactose-containing products and encourage eating small meals. – The BRAT (banana, rice, apples, toast) diet, without fiber (other vegetables and fruits), may be helpful. – 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.

GI = gastrointestinal; LLN = lower limit of normal.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
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, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 105 days, 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.
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.

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-related 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.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
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 105 days, 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 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 105 days, 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.

GI = gastrointestinal; IV = intravenous; 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-related 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.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 4	• Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor. [a] • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to gastrointestinal 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.

IV = intravenous; NSAID = non-steroidal anti-inflammatory drug.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related 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.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

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. **Acneiform rash:** • Consider topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) as clinically indicated.
Dermatologic event, Grade 3	• Withhold atezolizumab and cobimetinib. • Refer patient to dermatologist. A biopsy should be performed if appropriate. • 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 105 days, 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 105 days. [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]

[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-related 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.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

Event	Action to Be take
Elevations in ALT, AST, and/or bilirubin	
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin < 2 × ULN (Grade 1)	• Continue atezolizumab and cobimetinib. • Continue with the standard monitoring plan (i.e., LFTs Q4W before dosing).
AST/ALT > 3 × baseline values to < 5 × ULN with total bilirubin < 2 × ULN (Grade 2)	• Continue all study treatment. • Monitor LFTs at least weekly. • Consider referral to a hepatologist and liver biopsy. • For suspected immune-related events of > 5 days duration – Consider withholding atezolizumab [a] – 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 105 days. [b, c] – Permanently discontinue atezolizumab and cobimetinib if event does not resolve to Grade 1 or better within 105 days. [a, b, c]
AST/ALT > 5 × baseline values to < 10 × ULN with total bilirubin < 2 × ULN (Grade 3)	• Continue all study treatment. • Monitor LFTs at least weekly. • Consider referral to a hepatologist and liver biopsy. • For suspected immune-related 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 105 days. [a, b, c]

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

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related 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.

[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] 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.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

Event	Action to Be take
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT $>3\times$ ULN with bilirubin $>2\times$ 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 $<3\times$ ULN with bilirubin $<2\times$ 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 $>10\times$ 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 hours 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; TNF-α = tumor necrosis factor–alpha; 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-related 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.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

Event	Action to Be take
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-related 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 105 days. [a, b] • Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor if event does not resolve to Grade 1 or better within 105 days. [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-related 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.

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-related 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.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

Event	Action to Be Taken
Ocular toxicity	
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-related 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. Serous retinopathy can be managed with treatment interruption, dose reduction, or 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 0 "Eye Disorders–Other" scale [a, b, c, d]	**Serous retinopathy, Grade 1 [a] or 2 [b] (tolerable):** • Continue cobimetinib and atezolizumab without dose change. • Follow the monitoring schedule detailed in Section 4.4.7. **Serous retinopathy, Grade 2 [b] (intolerable) or Grade 3 or 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. • Follow the monitoring schedule detailed in Section 4.4.7. • The dose of cobimetinib should be reduced by one dose level when restarting. • Consider permanent discontinuation of cobimetinib if serous retinopathy recurs despite two dose level reductions.

ADL = activities of daily living; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OCT = optical coherence tomography; 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.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

Event	Action to Be Taken
Ocular toxicity (cont.)	
Potential immune-related ocular toxicity (e.g., uveitis, iritis, episcleritis, or retinitis)	• Follow guidelines provided in Appendix 8. • Continue cobimetinib as clinically indicated.
RVO (any grade)	• If RVO (any grade) is diagnosed, cobimetinib dosing should be permanently discontinued and RVO treated per institutional guidelines. • Continue atezolizumab.

RVO = retinal vein occlusion.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

Event		Action to Be Taken		
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.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

Event	Action to Be Taken
Rhabdomyolysis or CPK elevation	
General guidance	• Rule out cardiac cause (check electrocardiogram, 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 $\leq$ 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 $\leq$ 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 $\leq$ 3 within 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. • If CPK elevations do not improve to Grade $\leq$ 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.

CPK = creatine phosphokinase.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

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 in Table 5 (dose modifications for cobimetinib)	• Withhold all study treatment. • If event resolves to Grade 1 or better within 105 days, 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-related 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.

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 drug
- 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 drug
- 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 v4.0; 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 include the following:

- Significant liver toxicity
- 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
- Suspected transmission of an infectious agent by the study drug, 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 the study drug is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, systemic inflammatory response system
- Ocular toxicities

  Uveitis

  RVO

  Serous retinopathy

  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 will be reported until 90 days after the last dose of study drug. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see 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 timepoints. 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 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 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. In addition to Table 7, 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

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

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 as a diagnosis (e.g., "infusion-related reaction" on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

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 timepoints 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., alkaline phosphatase 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 metastatic melanoma should be recorded on the Death Attributed to Progressive Disease eCRF. All other on-study deaths, regardless of relationship to study drug, 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 drug administration or insertion of access device for study drug administration)
- 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 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not

itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded 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).

There is no clinical experience with an overdose of cobimetinib, and thus, no safety data related to overdosing are available. Please see the Cobimetinib Investigator's Brochure for more details.

There is no clinical experience with an overdose of atezolizumab, and thus, no safety data related to overdosing are available. Please see the Atezolizumab Investigator's Brochure for more details.

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 (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

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 IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted] M.D.

Email: [redacted]

Mobile Telephone No.: [redacted]

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.

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

5.4.2.1 Events That Occur before 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 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, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug. 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 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 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 90 days after the last dose of study drug. 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 study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should 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

Any 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).

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).

5.5 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, electronic mail, 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 90 days after the last dose of study drug), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF. 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.

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

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 study evaluates the preliminary efficacy, safety, and pharmacokinetics of atezolizumab plus cobimetinib in patients with *BRAF*^{V600} WT metastatic or unresectable locally advanced melanoma who have progressed on prior anti-PD-1 therapy (Cohorts A and B), and atezolizumab monotherapy in patients with *BRAF* ^{V600} WT metastatic or unresectable locally advanced melanoma who have not been previously treated (Cohort C).

The primary analysis will be conducted *in Cohorts A and B approximately 24 weeks after the last patient is enrolled in Cohort A. At this time, Cohorts A and B will have a minimum follow up of approximately 24 weeks. The primary analysis for Cohort C may be analyzed independently, with a minimum of 24 weeks follow up for patients in Cohort C.* Both separate and pooled efficacy and safety analyses will be performed on Cohorts A and B, given their similar patient populations. Additional tumor immunology and biomarker analyses will also be conducted on Cohort B. Study data will be described and summarized for Cohort C separately.

6.1 DETERMINATION OF SAMPLE SIZE

This study is designed for hypothesis generation with the intention to provide an informative evaluation on the selected efficacy endpoints. No formal inferential testing is planned. Approximately 152 patients are anticipated to be enrolled, with *approximately* 90 patients in Cohort A, 12 patients in Cohort B, and 50 patients in Cohort C.

A combined 102 patients in Cohorts A and B allows for a robust comparison against historical control of ipilumumab and chemotherapy in patients who have previously progressed on anti-PD1 therapy, which generally have response rates of less than 17%. For example, with 102 patients in Cohorts A and B, observing 26 patients with objective response corresponds to ORR (95% CI) of 25.5% (17.4%, 35.1%) and observing 60 patients with disease control corresponds to a DCR (95% CI) of 58.8% (48.6%, 68.52%).

Enrolling 50 patients in Cohort C provides reasonably reliable estimates of the ORR and DCR in patients who have not been previously treated to allow for an accurate understanding of the achievable magnitude of efficacy in this population.
For example, observing 17 patients with objective response corresponds to ORR (95% CI) of 34.0% (21.1%, 48.8%) and observing 32 patients with disease control corresponds to DCR (95% CI) of 64% (49.2%, 77.1%). Enrolling 50 patients in Cohort C also provides an opportunity to explore the preliminary efficacy in relevant patient subgroups including biomarker subgroups defined by PD-L1 expression.

6.2 SUMMARIES OF CONDUCT OF STUDY

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

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic variables and other baseline and disease characteristics will be summarized using descriptive statistics.

6.4 EFFICACY ANALYSES

Efficacy analyses will include all patients who receive at least one dose of study drug.

6.4.1 Primary Efficacy Endpoint

ORR is defined as the proportion of patients whose objective response is a CR or a PR. Objective response is defined as a CR or PR on two consecutive occasions $\geq$4 weeks apart, as determined by the investigators using RECIST v1.1. A 95% Clopper-Pearson CI will be calculated for the ORR.

DCR is defined as the proportion of patients with a CR, PR, or SD at 16 weeks after the baseline tumor assessment.

6.4.2 Secondary Efficacy Endpoints

For patients who achieve an objective response, DOR is defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or have not died will be censored at the last tumor assessment date. Data for patients with no post-baseline tumor assessment will be censored at 1 day after the first treatment date. Kaplan-Meier methodology will be used to estimate the median PFS, and the 95% CI of the median DOR arm will be constructed using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982).

PFS is defined as the time from Cycle 1, Day 1 to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from

any cause, whichever occurs first. The censoring and analysis method for PFS will be the same as that for DOR.

For Cohort C, ORR, DCR, DOR, and PFS will also be determined by the IRC according to RECIST v1.1 using the same methods as described above.

OS is defined as the time from Cycle 1, Day 1 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 1 day after the first treatment date. OS will be analyzed in a manner similar to PFS.

6.4.3 Exploratory Efficacy Endpoints

ORR, DOR, and PFS as determined by the investigator according to immune-modified RECIST (see Appendix 4) will be analyzed using the same methods as described above.

6.5 SAFETY ANALYSES

The safety analyses will include all patients who receive at least one dose of study drug.

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

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 NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grades ≥ 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.

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

All deaths and causes of death will be summarized.

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

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 (actual dose and actual sampling time recorded for each sample) is collected. Since only a few samples are collected from patients, data will be analyzed using the existing population PK model for post hoc

estimates of apparent clearance or systemic clearance for cobimetinib and atezolizumab respectively. Maximum or minimum concentration (C_{max} or C_{min}) will be reported for individual patients and summarized by study day, as data permit. In addition, the relationship between drug exposure (cobimetinib or atezolizumab) and safety and efficacy endpoints will be explored for exposure-response relationship.

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

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analyses for atezolizumab will include patients with any ADA result, with patients grouped by cohort.

The numbers and proportions of ADA-positive patients and ADA-negative patients during both the treatment and follow-up periods will be summarized by cohort. Patients are considered to be ADA positive if they are ADA negative or are missing data at baseline but develop an ADA response following study drug administration (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 4-fold greater (i.e., $\geq$0.60 titer unit) than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or are 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 4-fold 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 descriptively in subgroup analyses.

6.8 BIOMARKER ANALYSES

Descriptive statistics will be used to explore the biomarkers and their relations to response or escape of combined treatment in patients, these biomarkers include: PD-L1 expression, CD8 T-cell density, *NRAS* or *NF-1* mutation status, and other significant biological markers warranted by emerging scientific evidence 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 OPTIONAL INTERIM ANALYSES

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior

to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

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. Central laboratory data and other non–EDC system-captured 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.

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 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification 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, patient-reported outcomes, 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 7.5.

To facilitate source data verification, 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.

7.4 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRF 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 the analyses, data derived from exploratory biomarker specimens 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 60 study centers will participate in this study globally and enroll a total of approximately 152 patients. The Sponsor will provide clinical operations oversight, data management support, and medical monitoring.

An IxRS will be used to manage site drug supply. For patients not previously tested for tumor mutation 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.

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 website:

http://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

American Cancer Society. Melanoma Skin Cancer [resource on the Internet]. 2016 [updated 20 May 2016; cited 17 July 2016]. Available from: http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-key-statistics.

Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2099 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199–206.

Baldwin RM, Owzar K, Zembutsu H, et al. A genome-wide association study identifies novel loci for paclitaxel-induced sensory peripheral neuropathy in CALGB 40101. Clin Cancer Res 2012;18:5099–109.

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 JC, Kim TW, Goh BC, et al. Clinical activity and safety of cobimetinib (cobi) and atezolizumab in colorectal cancer (CRC) [abstract]. J Clin Oncol 2016;34:3502A.

Boni A, Cogdill AP, Dang P, et al. Selective *BRAF*V600E 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.

[CGAN] Cancer Genome Atlas Network. Genomic classification of cutaneous melanoma. https://www.ncbi.nlm.nih.gov/pubmed/26091043 Cell 2015;161:1681–96.

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 Mar 2013. Review. 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.

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.

De La Cruz-Merino L, Di Guardo L, Grob J-J, et al. Clinical features of cobimetinib-associated serous retinopathy in *BRAF*-mutated melanoma patients treated in the coBRIM study [abstract]. J Clin Oncol 2015;33:9033A.

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

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

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.

Favis R, Sun Y, van de Velde H, et al. Genetic variation associated with bortezomib-induced peripheral neuropathy. Pharmacogenet Genomics 2011;21:121–9.

Fehrenbacher L, Spira A, Ballinger M, et al., for the POPLAR Study Group. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lance 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;49:1374–1403.

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

Franco LM, Bucasas KL, Wells JM, et al Integrative genomic analysis of the human immune response to influenza vaccination. Elife. 2013;2:e00299.

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.

Haas 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.

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.

Hodi FS, Kluger H, Sznol M, et al. Durable, long-term survival in previously treated patients with advanced melanoma (MEL) who received nivolumab (NIVO) monotherapy in a phase I trial [abstract CT001]. In American Association of Cancer Research annual meeting 2016.

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. Pig Cell Mel Res 2014;27:1198.

Hu X, Daly M. What have we learned from six years of GWAS in autoimmune diseases, and what is next? Curr Opin Immunol 2012;24:571–5.

Hughes T, Klairmont M, Broucek J, et al. The prognostic significance of stable disease following highdose interleukin-2 (IL-2) treatment in patients with metastatic melanoma and renal cell carcinoma. Cancer Immunol Immunother 2015;64:459-65.

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 2,621 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.

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.

Knight JC. Genomic modulators of the immune response. Trends Genet 2013;29:74–83.

Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in *BRAF*-mutated melanoma. N Engl J Med 2014;371:1867–76.

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 J-H, Choi J-W, Kim Y-S. Frequencies of *BRAF* and *NRAS* mutations are different in histological types and sites of origin of cutaneous melanoma: a meta-analysis. British J Derm 2011;164:776-84.

Lecomte T, Landi B, Beaune P, et al. Glutathione S-transferases P1 polymorphism (Il3105Val) predicts cumulative neruopathy in patients receiveing oxaliplatin-based chemotherapy. Clin Cancer Res 2006;12:3050.

Liu I, Mayes PA, Eastman S, et al. The *BRAF* and MEK inhibitors dabrafenib and trametinib: effects on immune function and ombination 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, 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.

Michels AW, Ostrov DA. New approaches to predicting T cell-mediated drug reactions: a role for inducible and potentially preventable autoimmunity. J Allergy Clin Immunol 2015;136:252–7.

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 (A) + cobimetinib (C) in metastatic melanoma (mel): updated safety and clinical activity. J Clin Onc 2017; 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.

O'Dwyer PJ, Catalano RB. Uridine diphosphate glucuronosyltransferase (ugt) 1a1 and irinotecan: practical pharmacogenomics arrives in cancer therapy. J Clin Oncol 2006;24:4534–8.

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.

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, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015a;372:30-9.

Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without *BRAF* mutation. N Engl J Med. 2015b;22;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;34:9503A.

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.

Ruzzo A, Graziano F, Loupakis F, et al. Pharmacogenetic profiling in patients with advanced colorectal cancer treated with first-line FOLFOX-4 chemotherapy. J Clin Oncol 2007;25:1247–54.

Shirzadi M, Thorstensen K, Helde G, et al. Do Hla-A markers predict skin-reactions from aromatic antiepileptic drugs in a Norwegian population? A case control study. Epilepsy Res.2015;118:5–9.

Stamp LK, Day RO, Yun J, et al. Allopurinol hypersensitivity: investigating the cause and minimizing the risk. Nat Rev Rheumatol 2015;12:235–42.

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

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

Cohort A

	Screening [a]	Cycle 1		Cycle 2		Cycle 3+		Treatment Discontinuation [b]	Unplanned Visit [c]	Survival FU [d]
Day (window)	–35 to –1	1	15	1	15	1	15	30 (± 3) d after last dose		Q3M
Informed consent [e]	x									
Demographic data	x									
Medical history	x									
Vital signs [f, g]	x	x	x	x	x	x	x	x	x	
ECOG PS	x	x		x		x			x	
Weight	x	x		x		x		x		
Height	x									
Complete physical examination	x							x		
Limited physical examination		x [h]		x		x				
Hematology [i]	x	x		x		x		x	x	
Coagulation (INR and aPTT)	x									
BRAF^{V600} *WT* mutation status	x									
PK/ADA sample for atezolizumab	See Appendix 2								x	
PK sample for cobimetinib	See Appendix 2									
Serum samples for auto antibody tests [j]		x								
Optional WGS		x								

Appendix 1
Schedule of Activities (cont.)
Cohort A

	Screening [a]	Cycle 1		Cycle 2		Cycle 3+		Treatment Discontinuation [b]	Unplanned Visit [c]	Survival FU [d]
Day (window)	–35 to –1	1	15	1	15	1	15	30 (± 3) days after last dose		Q3M
Chemistry [k]	x	x		x		x		x	x	
Tumor assessments [l]	x	Scans will be done every 8 weeks ± 7 days								
ECHO/MUGA scan	x			x		x [m]		x	x	
ECG (average of triplicate measurements)	x								x	
Serology [n]	x									
Thyroid function [o]	x	x		x		x [o]		x		
Ophthalmologic exam	x	Perform ophthalmology investigations as per Section 4.4.7.								
Pregnancy test [p]	x	x		x		x [p]		x	x	
Urinalysis [q]	x									
Concomitant medications [r]	x [r]	x [r]		x		x		x [r]		
Adverse events [s]	x [s]	x [s]	x	x	x	x	x	x [s]		x [s]
Tumor biopsy [t]	x			x				x		
Biomarker blood samples		See Appendix 2								
Atezolizumab administration [u]		x	x	x	x	x	x			
Dispense cobimetinib [v]		x		x		x				
Survival and anti-cancer therapy FU										x

Appendix 1
Schedule of Activities (cont.)

ADA = anti-drug antibody; CPK = increased creatine phosphokinase; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic Case Report Form; FU = follow-up; HBcAb = hepatitis B core antibody; HBcAg = hepatitis B core antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition; PD = progressive disease; PK = pharmacokinetic; Q3M = every 3 months; RECIST = Response Evaluation Criteria in Solid Tumors; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WGS = whole genome sequencing; WT = wild type.

Notes: All assessments should be performed within ±3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed before dosing, unless otherwise specified. On treatment days, pre-infusion laboratory samples should be drawn up to 4 hours before the start of infusion, and post-infusion laboratory samples should be drawn up to 30 minutes after the end of infusion, unless otherwise specified.

[a] Results of standard-of-care tests or examinations performed before obtaining informed consent and within 35 days before Day 1 may be used; such tests do not need to be repeated for screening. *BRAF*^{V600} status must be known before 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. Test results should be reviewed before study treatment is given.

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit at 30 (±3) days. The visit at which response assessment shows PD may be used as the study discontinuation visit.

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

[d] 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.

[e] 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.

[f] Includes respiratory rate, heart rate, and systolic and diastolic blood pressure (after patient has been in a seated position for 5 minutes) and temperature (oral or tympanic); resting oxygen saturation may be measured at screening. 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.

[g] Vital signs at the first atezolizumab infusion will be collected within 60 min before the infusion, every 15 (±5) min during the atezolizumab infusion, and 30 (±10) min after the infusion. For subsequent infusions, vital signs will be collected within 60 min before infusion and during the infusion (if clinically indicated or if symptoms occurred in the prior infusion), and 30 (±10) min after the infusion.

[h] 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 Cycle 1, Day 1 visit, they do not have to be repeated at Day 1.

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

[j] Includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[k] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, bicarbonate (or total carbon dioxide), BUN or urea, creatinine, total protein, magnesium, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, CPK, LDH, uric acid; albumin, non-fasting glucose (fasting blood glucose after a minimum 8-hour fast, at screening only), lipids, (Fasting lipids: total cholesterol, LDL cholesterol, and triglycerides after a minimum 8-hour fast, at screening only).

[l] Tumor assessments will continue until disease progression per RECIST v1.1, loss of clinical benefit (patients who continue treatment after disease progression according to RECIST v1.1), consent withdrawal, study termination by the Sponsor, or death, whichever occurs first. At the investigator's discretion, tumor assessments may be repeated at any time if disease progression is suspected. 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.

[m] All patients will undergo evaluation of left ventricular dysfunction, either by ECHO or MUGA scan, at screening. Evaluation of LVEF by ECHO or MUGA scan must be performed at the following time points only for patients taking cobimetinib:

- Cycle 2, Day 1 (±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.
- All patients restarting treatment with a dose reduction of cobimetinib because of a decrease in LVEF should have LVEF measurements taken after approximately 2, 4, 10, and 16 weeks, and then resume monitoring LVEF every three treatment cycles.

[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, total HBcAg antibody (anti-HBcAb). HBV DNA should be obtained prior to study start 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 study start if patient tests positive for anti-HCV.

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

[p] 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 and at the treatment discontinuation visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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

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

[s] 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 90 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. 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.

[t] Archival (< 5 years old) or fresh baseline tumor tissue collected during screening. If a patient provides a fresh biopsy for *BRAF*^{V600} testing, this sample will be used also as baseline for biomarker analysis. Therefore predose specimens are not required for patients who provide a fresh biopsy before treatment start. If archival tissue is used availability of adequate tumor tissue must be confirmed prior to any screening procedures (paraffin-embedded tumor block or a minimum of 20 unstained slides). Submit archival tissue and associated pathology report within 30 days after Cycle 1, Day 1. If a predose fresh biopsy is collected this sample should be obtained after eligibility criteria have been fulfilled and prior to Cycle 1, Day 1. For patients who have consented to optional biopsies a subsequent biopsy may be performed 4-6 weeks after the first atezolizumab administration; an additional optional biopsy may be collected at the time of radiographic progression if clinically feasible. See Section 3.1.1 and the laboratory manual for further details.

[u] In Cohort A, atezolizumab will be given on Days 1 and 15 of all cycles. 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 from the scheduled Day 1 and 15 of each cycle.

[v] Cobimetinib 60 mg/day by mouth will be given in a 21/7 dosing schedule.

Appendix 1
Schedule of Activities (cont.)

Cohort B: Biopsy Cohort

	Screening[a]	Cycle 1		Cycle 2		Cycle 3+		Treatment Discontinuation[b]	Unplanned Visit[c]	Survival FU[d]
Day (window)	–35 to –1	1	15	1	15	1	15	30 (±3) days after last dose		Q3M
Informed consent[e]	x									
Demographic data	x									
Medical history	x									
Vital signs[f,g]	x	x	x	x	x	x	x	x	x	
ECOG PS	x	x		x		x			x	
Weight	x	x		x		x		x		
Height	x									
Complete physical examination	x							x		
Limited physical examination		x[h]		x		x				
Hematology[i]	x	x		x		x		x	x	
Coagulation (INR and aPTT)	x									
BRAF^{V600} WT mutation status	x									
PK and ADA sample for atezolizumab	See Appendix 2								x	x
PK sample for cobimetinib	See Appendix 2									
Serum samples for auto-antibody tests[j]		x								

Appendix 1
Schedule of Activities (cont.)
Cohort B: Biopsy Cohort

	Screening [a]	Cycle 1		Cycle 2		Cycle 3+		Treatment Discontinuation [b]	Unplanned Visit [c]	Survival FU [d]
Day (window)	–35 to –1	1	15	1	15	1	15	<30 (±3) days after last dose		Q3M
Optional WGS		x								
Chemistry [k]	x	x		x		x		x	x	
Tumor assessments [l]	x	Scans will be done every 8 weeks ± 7 days								
ECHO/MUGA scan	x			x		x [m]		x	x	
ECG (average of triplicate measurements)	x								x	
Serology [n]	x									
Thyroid function [o]	x	x		x		x [o]		x		
Ophthalmologic exam	x	Perform ophthalmology investigations as per Section 4.4.7.								
Pregnancy test [p]	x	x		x		x [p]		x	x	
Urinalysis [q]	x									
Concomitant medications [r]	x [r]	x [r]		x		x		x [r]		
Adverse events [s]	x [s]	x [s]	x	x	x	x	x	x [s]		x [s]
Tumor biopsy [t]	x		x [u]	x				x		
Biomarker blood samples		See Appendix 2								
Atezolizumab administration [v]			x	x	x	x	x			
Dispense cobimetinib [w]		x		x		x				
Survival and anti-cancer therapy FU										x

Appendix 1
Schedule of Activities (cont.)

ADA = anti-drug antibody; CPK = increased creatine phosphokinase; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic Case Report Form; FU = follow-up; HBcAb = hepatitis B core antibody; HBcAg = hepatitis B core antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition; PD = progressive disease; PK = pharmacokinetic; Q3M = every 3 months; RECIST = Response Evaluation Criteria in Solid Tumors; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WGS = whole genome sequencing; WT = wild type.

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 up to 4 hours before the start of infusion, and post-infusion laboratory samples should be drawn up to 30 minutes after the end of infusion, unless otherwise specified.

[a] Results of standard-of-care tests or examinations performed before obtaining informed consent and within 35 days before Day 1 may be used; such tests do not need to be repeated for screening. *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. Test results should be reviewed before study treatment is given.

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit at 30 (±3) days. The visit at which response assessment shows PD may be used as the study discontinuation visit.

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

[d] 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.

[e] 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.

[f] Includes respiratory rate, heart rate, and systolic and diastolic blood pressure (monitored after the patient has been in a seated position for 5 min), and temperature (oral or tympanic). Resting oxygen saturation may be measured at screening. 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.

[g] Vital signs at the first atezolizumab infusion will be collected within 60 minutes before the infusion, every 15 (±5) min during the atezolizumab infusion, and 30 (±10) min after the infusion. For subsequent infusions, vital signs will be collected within 60 min before the infusion and during the infusion (if clinically indicated or if symptoms occurred in the prior infusion), and 30 (±10) min after the infusion.

Appendix 1
Schedule of Activities (cont.)

[h] 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 Cycle 1, Day 1 visit, they do not have to be repeated at Day 1.

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

[j] Includes: anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, perinuclear anti-neutrophil cytoplasmic antibody.

[k] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, bicarbonate (or total carbon dioxide), BUN or urea, creatinine, total protein, magnesium, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, CPK, LDH, uric acid; albumin, non-fasting glucose (fasting blood glucose after a minimum 8-hour fast, at screening only), and lipids (fasting lipids: total cholesterol, LDL cholesterol, and triglycerides after a minimum 8-hour fast, at screening only).

[l] Tumor assessments will continue until disease progression per RECIST v1.1, loss of clinical benefit (patients who continue treatment after disease progression according to RECIST v1.1), consent withdrawal, study termination by the Sponsor, or death, whichever occurs first. At the investigator's discretion, tumor assessments may be repeated at any time if disease progression is suspected. 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.

[m] All patients will undergo evaluation of left ventricular dysfunction, either by ECHO or MUGA scan, at screening. Evaluation of LVEF by ECHO or MUGA scan must be performed at the following time points only for patients receiving cobimetinib:

- Cycle 2, Day 1 $\pm$1 week
- Day 1 of Cycles 5, 8, 11, 14, 17, etc. (every three treatment cycles; $\pm$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.
- All patients restarting treatment with a dose reduction of cobimetinib because of a decrease in LVEF should have LVEF measurements taken after approximately 2, 4, 10, and 16 weeks, and then resume monitoring LVEF every three treatment cycles.

[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, total HBcAg antibody (anti-HBcAb). HBV DNA should be obtained before study start 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 study start if patient tests positive for anti-HCV.

Appendix 1
Schedule of Activities (cont.)

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

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

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

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

[s] After informed consent has been obtained but before 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 90 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. 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.

[t] In Cohort B. If a patient provides a fresh biopsy for *BRAF*^{V600} test, this sample will be used also as baseline for biomarker analysis. Therefore, predose specimens are not required for patients who provide a fresh biopsy before treatment start..

A subsequent mandatory biopsy will be performed between Days 10 and 14 of Cycle 1. An additional optional biopsy may be collected during Cycle 2, approximately 4–6 weeks after the first atezolizumab administration. A mandatory biopsy will be collected at the time of radiographic progression, if clinically feasible.

[u] Days 10–14.

[v] In Cohort B, atezolizumab will be given on Cycle 1, Day 15 and on Days 1 and 15 of all subsequent cycles. 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 a loss of clinical benefit. Study drug administration may be ±3 days from the scheduled Day 1 and 15 of each cycle.

[w] Cobimetinib 60 mg/day by mouth will be given in a 21/7 dosing schedule. Dosing will start on Cycle 1, Day 1, 14 days before the first atezolizumab administration.

Appendix 1
Schedule of Activities (cont.)
Cohort C: Atezolizumab Monotherapy (21-Day Cycle)

	Screening [a]	Cycle 1	Cycle 2	Cycle 3+	Treatment Discontinuation [b]	Unplanned Visit [c]	Survival FU [d]
Day (window)	–35 to –1	1	1	1	30 (± 3) d after last dose		Q3M
Informed consent [e]	x						
Demographic data	x						
Medical history	x						
Vital signs [f, g]	x	x	x	x	x	x	
ECOG PS	x	x	x	x		x	
Weight	x	x	x	x	x		
Height	x						
Complete physical examination	x				x		
Limited physical examination		x [h]	x	x			
Hematology [i]	x	x	x	x	x	x	
Coagulation (INR and aPTT)	x						
BRAF^{V600} WT mutation status	x						
PK/ADA sample for atezolizumab	See Appendix 2						
Serum samples for auto antibody tests [j]		x					
Optional WGS		x					

Appendix 1
Schedule of Activities (cont.)

Cohort C: Atezolizumab Monotherapy (21-Day Cycle)

	Screening [a]	Cycle 1	Cycle 2	Cycle 3+	Treatment Discontinuation [b]	Unplanned Visit [c]	Survival FU [d]
Day (window)	–35 to –1	1	1	1	30 (± 3) days after last dose		Q3M
Chemistry [k]	x	x	x	x	x	x	
Tumor Assessments [l]	x	Scan assessments every 8 weeks± 7 days					
ECHO/MUGA scan [m]	x						
ECG (average of triplicate measurements)	x					x	
Serology [n]	x						
Thyroid function [o]	x	x	x	x [o]	x		
Pregnancy test [p]	x	x	x	x [p]	x	x	
Urinalysis [q]	x						
Concomitant medications [r]	x [r]	x [r]	x	x	x [r]		
Adverse events [s]	x [s]	x [s]	x	x	x [s]		x [s]
Collection of archival tissue or tumor biopsy [t]	x				x		
Biomarker blood samples		See Appendix 2					
Atezolizumab administration [u]		x	x	x			
Survival and anti-cancer therapy FU							x

Appendix 1
Schedule of Activities (cont.)

ADA = anti-drug antibody; CPK = increased creatine phosphokinase; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic Case Report Form; FU = follow-up; HBcAb = hepatitis B core antibody; HBcAg = hepatitis B core antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition; PD = progressive disease; PK = pharmacokinetic; Q3M = every 3 months; RECIST = Response Evaluation Criteria in Solid Tumors; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WGS = whole genome sequencing; WT = wild type.

Notes: All assessments should be performed within ±3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed before dosing, unless otherwise specified. On treatment days, pre-infusion laboratory samples should be drawn up to 4 hours before the start of infusion, and post-infusion laboratory samples should be drawn up to 30 minutes after the end of infusion, unless otherwise specified.

[a] Results of standard-of-care tests or examinations performed before obtaining informed consent and within 35 days before Day 1 may be used; such tests do not need to be repeated for screening. *BRAF*^{V600} status must be known before 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. Test results should be reviewed before study treatment is given.

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit at 30 (±3) days. The visit at which response assessment shows PD may be used as the study discontinuation visit.

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

[d] 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. PK/ADA sample is required 120 days +/- 30 days after last atezolizumab infusion

[e] 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.

[f] Includes respiratory rate, heart rate, and systolic and diastolic blood pressure (after patient has been in a seated position for 5 minutes) and temperature (oral or tympanic); resting oxygen saturation may be measured at screening. 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.

[g] Vital signs at the first atezolizumab infusion will be collected within 60 min before the infusion, every 15 (±5) min during the atezolizumab infusion, and 30 (±10) min after the infusion. For subsequent infusions, vital signs will be collected within 60 min before infusion and during the infusion (if clinically indicated or if symptoms occurred in the prior infusion), and 30 (±10) min after the infusion.

[h] 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 Cycle 1, Day 1 visit, they do not have to be repeated at Day 1.

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

[j] Includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[k] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, bicarbonate (or total carbon dioxide), BUN or urea, creatinine, total protein, magnesium, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, CPK, LDH, uric acid; albumin, non-fasting glucose (fasting blood glucose after a minimum 8-hour fast, at screening only), lipids, (Fasting lipids: total cholesterol, LDL cholesterol, and triglycerides after a minimum 8-hour fast, at screening only).

[l] Tumor assessments will continue until disease progression per RECIST v1.1, loss of clinical benefit (patients who continue treatment after disease progression according to RECIST v1.1), consent withdrawal, study termination by the Sponsor, or death, whichever occurs first. At the investigator's discretion, tumor assessments may be repeated at any time if disease progression is suspected. 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.

[m] All patients will undergo evaluation of left ventricular dysfunction, either by ECHO or MUGA scan, at screening. 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.

[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, total HBcAg antibody (anti-HBcAb). HBV DNA should be obtained prior to study start 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 study start if patient tests positive for anti-HCV.

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

[p] 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 and at the treatment discontinuation visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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

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

[s] 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 90 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. 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.

[t] Archival (<5 years) or fresh baseline tumor tissue collected during screening. If a patient provides a fresh biopsy for *BRAF* test, this sample will be used also as baseline for biomarker analysis. Therefore predose specimens are not required for patients who provide a fresh biopsy before treatment start.

If archival tissue is used availability of adequate tumor tissue must be confirmed prior to any screening procedures (paraffin-embedded tumor block or a minimum of 20 unstained slides). Submit archival tissue and associated pathology report within 30 days after Cycle 1, Day 1. If a predose fresh biopsy is collected this sample should be obtained after eligibility criteria have been fulfilled and prior to Cycle 1, Day 1. For patients who have consented to optional biopsies; an additional optional biopsy may be collected at the time of radiographic progression if clinically feasible. See Section 3.1.1 and the laboratory manual for further details.

[u] In Cohort C, atezolizumab (1200 mg) will be given on Cycle 1, Day 1 IV Q3W. 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 a loss of clinical benefit. Study drug administration may be ± 3 days from the scheduled Day 1 of each cycle.

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Cohort A

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 after the cobimetinib dose	Cobimetinib PK (plasma)
Cycle 1, Day 15	Prior to cobimetinib dose 2–4 hours post cobimetinib dose	Cobimetinib PK (plasma)
Cycles 2, 3, 4, 8, 12, and 16	Prior to the first infusion	Atezolizumab PK and ADA (serum)
Cycles 1 and 2, Day 1 At time of tumor assessments (preferably within 3 days) At disease progression	Predose	Biomarker (plasma, PBMC)
Treatment discontinuation visit [a]	At visit	Atezolizumab PK and ADA (serum) Biomarker (plasma, PBMC) [b]
120 days ±30 days after last atezolizumab infusion	At visit	Atezolizumab PK and ADA (serum)

ADA = anti-drug antibody; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ±3 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit 30 (±3) 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.

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

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

Cohort B

Visit	Timepoint	Sample Type(s)
Cycle 1, Day 15	Prior to the first infusion	Atezolizumab PK and ADA (serum)
	30 (±10) minutes following the end of atezolizumab infusion	Atezolizumab PK (serum)
	Prior to cobimetinib dose 2–4 hours post cobimetinib dose	Cobimetinib PK (plasma)
Cycles 2, 3, 4, 8, 12, and 16	Prior to the first infusion	Atezolizumab PK and ADA (serum)
Cycles 1 and 2, Day 1 At time of tumor assessments (preferably within 3 days) At disease progression	Predose	Biomarker (plasma, PBMC)
Treatment discontinuation visit [a]	At visit	Atezolizumab PK and ADA (serum) Biomarker (plasma, PBMC) [b]
120 days ±30 days after last atezolizumab infusion	At visit	Atezolizumab PK and ADA (serum)

ADA = anti-drug antibody; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Except for Day 15 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ±3 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit 30 (±3) 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.

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

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

Cohort C

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)
Cycles 2, 3, 4, 8, 12, and 16	Prior to the first infusion	Atezolizumab PK and ADA (serum)
Cycles 1 and 2, Day 1 At time of tumor assessments (preferably within 3 days) At disease progression	Predose	Biomarker (plasma, PBMC)
Treatment discontinuation visit [a]	At visit	Atezolizumab PK and ADA (serum) Biomarker (plasma, PBMC) [b]
120 days ±30 days after last atezolizumab infusion	At visit	Atezolizumab PK and ADA (serum)

ADA = anti-drug antibody; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ±3 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit 30 (±3) 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.

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

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 [1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable Tumor 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 of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-target Lesions" for information on lymph node measurement.

Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), 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 masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

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[1] 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.

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

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Special Considerations Regarding Lesion Measurability

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

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure 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 noncystic 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. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of 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.

Method of Assessment

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

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 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 due to 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 nonenhanced) 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 on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION 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 in instances where 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 recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but additionally, 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. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, 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 <10 mm are considered non-pathological and should not be recorded or followed.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, 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").

RESPONSE CRITERIA

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- **Complete response (CR)**: disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

- **Partial response (PR)**: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- **Progressive disease (PD)**: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

- **Stable disease (SD)**: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Special Notes on the Assessment of Target Lesions

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 nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While in the study, all lesions (nodal and non-nodal) that are recorded at baseline should be recorded as actual measurements 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 the CT scan that the radiologist may not feel comfortable assigning an exact measure 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 below measurable limit (BML) 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 BML should also be ticked.)

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

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. 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 maximal longest diameter for the coalesced lesion.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. 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 protocol.

- **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 lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- **PD**: unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Non-target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, 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 disease in the face of SD or PR of target disease will therefore be extremely rare.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread or may be described in protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

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 partial or complete response. 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, then progression should be declared using the date of the initial scan.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 Timepoint Response: 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 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.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Table 2 Timepoint Response: Patients with Non-target Lesions Only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

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 only a subset of lesion measurements are made at an assessment, 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 lesion(s) 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.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

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

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Patients with a global deterioration of 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 disease as shown in Table 1 , Table 2, and Table 3.

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.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 4
Response Evaluation Criteria in Solid Tumors: Modified-Immune Criteria (Excerpt from Original Publication)

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
Response Evaluation Criteria in Solid Tumors: Modified-Immune Criteria (Excerpt from Original Publication) (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
Response Evaluation Criteria in Solid Tumors: Modified-Immune Criteria (Excerpt from Original Publication) (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.

Appendix 4
Response Evaluation Criteria in Solid Tumors: Modified-Immune Criteria (Excerpt from Original Publication) (cont.)

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.

Appendix 4
Response Evaluation Criteria in Solid Tumors: Modified-Immune Criteria (Excerpt from Original Publication) (cont.)

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").

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,

Appendix 4
Response Evaluation Criteria in Solid Tumors: Modified-Immune Criteria (Excerpt from Original Publication) (cont.)

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).

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Response Evaluation Criteria in Solid Tumors: Modified-Immune Criteria (Excerpt from Original Publication) (cont.)

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

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Response Evaluation Criteria in Solid Tumors: Modified-Immune Criteria (Excerpt from Original Publication) (cont.)

- 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.

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.

Appendix 4
Response Evaluation Criteria in Solid Tumors: Modified-Immune Criteria (Excerpt from Original Publication) (cont.)

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 1.

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.

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

PRECAUTIONS

Equipment needed:

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

PROCEDURES

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

1. Stop the drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3. Maintain adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by physician in charge.
5. Continue to observe the patient and document observations

Appendix 8
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.

Although most immune-related adverse events observed with immunomodulatory agents 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-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit–risk balance a given patient may be experiencing 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-related 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.

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 8
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-related 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 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

HEPATIC EVENTS

Immune-related 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 tests.

[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-related 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 8
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 tests.

[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-related 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-related 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 8
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-related 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 8
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-related 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 8
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 ≥ 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-related 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 ≤ 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-related 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 8
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-related 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 8
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-related 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 8
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-related 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 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-RELATED MYOCARDITIS

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related 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 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 6 Management Guidelines for Immune-Related Myocarditis

Event	Management
Immune-related myocarditis, Grade 1	• Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.
Immune-related 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-related 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-related 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 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

INFUSION-RELATED REACTIONS

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

Guidelines for medical management of IRRs during Cycle 1 are provided in Table 7. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 7 Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	• Interrupt atezolizumab infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs.
IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue atezolizumab and contact Medical Monitor. [a]

IRR = infusion-related reaction.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related 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 8
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 work-up 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-related 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 8
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-related 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-related 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-related 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 8
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. 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. • 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. • 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]

[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-related 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 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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 work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-related neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-related 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-related 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-related 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 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-RELATED MENINGOENCEPHALITIS

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related 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-Related Meningoencephalitis

Event	Management
Immune-related 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-related 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 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

RENAL EVENTS

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and 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.

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.

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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-related 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.*

SYSTEMIC IMMUNE ACTIVATION

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when atezolizumab is given in combination with other immunomodulating agents.

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Recommendations regarding early identification and management of systemic immune activation are provided below. In the event of suspected systemic immune activation, atezolizumab should be withheld and clinical specialists (e.g., rheumatology, clinical immunology, or solid organ or hematopoietic stem cell transplant specialists) and the Medical Monitor should be consulted for additional guidance.

Early disease recognition is critical, and systemic immune activation should be suspected if, in the absence of an alternative etiology, the patient meets two or more of the following criteria:

- Hypotension that is refractory to aggressive IV fluid challenge

  Vasopressor support may be required.
- Respiratory distress that requires aggressive supportive care

  Supplemental oxygen and intubation may be required.
- Fever $>38.5°C$
- Acute renal or hepatic failure
- Bleeding from coagulopathy
- Any of the following unexplained laboratory abnormalities (change from baseline): cytopenias (in two or more lineages), significant transaminitis, or coagulopathy

For patients with suspected systemic immune activation, an initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Soluble interleukin 2 (IL-2) receptor (soluble CD25)
- Triglycerides
- AST, ALT, and direct bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

Laboratory tests with normal results should be repeated frequently in patients for whom a high clinical suspicion of systemic immune activation exists.

If neurologic abnormalities are present, consider cerebrospinal fluid analysis and/or an MRI of the brain.

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

If cytopenias are present (Grade ≥2 in two or more lineages) or ferritin is ≥3000 ng/mL, the following evaluations should also be performed:

- Bone marrow biopsy and aspirate (assess for evidence of hemophagocytosis)
- Adenovirus, cytomegalovirus, Epstein-Barr virus, herpes-simplex virus, and human herpesvirus 6, 7, and 8 evaluation (for reactivated or active disease)

Diagnostic criteria and recommended management for systemic immune activation are provided in Table 13. The diagnostic criteria apply only when alternative etiologies have been excluded.

An adverse event of systemic immune activation should be reported on the Adverse Event eCRF if it meets the criteria for "consistent with systemic immune activation" or "probable systemic immune activation" as outlined in Table 13.

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 13 Diagnostic Criteria and Recommended Management for Systemic Immune Activation

Systemic Immune Activation Diagnostic Criteria (applicable only when alternative etiologies have been excluded)	
Major Criteria	Minor Criteria
• Fever ≥38.5°C on more than one occasion • Ferritin ≥3000 ng/mL • Cytopenias (Grade ≥2 in two or more lineages) • Age-adjusted soluble interleukin-2 receptor elevated by ≥2 standard deviations • Severe (Grade ≥3) or progressive dysfunction in two or more organs • Decreased fibrinogen	• Splenomegaly • Hemophagocytosis in bone marrow, spleen, or lymph nodes • Elevated γ-glutamyl transpeptidase (GGT) or liver function tests (AST, ALT, or direct bilirubin) • Elevated triglycerides • Elevated LDH • Decreased natural killer cell activity

Diagnosis and Management of Systemic Immune Activation		
Number of Criteria	Diagnosis	Action to Be Taken
≥4 major criteria	Consistent with systemic immune activation	• Permanently discontinue atezolizumab. • Consider treatment with an immunosuppressive agent (i.e.,cytokine inhibitors) and IV corticosteroids (i.e., methylprednisolone 1 g once daily or equivalent, or dexamethasone ≥10 mg/m^2 once daily if neurologic abnormalities are present). • Contact the Medical Monitor for additional recommendations. • Consider HLH-2004 protocol if there is no clinical improvement.
3 major criteria OR 2 major plus ≥3 minor criteria	Probable systemic immune activation	• Depending on clinical severity, follow guidelines for "Consistent with systemic immune activation" or "Possible systemic immune activation" diagnosis. • Clinical specialistis and the Medical Monitor may be contacted for recommendations.
2 major plus ≤2 minor criteria OR 1 major plus ≥4 minor criteria	Possible systemic immune activation	• Withhold atezolizumab. • Consider treatment with IV corticosteroids. • Clinical specialistis and the Medical Monitor may be contacted for additional recommendations. • Follow guidelines for "Consistent with systemic immune activation" diagnosis if there is no clinical improvement or if clinical worsening occurs. • If clinical improvement occurs, atezolizumab may be resumed following a benefit-risk assessment by the Medical Monitor.

Notes: Criteria are adapted from a Delphi Survey of 26 experts who provided helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients (Hejblum et al. 2014).

Grades are based on National Cancer Institute Common Terminology Criteria for Adverse Events.

These recommendations do not replace clinical judgment and are intended as suggested guidance.

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

REFERENCES

Hejblum G, Lambotte O, Galicier L, et al. A web-based Delphi study for eliciting helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients. PLoS ONE 2014;9(4):e94024. doi: 10.1371/journal.pone.0094024.