Official Title: A PHASE III, DOUBLE-BLINDED, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB PLUS COBIMETINIB AND VEMURAFENIB VERSUS PLACEBO PLUS COBIMETINIB AND VEMURAFENIB IN PREVIOUSLY UNTREATED BRAFV600 MUTATION–POSITIVE PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC MELANOMA

NCT Number: NCT02908672

Document Date: Protocol Version 5: 30-Oct-18

PROTOCOL

TITLE:	**A PHASE III, DOUBLE-BLINDED, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB PLUS COBIMETINIB AND VEMURAFENIB VERSUS PLACEBO PLUS COBIMETINIB AND VEMURAFENIB IN PREVIOUSLY UNTREATED *BRAF*^{V600} MUTATION–POSITIVE PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC MELANOMA**
PROTOCOL NUMBER:	CO39262
VERSION NUMBER:	5
EUDRACT NUMBER:	2016-002482-54
IND NUMBER:	111,271
TEST PRODUCTS:	Atezolizumab (RO5541267) Cobimetinib (RO5514041) Vemurafenib (RO5185426)
MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 15 August 2016
DATES AMENDED:	Version 2 (UK Only): 23 November 2016 Version 2 (France Only): 6 December 2016 Version 2 (Germany Only): 18 December 2016 Version 3: 24 July 2017 Version 4: 5 March 2018 Version 5: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	30-Oct-2018 22:41:12

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Protocol CO39262 has been amended to update the risks associated with study treatment, including guidelines for management of atezolizumab-associated adverse events. Changes to the protocol, along with a rationale for each change, are summarized below:

- The inclusion criterion that addresses female contraception has been modified to specify when women must refrain from donating eggs (Section 4.1.1).
- Section 4.4.2 has been amended to align with language in Appendix 10 related to prohibited therapy for treating atezolizumab-associated infusion-related reactions.
- The incidence and characterization of cutaneous squamous cell carcinoma (cuSCC) and non-cuSCC in relation to vemurafenib is well defined; as such, the additional requirement for submission of specimen blocks or sections of suspicious lesions (along with a paired normal skin sample) for pathologic examination by the central laboratory has been removed(Sections 4.5.6.1 and 4.5.7, Table 3, and Appendix 1).
- Lists of risks for atezolizumab and guidelines for managing patients who experience atezolizumab-associated adverse events have been revised to include nephritis (Section 5.1.1 and Appendix 10).
- The maximum time for interrupting atezolizumab treatment has been changed from 105 days to 12 weeks for consistency with the guidelines for management of atezolizumab-associated adverse events (Section 5.1.5.3 and Table 3).
- It has been clarified that if vemurafenib is discontinued and study treatment (cobimetinib and or atezolizuamb/atezolizumab placebo) continues, ECGs are required as per standard of care or as clinically indicated (Appendix 1).
- Appendix 2 has been amended to indicate that biomarker plasma samples are no longer required after atezolizumab is discontinued.

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 III, DOUBLE-BLINDED, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB PLUS COBIMETINIB AND VEMURAFENIB VERSUS PLACEBO PLUS COBIMETINIB AND VEMURAFENIB IN PREVIOUSLY UNTREATED *BRAF*^{V600} MUTATION–POSITIVE PATIENTS WITH METASTATIC OR UNRESECTABLE LOCALLY ADVANCED MELANOMA**
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SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, DOUBLE-BLINDED, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB PLUS COBIMETINIB AND VEMURAFENIB VERSUS PLACEBO PLUS COBIMETINIB AND VEMURAFENIB IN PREVIOUSLY UNTREATED *BRAF*^{V600} MUTATION–POSITIVE PATIENTS WITH METASTATIC OR UNRESECTABLE LOCALLY ADVANCED MELANOMA**
PROTOCOL NUMBER:	CO39262
VERSION NUMBER:	5
Eudract Number:	2016-002482-54
IND NUMBER:	111, 271
TEST PRODUCTS:	Atezolizumab (RO5541267) Cobimetinib (RO5514041) Vemurafenib (RO5185426)
PHASE:	Phase III
INDICATION:	Metastatic or unresectable locally advanced melanoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

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

Objectives and Corresponding Endpoints

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

Objectives and Corresponding Endpoints (cont.)

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

Objectives and Corresponding Endpoints (cont.)

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

Objectives and Corresponding Endpoints (cont.)

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

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

Study Design

Description of Study

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Number of Patients

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

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

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

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

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

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

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

  Hormonal contraceptive methods must be supplemented by a barrier method.

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

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

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

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

Exclusion Criteria

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

Cancer-Related Exclusion Criteria

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

- Palliative radiotherapy within 14 days prior to initiation of study treatment
- Active malignancy (other than *BRAF*^{V600} mutation–positive melanoma) or malignancy within 3 years prior to screening are excluded, with the exception of resected melanoma, resected basal cell carcinoma (BCC), resected cutaneous squamous cell carcinoma (SCC), resected carcinoma in situ of the cervix, resected carcinoma in situ of the breast, in situ prostate cancer, limited-stage bladder cancer, or any other curatively treated malignancies from which the patient has been disease-free for at least 3 years

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

Ocular Exclusion Criteria

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

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

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

Cardiac Exclusion Criteria

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

Central Nervous System Exclusion Criteria

- Untreated or actively progressing CNS lesions (carcinomatous meningitis)

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

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

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

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

Additional Exclusion Criteria

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

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.
- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, anti–phospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

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

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

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

  - Rash must cover < 10% of body surface area
  - Disease is well controlled at baseline and requires only low-potency topical corticosteroids

  - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months
- Known clinically significant liver disease, including alcoholism, cirrhosis, fatty liver, and other inherited liver disease as well as active viral disease including:
  - Positive HIV test at screening
  - Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening

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

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study
- Treatment with systemic immunosuppressive medication (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study

  Patients who have received acute, low-dose systemic immunosuppressant medication ($\leq$ 10 mg/day oral prednisone or equivalent) $\geq$ 4 weeks prior to initiation of study treatment or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.

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

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

End of Study

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

Length of Study

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

Investigational Medicinal Products

Test Products (Investigational Drugs)

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

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

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

Statistical Methods

Primary Analysis

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

The statistical hypothesis of this study is as follows:

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

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

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

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

Determination of Sample Size

Progression-Free Survival

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

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

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

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

Overall Survival

The type I error (α) for the analysis of the secondary endpoint of overall survival (OS) is 0.05 (two sided). The final analysis of OS will be performed after the occurrence of approximately 385 deaths.

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

Interim Analyses

Planned Interim Analysis of the Primary Efficacy Endpoint

[redacted].

Interim Efficacy Analysis of Secondary Efficacy Endpoint

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

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALP	alkaline phosphatase
ADA	anti-drug antibody
atezo	atezolizumab
atezo placebo	placebo for atezolizumab
AUC	area under the concentration-time curve
BCC	basal cell carcinoma
BID	twice daily
cobi	cobimetinib
CR	complete response
CrCl	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T lymphocyte antigen-4
cuSCC	cutaneous squamous cell carcinoma
DOR	duration of response
EC	Ethics Committee
ECHO	echocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
ePRO	electronic patient-reported outcome
[redacted]	[redacted]
FDA	Food and Drug Administration
[redacted]	[redacted]
GGT	γ-glutamyltransferase
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
HR	hazard ratio
HRQoL	health-related quality of life

Abbreviation	Definition
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IFN	interferon
IL-2	interleukin-2
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
ITT	intent-to-treat
IRB	Institutional Review Board
IRC	independent review committee
IV	intravenous
IWRS	Interactive Web Response System
KA	keratoacanthoma
LVEF	left ventricular ejection fraction
MHC	major histocompatibility complex
MUGA	multigated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
[redacted]	[redacted]
NSAIDs	non-steroidal anti-inflammatory drugs
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
Pap	Papanicolaou
PD-1	programmed death-1
PD-L1	programmed death ligand-1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PO	orally
PR	partial response
PRO	patient-reported outcome
PVC	polyvinylchloride
QD	once daily
QLQ-C30	Core Quality of Life Questionnaire
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RVO	retinal vein occlusion

Abbreviation	Definition
SCC	squamous cell carcinoma
T3	free triiodothyronine
TNF	tumor necrosis factor
ULN	upper limit of normal
vem	vemurafenib
vem placebo	placebo for vemurafenib
[redacted]	[redacted]

1. BACKGROUND

1.1 BACKGROUND ON MELANOMA

Melanoma is a potentially deadly form of skin cancer that originates from melanocytes. Although the outcome for promptly diagnosed superficial tumors is good, in the metastatic setting, melanoma is associated with high rates of mortality and disease-related morbidity. The clinical outcome of patients with melanoma is highly dependent on the stage at presentation. Despite recent therapeutic advances, metastatic melanoma continues to be one of the most deadly cancers, with a relative 5-year survival rate of 15%–17%.

In 2012, there were around 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 et al. 2002); estimates suggest a doubling of melanoma incidence every 10–20 years (Garbe et al. 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).

Approximately 50% of all cutaneous melanomas harbor an activating mutation in *BRAF*, a major driver of signaling in the RAS/RAF/MEK/ERK MAP kinase (MAPK) pathway. More than 40 distinct *BRAF* mutations have been described, the most common of which occurs in exon 15 and involves a substitution of glutamate for valine at codon 600 (V600E; Davies et al. 2002). Other less common types of *BRAF* mutation include V600K and V600G/R, which occur in approximately 16% and 3% of cases, respectively (Long et al. 2011). Mutations in the *BRAF* oncogene trigger constitutive activation of the MAPK pathway, which in turn drives oncogenesis through growth factor–independent cellular proliferation and survival.

In the past several years, new agents, including targeted therapies and immunotherapies, have been approved in the European Union and the United States for the treatment of *BRAF*^{V600} mutation–positive advanced melanoma.

Targeting of the MAPK pathway is an effective treatment strategy in *BRAF*^{V600} mutation–positive melanoma (Richman et al. 2015). Melanoma cells are also highly immunogenic and thus an appropriate target for immunotherapy (Zhu et al. 2016). Several immunotherapeutic agents that interrupt T-cell suppression, thereby rendering melanoma cells susceptible to immune attack, are currently available or in development for treatment of melanoma (Zhu et al. 2016).

Approved therapies for malignant melanoma in the European Union and the United States include the following (please refer to local prescribing information for further details):

- Targeted therapies: vemurafenib (BRAF inhibitor), cobimetinib (MEK inhibitor) plus vemurafenib, trametinib (MEK inhibitor), dabrafenib (BRAF inhibitor), and trametinib plus dabrafenib
- Immunotherapies: ipilimumab (anti–cytotoxic T lymphocyte antigen-4 [CTLA-4]), pembrolizumab, or nivolumab (anti-programmed death–1 [PD-1] antibodies), ipilimumab plus nivolumab (in the European Union)

  In the United States, ipilimumab plus nivolumab received accelerated approval for the treatment of patients with unresectable or metastatic melanoma.
- Vaccine: talimogene laherparepvec (recombinant viral vector vaccine, CSF2 gene stimulator)

Combined targeted therapy with BRAF and MEK inhibition, consisting of either dabrafenib plus trametinib (Long et al. 2014) or vemurafenib plus cobimetinib, has improved efficacy (as compared with monotherapy with a BRAF inhibitor), with response rates of approximately 70% and progression-free survival (PFS) of 11–14 months across trials.

Immunotherapeutic agents that target co-inhibitory receptors or “immune checkpoints” that suppress T-cell activation have also significantly advanced treatment of advanced melanoma. Response rates for immunotherapeutic agents in patients with *BRAF*-mutant and *BRAF*–wild-type melanoma are lower than rates achieved with combined BRAF and MEK inhibition, with approximately 30% of patients treated with nivolumab or pembrolizumab and 10%–15% of those treated with ipilimumab achieving a response. However, patients can have prolonged responses to these agents. Combination immunotherapy with ipilimumab plus nivolumab has demonstrated an increased overall response rate and improved PFS for treatment of *BRAF*–wild-type and *BRAF*^{V600} mutation–positive unresectable or metastatic melanoma, but results in challenging toxicity, with more than 50% of patients experiencing Grade $\geq$ 3 adverse events and an unknown OS benefit (Larkin et al. 2015).

Despite recent advances in treatments for patients with advanced melanoma, a significant unmet medical for more efficacious treatment options remains.

1.2 BACKGROUND ON ATEZOLIZUMAB

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

Atezolizumab has minimal binding to Fc・receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and 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 who have disease progression during or following platinum-containing chemotherapy. Additionally, atezolizumab is currently in clinical development in combination with other agents for other indications.

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

1.3 BACKGROUND ON 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 G1 phase growth arrest in melanoma cells (Solit et al. 2006; Haass et al. 2008). In vitro, MEK inhibitors reduce cell proliferation, soft agar colony formation, and matrigel invasion of *BRAF*^{V600} mutation–positive melanoma cells, and are also effective against *BRAF*^{V600} mutation–positive melanoma xenografts, which is suggestive of a potentially important role for MEK inhibitors in melanoma and other tumors that harbor the *BRAF*^{V600} mutation (Solit et al. 2006).

Cobimetinib is approved for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation, in combination with vemurafenib.

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

1.4 BACKGROUND ON VEMURAFENIB

Vemurafenib is a compound that selectively inhibits oncogenic BRAF kinase. Discovery of oncogenic *BRAF* mutations highlights the central role of this kinase in signaling pathways that control cellular proliferation. Oncogenic mutations in *BRAF* result in constitutive activation of BRAF kinase, which causes dysregulated downstream signaling via MEK and ERK, leading to increased cell proliferation and survival.

Vemurafenib is approved as a treatment for adult patients with unresectable or metastatic *BRAF*^{V600} mutation–positive melanoma in numerous countries worldwide, including the European Union, Switzerland, Canada, Australia, New Zealand, and Israel, and as a treatment for *BRAF*^{V600E} mutation–positive melanoma in the United States, Brazil, and Korea.

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

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.5.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.5.2

1.5.2.1

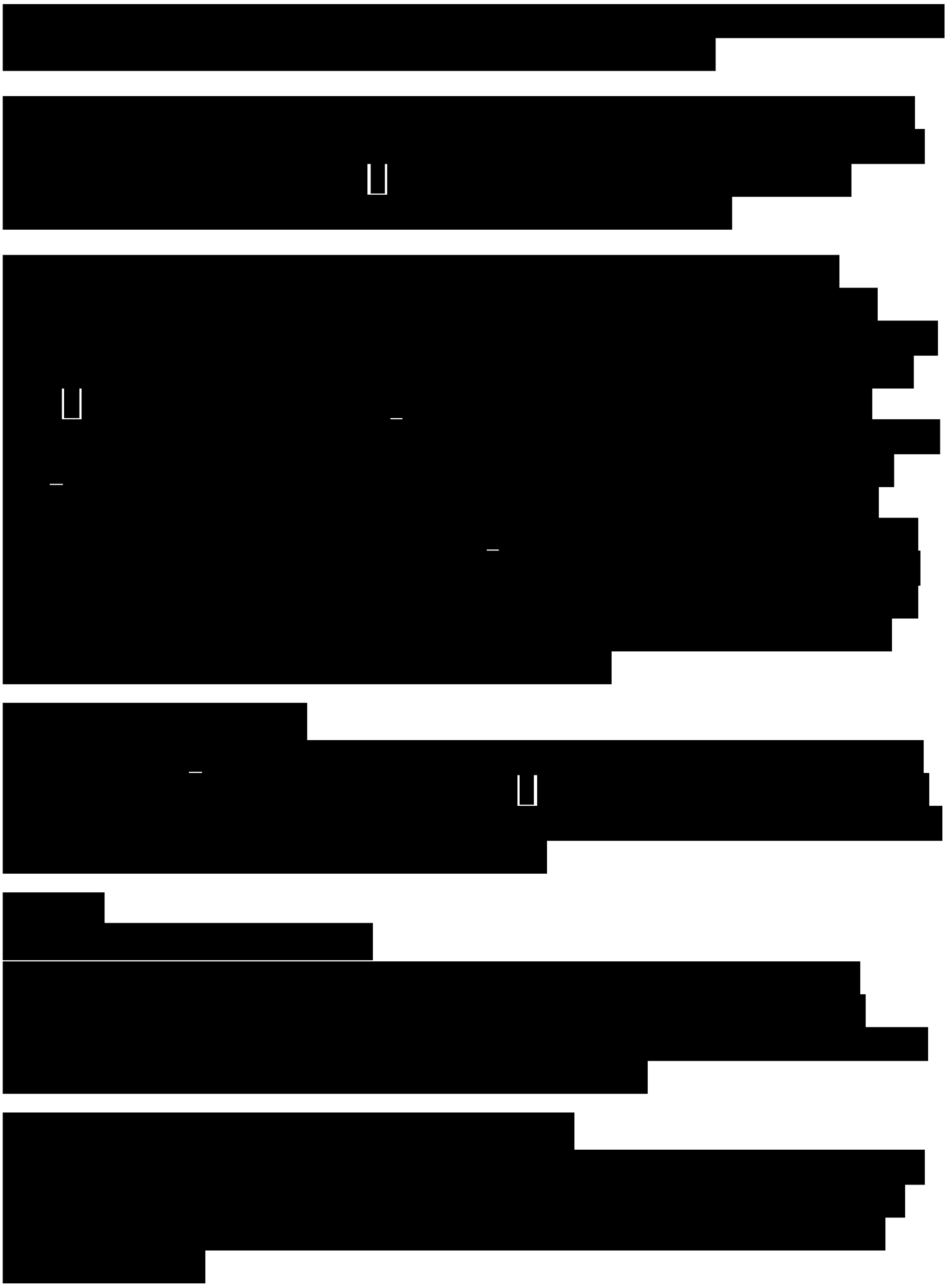
[redacted]

[redacted]

[redacted]

[redacted]a

21 days on/7 days off schedule. All cohorts except Cohort 1 include a run-in period



[redacted]

[redacted] an adverse event (elevation in ALT/AST [n=3], dyspnea [n=2], myalgia, and rash).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.5.2.2

[redacted]

[redacted]

[redacted]

1.5.2.3 [redacted]

[redacted]

1.5.3 Benefit-Risk Assessment

This Phase III protocol includes eligibility criteria, baseline measurements, and recommendations for management of adverse events, including criteria for dose modifications, delays, and discontinuation of one or more of the study drugs that are designed to enhance the safety of patients in this trial. In addition to the oversight provided by the Medical Monitor and drug safety personnel for this trial, an independent Data Monitoring Committee (iDMC) will be employed to monitor and evaluate patient safety throughout the study.

Taking into account the efficacy and safety data of cobi + vem and of single-agent atezolizumab, the acceptable safety profile of atezo + cobi + vem observed in the Phase Ib study, and the extent of safety monitoring proposed, the potential benefits for patients with metastatic or unresectable locally advanced *BRAF*^{V600} mutation–positive melanoma outweigh the potential risks.

Given the unmet need that still exists in advanced *BRAF*^{V600} mutation–positive melanoma, these data support development of atezo + cobi + vem in this indication.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of atezo + cobi + vem compared with placebo plus cobimetinib plus vemurafenib (placebo + cobi + vem) in patients with previously untreated, *BRAF*^{V600} mutation–positive, metastatic or unresectable locally advanced melanoma. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of atezo + cobi + vem compared with placebo + cobi + vem	• PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of atezo + cobi + vem compared with placebo + cobi + vem	• PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by an IRC according to RECIST v1.1, or death from any cause, whichever occurs first • Objective response, defined as a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1 • DOR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first • OS, defined as the time from randomization to death from any cause • 2-year landmark survival, defined as survival at 2 years

Table 1 Objectives and Corresponding Endpoints (cont.)

Secondary Efficacy Objective (cont.)	Corresponding Endpoints
• To evaluate the efficacy of atezo + cobi + vem compared with placebo + cobi + vem	• Time to deterioration in global health status, defined as the time from randomization to first observed ≥ 10-point decrease in EORTC QLQ-C30 linearly transformed global health status scale score that is sustained for two consecutive assessments or followed by death while the patient is on treatment • Time to deterioration in physical functioning, defined as the time from randomization to first observed ≥ 10-point decrease in EORTC QLQ-C30 linearly transformed physical functioning scale score that is sustained for two consecutive assessments or followed by death while the patient is on treatment
Exploratory Efficacy Objective	**Corresponding Endpoints**
• [redacted]	• [redacted]
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of atezo + cobi + vem compared with placebo + cobi + vem	• Occurrence, frequency, and severity of adverse events, with severity determined through use of NCI CTCAE v4.0 • Change from baseline in targeted vital signs during and following treatment • Change from baseline in targeted clinical laboratory test results during and following treatment
PK Objective	**Corresponding Endpoints**
• To characterize the pharmacokinetics of atezolizumab, cobimetinib, and vemurafenib when administered together and to characterize the pharmacokinetics of cobimetinib and vemurafenib when administered together	• Serum concentration of atezolizumab at specified timepoints • Plasma concentration of cobimetinib and vemurafenib at specified timepoints

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory PK Objectives	Corresponding Endpoint
• [redacted]	• [redacted]
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to atezolizumab in the atezo + cobi + vem arm	• Presence of ADAs against atezolizumab during the study relative to the presence of ADAs at baseline
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• [redacted]	• [redacted]
Exploratory Biomarker Objective	**Corresponding Endpoint**
• [redacted]	• [redacted]
Exploratory Health Status Utility Objective	**Corresponding Endpoint**
• [redacted]	• [redacted]

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

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

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

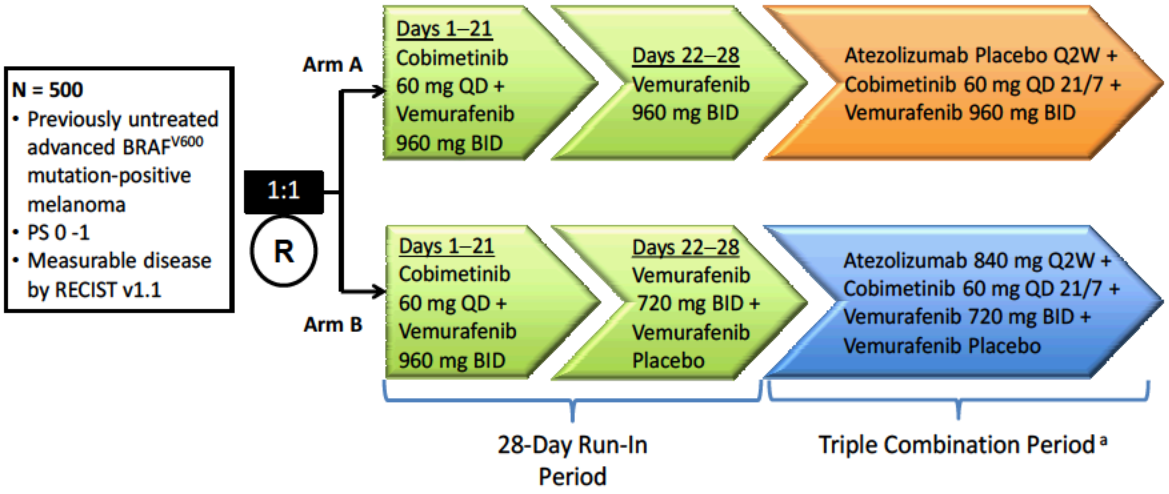
Approximately 500 patients will be randomized in the study. Patients will be randomized in a 1:1 ratio to Arm A (placebo + cobi + vem) or Arm B (atezo + cobi + vem). Patients in both arms will be treated with cobimetinib and vemurafenib during a run-in period of 28 days. Patients in Arm A (control arm) will receive atezolizumab placebo, cobimetinib, and vemurafenib (960 mg twice daily [BID]). Patients in Arm B (experimental arm) will receive active atezolizumab, cobimetinib, and vemurafenib (720 mg BID) (see Section 3.3.2 for rationale for dosing regimen).

As the vemurafenib doses are different between in the two treatments arms, vemurafenib will be blinded in both study arms. To ensure adequate blinding, patients in both arms will receive the same number of vemurafenib tablets, with patients in Arm A receiving all active vemurafenib tablets and patients in Arm B receiving a combination of active vemurafenib tablets and vemurafenib placebo tablets, as described in Table 2.

Following randomization, patients will enter a 28-day run-in period to receive treatment with cobi + vem, followed by treatment with either atezo placebo + cobi + vem (Arm A) or atezo + cobi + vem + vem placebo (Arm B) in the triple combination period, as outlined in Table 2.

A study schema is presented in Figure 2. The treatment regimens for Arms A and B are described in Table 2.

Figure 2 Study Treatment Schema



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

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

Table 2 Treatment Regimens for Arm A and Arm B

Treatment Arm	Run-In Period, Days 1–21	Run-In Period, Days 22–28	Triple Combination Period (28-Day Cycles)
Arm A (atezo placebo + cobi + vem)	• Vemurafenib 960 mg (four tablets from large bottle) PO BID • Cobimetinib 60 mg (three tablets) PO QD	• Vemurafenib 960 mg (four tablets [three tablets from large bottle and one tablet from small bottle]) PO BID	• Atezolizumab placebo IV on Days 1 and 15 of Cycle 1 and all subsequent cycles • Cobimetinib 60 mg (three tablets) PO QD on Days 1–21 • Vemurafenib 960 mg (four tablets [three tablets from large bottle and one tablet from small bottle]) PO BID on Days 1–28
Arm B (atezo + cobi + vem + vem placebo)	• Vemurafenib 960 mg (four tablets from large bottle) PO BID • Cobimetinib 60 mg (three tablets) PO QD	• Vemurafenib 720 mg (three tablets from large bottle) PO BID • Vemurafenib placebo (one tablet from small bottle) PO BID	• Atezolizumab 840 mg IV on Days 1 and 15 of Cycle 1 and all subsequent cycles • Cobimetinib 60 mg (three tablets) PO QD on Days 1–21 • Vemurafenib 720 mg (three tablets from large bottle) PO BID on Days 1–28 • Vemurafenib placebo (one tablet from small bottle) PO BID on Days 1–28

atezo = atezolizumab; BID = twice daily; cobi = cobimetinib; IV = intravenous; PO = by mouth; QD = once daily; vem = vemurafenib.

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

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

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

All patients will be closely monitored for safety and tolerability throughout the study. The National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 4.0 (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 5.1).

Tumor response will be evaluated by the investigator and by an independent review committee (IRC) according to RECIST v1.1 (see Appendix 4). [redacted] will only be assessed by the investigator (Eisenhauer et al. 2009; see Appendix 5). All measurable and non-measurable lesions will be documented at screening. Response will be assessed by the investigator at 8- or 12-week intervals (see Section 4.5.5 for details) until investigator-determined disease progression (according to RECIST v1.1) or death, whichever occurs first. Patients who experience disease progression (RECIST v1.1) must have scans repeated 4–8 weeks after initial documentation of progression to confirm disease progression as required per the protocol. Tumor assessments (RECIST v1.1 and [redacted]) are to continue according to schedule in patients who discontinue treatment for reasons other than confirmed disease progression.

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

Study treatment will continue for all patients until investigator-determined disease progression according to RECIST v1.1 (or subsequent clinical deterioration or confirmed disease progression 4–8 weeks later), for clinically stable patients with a favorable benefit-risk ratio), death, unacceptable toxicity, or pregnancy, whichever occurs first. Patients who discontinue one study drug may be able to continue other study drugs, per guidelines for management of specific adverse events provided in Section 5.1. After treatment discontinuation, patients will be followed for disease progression if applicable, and followed for survival until death, withdrawal of consent, or loss to follow-up, whichever occurs first.

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

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

A schedule of activities is provided in Appendix 1.

3.2 END OF STUDY AND LENGTH OF STUDY

The study will end when all patients enrolled have been followed until death, withdrawal of consent, lost to follow-up, or the Sponsor decides to end the trial, whichever occurs first. Patients may continue on study treatment until the development of progressive disease, unacceptable toxicity, and/or consent withdrawal. Patients who discontinue study treatment for any reason will be followed for safety according to protocol, followed for disease progression and followed for survival until death, withdrawal of consent, or they are lost to follow-up. Patients who start subsequent anti-cancer treatment after study treatment discontinuation will still need to be followed for disease progression, survival, and safety per the protocol. The length of the study, from screening of the first patient to the last patient last visit, is expected to be approximately 90 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Run-In Period

This study will employ a 28-day run-in period. This is the shortest run-in period determined to be compatible with improved tolerability, and it was considered to be potentially advantageous with regard to the timing of immune modulation observed with the use of RAF plus MEK inhibitors in melanoma (Wilmott et al. 2012; Frederick et al. 2013).

Co-administration of vem±cobi+atezo was evaluated in the Phase Ib Study GP28384. In the first cohort (Cohort 1), 2 of 3 patients treated with vem+atezo experienced Grade 3 skin toxicities including rash and exfoliative dermatitis. In addition, 2 of the

3 patients experienced Grade 3 ALT or AST elevation. As a result of these toxicities, subsequent cohorts incorporated a run-in period in which vemurafenib was given alone prior to initiation of vem+atezo. A 56-day run-in period was tolerated in Cohort 2, so a shorter run-in period of 28-days was tested and tolerable found to be tolerable in Cohort 3. Evaluation of adverse events across the three cohorts demonstrated a higher incidence of both atezolizumab-related and vemurafenib-related Grade 3 adverse events. Specifically, all patients in Cohort 1 had vemurafenib-related Grade 3 events, and 67% of patients had atezolizumab-related adverse events compared with Cohorts 2 and 3, where 50% and 67% of patients experienced vemurafenib-related events and 38% and 33% of patients experienced atezolizumab-related events, respectively. These data suggest that a run-in period with targeted therapy prior to administration of atezolizumab provides an ameliorative effect, potentially due to increased tolerability as patients acclimate to treatment, thus supporting the use of a run-in period when combining these agents. Subsequent cohorts (following Cohort 3) assessed administration of cobi+vem+atezo and included a run-in period of cobi+vem for 28 days prior to the introduction of atezolizumab.

3.3.2 Rationale for Treatment Regimens

In Study GP28384, patients in atezo+cobi+vem cohorts received atezolizumab 800 mg on Days 1 and 15 (every 2 weeks), cobimetinib 60 mg QD on Days 1–21, and vemurafenib 720 mg BID on Days 1–28 of each 28-day cycle. This treatment regimen was found to be manageable and tolerable and was associated with encouraging preliminary efficacy data (see Section 1.5.2.1).

3.3.2.1 Run-In Period

The initial treatment regimen for cobimetinib and vemurafenib during the run-in period in this study (cobimetinib 60 mg QD and vemurafenib 960 mg BID on Days 1–21) is the approved dosage for cobimetinib and vemurafenib, respectively.

Arm A (Atezo Placebo+Cobi+Vem)

Patients will receive vemurafenib 960 mg BID on Days 22–28 of the run-in period.

Arm B (Atezo+Cobi+Vem+Vem Placebo)

Patients will receive vemurafenib at a reduced dose of 720 mg BID on Days 22–28.

The reduced dose of 720 mg BID (one dose level below the maximum-tolerated dose) was selected with the intention of balancing considerations for an experimental regimen with the need for patients to receive a therapeutic dose of this approved agent. This dose and schedule has been shown to be highly efficacious in the Phase Ib study GP28384 (see Section 1.5.1), which first assessed the combination of atezo+cobi±vem in patients with *BRAF*^{V600} mutation–positive metastatic melanoma. [redacted]

[redacted]

3.3.2.2 Triple Combination Period

Arm A (Atezo Placebo+Cobi+Vem)

Patients will continue to receive cobimetinib 60 mg QD on Days 1–21 and vemurafenib 960 mg BID on Days 1–28 of each 28-day cycle.

Arm B (Atezo+Cobi+Vem+Vem Placebo)

Patients will receive cobimetinib 60 mg QD on Days 1–21 and vemurafenib 720 mg BID and vemurafenib placebo BID on Days 1–28 of each 28-day cycle, as well as atezolizumab at a fixed dose of 840 mg on Days 1 and 15 of Cycle 1 and Days 1 and 15 (i.e., every 2 weeks) of subsequent cycles.

The treatment regimen for atezo+cobi+vem cohorts in Study GP28384, which included atezolizumab at a dose of 800 mg on Days 1 and 15 (every 2 weeks), was generally well tolerated and was associated with encouraging preliminary efficacy data (see Section 1.5.2.1). 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. [redacted]

3.3.3 [redacted]

[redacted]

[redacted]

3.3.4 [redacted]

3.3.4.1 [redacted]

[redacted]

3.3.4.2 [redacted]

[redacted]

[redacted]

3.3.5 [redacted]

[redacted]

3.3.6 [redacted]

[redacted]

[redacted]

[redacted]

3.3.7 [redacted]

3.3.7.1 [redacted]

[redacted]

3.3.7.2 [redacted]

[redacted]

[redacted]

3.3.8 [redacted]

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

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

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Able to comply with the study protocol, in the investigator's judgment
- Histologically confirmed Stage IV (metastatic) or unresectable Stage IIIc (locally advanced) melanoma, as defined by the American Joint Committee on Cancer, 7th revised edition
- Naïve to prior systemic anti-cancer therapy for melanoma (e.g., chemotherapy, hormonal therapy, targeted therapy, immunotherapy, or other biologic therapies), with the following exceptions:
  - Neoadjuvant and or adjuvant treatment with chemotherapy, if discontinued at least 28 days prior to initiation of study treatment
  - Adjuvant treatment with IFN, IL-2, or vaccine therapies, if discontinued at least 28 days prior to initiation of study treatment
  - Adjuvant treatment with herbal therapies, if discontinued at least 7 days prior to initiation of study treatment
- Documentation of *BRAF*^{V600} mutation–positive status in melanoma tumor tissue [redacted]

Molecular and Genetics Quality Network], EMQN for clinical diagnosis,CE-marked [European conformity] in vitro diagnostic in E.U. countries, or equivalent)

[redacted]

- Eastern Cooperative Oncology Group Performance Status of 0 or 1 (see Appendix 3)
- Measurable disease according to RECIST v1.1 (must be outside of CNS)
- [redacted]
- Life expectancy ≥ 18 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment, with the exception of amylase, lipase, and LDH where up to 28 days is acceptable (using central laboratory result)
  - ANC $\geq 1.5 \times 10^9$/L without granulocyte colony-stimulating factor support
  - WBC count $\geq 2.5 \times 10^9$/L
  - Lymphocyte count $\geq 0.5 \times 10^9$/L
  - Platelet count $\geq 100 \times 10^9$/L without transfusion
  - Hemoglobin ≥ 90 g/L without transfusion
  - Serum albumin ≥ 25 g/L
  - Total bilirubin $\leq 1.5 \times$ ULN
  - AST and ALT $\leq 2.0 \times$ ULN
  - Amylase and lipase $\leq 1.5 \times$ ULN
  - ALP $\leq 2.5 \times$ ULN or, for patients with documented liver or bone metastases, ALP $\leq 5 \times$ ULN
  - 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:

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

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

- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen and stable INR during the 28 days immediately preceding initiation of study treatment
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $<1\%$ per year during the treatment period and for 6 months after the last dose of study treatment. *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.

  Hormonal contraceptive methods must be supplemented by a barrier method.

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

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

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

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

4.1.2 Exclusion Criteria

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

Cancer-Related Exclusion Criteria

- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the course of the study

- Traumatic injury within 2 weeks prior to initiation of study treatment
- Palliative radiotherapy within 14 days prior to initiation of study treatment
- Active malignancy (other than *BRAF*^{V600} mutation–positive melanoma) or malignancy within 3 years prior to screening are excluded, with the exception of resected melanoma, resected basal cell carcinoma (BCC), resected cutaneous squamous cell carcinoma (SCC), resected carcinoma in situ of the cervix, resected carcinoma in situ of the breast, in situ prostate cancer, limited-stage bladder cancer, or any other curatively treated malignancies from which the patient has been disease-free for at least 3 years

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

Ocular Exclusion Criteria

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

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

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

Cardiac Exclusion Criteria

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

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

Central Nervous System Exclusion Criteria

- Untreated or actively progressing CNS lesions (carcinomatous meningitis)

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

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

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

Additional Exclusion Criteria

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

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

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

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, anti–phospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 9 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

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

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

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

  – Rash must cover $<10\%$ of body surface area
  – Disease is well controlled at baseline and requires only low-potency topical corticosteroids
  – No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months
- Known clinically significant liver disease, including alcoholism, cirrhosis, fatty liver, and other inherited liver disease as well as active viral disease including:
  – Positive HIV test at screening
  – Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening

    Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study.
  – Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test and a positive HCV RNA test at screening
- Active tuberculosis

- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of clinically relevant infection within 2 weeks prior to initiation of study treatment
- Any Grade ≥ 3 hemorrhage or bleeding event within 4 weeks prior to initiation of study treatment
- History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to initiation of study treatment
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Treatment with therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study
- Treatment with systemic immunosuppressive medication (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor (TNF)-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study

  Patients who have received acute, low-dose systemic immunosuppressant medication (≤10 mg/day oral prednisone or equivalent) ≥4 weeks prior to initiation of study treatment or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.

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

- Inability or unwillingness to swallow pills
- Requirement for concomitant therapy or food that is prohibited during the study, as described in Sections 4.4.2 and 4.4.3, respectively

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

After written informed consent has been obtained and eligibility has been established, each patient will be assigned an identification number and be randomized to one of the two treatment arms through use of an interactive web-based response system (IWRS).

Randomization will be stratified by geographic region (North America vs. Europe vs. Australia, New Zealand, and others) and baseline LDH ($\leq$ULN vs. $>$ULN, using central laboratory result). A stratified, permuted block randomization scheme will be used to obtain approximately a 1:1 ratio between the two treatment groups.

The investigator, patient, and Sponsor will be blinded to treatment assignment except as described below.

Dose modifications will be managed via the IWRS to avoid unblinding due to differences in permitted dose reductions in Arm A vs. Arm B (see Section 5.1.5.1 for details).

Treatment codes should not be broken except in emergency situations. The investigator can request unblinding of a patient's treatment assignment when such knowledge is essential for the safety of the patient. In such cases, an individual patient's treatment assignment can be accessed through the IWRS by the treating investigator. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding or unblinding due to a serious adverse event).

As per health authority reporting requirements, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study treatment. The treatment code will be available to the Sponsor's drug safety group through the IWRS. The patient may continue to receive treatment, and the investigator, patient, and remaining Sponsor personnel will remain blinded to treatment assignment.

Unblinding may be recommended by the iDMC. In such cases, an individual patient's treatment assignment can be accessed through the IWRS by the treating investigator.

4.3 STUDY TREATMENT

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

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab or Placebo

Atezolizumab will be supplied by the Sponsor as sterile liquid in 20-mL glass vials. Extraction of 14 mL of atezolizumab solution from a 1200 mg per vial contains 840-mg dose. For information on the formulation and handling of atezolizumab, refer to the Investigator's Brochure and Pharmacy Manual.

4.3.1.2 Cobimetinib

Cobimetinib will be supplied as 20-mg, film-coated tablets packaged in blister packs (21 tablets per pack; 3 packs per box) for oral administration. For information on the formulation and handling of cobimetinib, see the Cobimetinib Investigator's Brochure.

4.3.1.3 Vemurafenib and/or Placebo

During Days 1–21 of the run-in period, vemurafenib will be supplied as 240-mg, film-coated tablets, packaged in bottles (a large bottle containing 180 tablets per bottle), for oral administration. During Days 22-28 of the run-in period and at all subsequent timepoints, vemurafenib (both active and placebo) will be supplied as film-coated tablets (240-mg strength for active drug), packaged in bottles (a small bottle containing 60 tablets per bottle), for oral administration. Detailed dosing instructions will be provided to investigative sites. For information on the formulation and handling of vemurafenib, see the Vemurafenib Investigator's Brochure.

4.3.2 Dosage, Administration, and Compliance

The treatment regimens are summarized by treatment arm in Table 2 (see Section 3.1). The duration of a treatment cycle is 28 days.

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

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

4.3.2.1 Atezolizumab and Atezolizumab Placebo

Atezolizumab 840 mg or placebo will be administered by IV infusion on Days 1 and 15 of Cycle 1 and Days 1 and 15 (every 2 weeks) of subsequent cycles (see Table 2 in Section 3.1 for a summary of the treatment regimens).

Administration of atezolizumab will be performed in a setting with medical facilities and staff who are trained to monitor for and respond to medical emergencies. For anaphylaxis precautions, see Appendix 6.

No premedication will be allowed for the first dose of atezolizumab. Patients who experience an infusion-related reaction with the first infusion may receive premedication with antihistamines or antipyretics or analgesics (excluding acetaminophen; see Section 4.4.2) for subsequent infusions.

The initial dose of atezolizumab will be administered over 60 (±15) minutes. Subsequent infusions will be administered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Vital signs are to be measured before, as well as during, and after infusions, if clinically indicated, as outlined in Section 4.5.4.

Guidelines for medical management of infusion-related reactions are provided in Appendix 10.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation are provided in Section 5.1.5.4 and Appendix 10.

4.3.2.2 Cobimetinib

All patients will receive cobimetinib at a dose of 60 mg (three 20-mg tablets) orally (PO) QD on Days 1–21 of each 28-day cycle during the run-in and triple combination periods (see Table 2 in Section 3.1 for a summary of the treatment regimens). Cobimetinib should be taken approximately the same time each day, with the morning vemurafenib dose, and no later than 4 hours after the scheduled time. Cobimetinib may be taken with or without a meal. Cobimetinib should be swallowed whole with a glass of water and should not be chewed, cut, or crushed. If a dose of cobimetinib is missed (i.e., not taken within 12 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5.4.

4.3.2.3 Vemurafenib and Vemurafenib Placebo

Each dose of vemurafenib will consist of four tablets, with patients in Arm A (atezo placebo + cobi + vem) receiving four active tablets and patients in Arm B (atezo + cobi + vem + vem placebo) receiving three active tablets plus one placebo tablet. All patients will receive vemurafenib at a dose of 960 mg (four 240-mg tablets) PO BID on Days 1–21 of the run-in period. Patients in Arm A will continue to receive vemurafenib at a dose of 960 mg PO BID on Days 22–28 of the run-in period and Days 1–28 of each 28-day cycle during the triple combination period. Patients in Arm B will receive vemurafenib at a dose of 720 mg (three 240-mg tablets) plus vemurafenib placebo (one tablet) PO BID on Days 22–28 of the run-in period and Days 1–28 each 28-day cycle during the triple combination period (see Table 2 in Section 3.1 for a summary of the treatment regimens).

Placebo and active vemurafenib tablets are identical for blinding purposes. Vemurafenib will be dosed as follows (one dose represented): 4 active tablets PO BID (Arm A) or 3 active tablets and one placebo tablet PO BID (Arm B). Two distinct bottles will be utilized such that patients in both arms take 3 pills from one bottle and the fourth pill will be blinded and taken from a second bottle thus ensuring the dose level is blinded (see Section 3.3.4.2 for additional information).

Vemurafenib should be taken in the morning and in the evening, approximately 12 hours later. Vemurafenib may be taken with or without a meal. Vemurafenib tablets should be swallowed whole with a glass of water and should not be chewed, cut, or crushed. If a dose of vemurafenib is missed (i.e., not taken within 4 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5.4.

4.3.2.4 Dosing of Study Treatment Beyond Disease Progression

Patients and investigators must meet all of the following criteria to be allowed to receive study treatment beyond disease progression:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

4.3.3 Assessment of Compliance

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

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (cobimetinib, vemurafenib, and atezolizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs, using the IWRS 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.

4.3.5 [redacted]

[redacted]

4.4 CONCOMITANT THERAPY AND ADDITIONAL RESTRICTIONS

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to signing of the Informed Consent Form through 30 days after the last dose of study treatment. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients who use oral contraceptives, hormone-replacement therapy, prophylactic anticoagulation therapy (such as low-molecular-weight heparin at a stable dose level), or other allowed maintenance therapy should continue their use. Male and female patients of reproductive potential should use highly effective means of contraception (see Section 4.1.1).

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated influenza vaccinations
- Megestrol administered as an appetite stimulant
- Inhaled corticosteroids

- Mineralocorticoids
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Pain medications as indicated, as per standard practice

At the discretion of the investigator, anti-emetic medications, antidiarrheal medications, and may be administered prophylactically per standard local practice before the second and subsequent doses of study treatment. Anti-emetic medications, antidiarrheal medications, and hematopoietic growth factors are not to be administered prophylactically prior to initiation of study treatment.

Patients requiring treatment for toxicities or for co-existent conditions may be treated as clinically indicated. Planned use of other medications should be discussed with the Medical Monitor.

Premedication with antihistamines may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

Patients who experience infusion-associated symptoms may be treated symptomatically with ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice (acetaminophen is prohibited; see Section 4.4.2). 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; see Appendix 6).

4.4.2 Prohibited Therapy

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

Prohibited therapies applicable to all patients

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy for palliative or other purposes, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment until disease progression is documented and the patient has discontinued study treatment.
- Investigational therapy is prohibited during the study.
- Anti-emetic medications, antidiarrheal medications, and hematopoietic growth factors are not to be administered prophylactically prior to initiation of study treatment.

- Anti-arrhythmic agents and medications with a risk of torsades de pointes are prohibited within 7 days prior to initiation of study treatment, during study treatment, and for 30 days after the last dose of study treatment.
- Acetaminophen is prohibited within 7 days prior to initiation of study treatment, during study treatment, and for 30 days after the last dose of study treatment, unless the patient has an absolute contraindication to the use of non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin (i.e., severe allergy or reactive airway disease sensitive to NSAIDs or aspirin).

<u>Prohibited therapies applicable to patients receiving atezolizumab (or atezolizumab placebo)</u>

- Denosumab (a RANKL inhibitor) is prohibited during atezolizumab treatment because it could potentially alter the efficacy and safety of atezolizumab. Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while in the study.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of atezolizumab, during atezolizumab treatment, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or five half-lives of the drug, whichever is longer, prior to initiation of atezolizumab and during atezolizumab treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during atezolizumab treatment because these agents could potentially alter the efficacy and safety of atezolizumab. However, systemic corticosteroids can be given as premedication to patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance).
- *Metamizole (dipyrone) is prohibited in treating atezolizumab-associated infusion-related reactions because of its potential for causing agranulocytosis.*

<u>Prohibited therapies applicable to patients receiving cobimetinib or vemurafenib:</u>

- St. John's wort is prohibited during cobimetinib and vemurafenib treatment and for 2 weeks after the last dose of cobimetinib or vemurafenib (whichever is later)

Patients who require the use of any of the agents listed above will be discontinued from study treatment (unless use is agreed upon in consultation with the Medical Monitor) and followed for safety outcomes for 30 days after their last dose of study treatment or until they receive another anti-cancer therapy, whichever occurs first.

4.4.3 Prohibited Foods and Drinks

Use of grapefruit juice, a potent CYP3A4 enzyme inhibitor, is prohibited during the study and for 30 days after the last dose of study treatment. Patients must not drink alcohol while receiving study treatment. The alcohol restriction will be periodically reviewed throughtout the study. If the safety data are supportive and the iDMC approve, the alcohol restriction will be lifted to allow a small daily or weekly allowance for alcohol consumption.

4.4.4 Cautionary Medications

Antiplatelet agents should be used with caution during study treatment.

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. For treatment of vemurafenib-related adverse events (other than hepatotoxicity as outlined in Section 5.1.5.4), systemic corticosteroids may be administered at the lowest effective dose and for the shortest possible duration necessary. If feasible, alternatives to these agents should be considered. Topical corticosteroids are allowed for suspected cutaneous autoimmune reactions. Megestrol may be administered as an appetite stimulant during the study. 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.

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (see Section 5.1.5.4).

4.4.4.1 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

Cautionary therapies applicable to patients receiving cobimetinib

- Concomitant use of strong and moderate inhibitors of CYP3A (e.g., clarithromycin, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) should be avoided during cobimetinib treatment because 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).
- Strong and moderate CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, and phenobarbital) should be avoided during cobimetinib treatment because 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.

Cautionary therapies applicable to patients receiving vemurafenib

- Vemurafenib is a moderate CYP1A2 inhibitor and a CYP3A4 inducer. Concomitant use of vemurafenib with agents with a narrow therapeutic window that are metabolized by CYP1A2 and CYP3A4 is not recommended. If co-administration cannot be avoided, exercise caution, as vemurafenib may increase plasma exposure of CYP1A2 substrate drugs and decrease plasma exposure of CYP3A4 substrate drugs. Dose reduction of the concomitant CYP1A2 substrate drug may be considered, if clinically indicated.
- In two drug-drug interaction studies, vemurafenib increased the exposure of a single, oral dose of digoxin. An approximate 1.8- and 1.5-fold increase in digoxin area under the concentration-time curve (AUC) from Time 0 to the last measurable concentration and maximum concentration, respectively, was observed in Study GO28394. Digoxin and other p-glycoprotein substrates with a narrow therapeutic window are prohibited within 7 days prior to initiation of vemurafenib, during vemurafenib treatment, and for 30 days after the last dose of vemurafenib.
- Warfarin and vemurafenib should be co-administered with caution, as vemurafenib has been shown to increase the AUC of S-warfarin, a CYP2C9 substrate. If warfarin is given, additional INR monitoring should be considered.
- In vitro data have demonstrated that vemurafenib is a moderate inhibitor of CYP2C8. CYP2C8 substrates with a narrow therapeutic window should be used with caution, as their concentration may be increased when co-administered with vemurafenib.
- In vitro data have demonstrated that vemurafenib is a substrate of CYP3A4. Thus, strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfainavir, voriconazole) and inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) should be used with caution when co-administered with vemurafenib.

The above-listed cautionary medications are not necessarily comprehensive. The investigator should consult the prescribing information for any concomitant medication when determining whether it can be safely co-administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.4.4.2 Medications Affecting the QT Interval

Caution should be exercised when the study drugs are co-administered with drugs that cause QT prolongation or cardiac arrhythmia, especially in patients with a preexisting cardiac disease or ECG abnormality that may predispose them to cardiac dysrhythmia. Investigators should closely monitor patients who are on medications or supplements that may affect the QT interval. Alternative treatment options for medications known to affect QT interval should be discussed with each patient prior to their randomization in this study. Additional information is available at the following Internet site:

https://crediblemeds.org/healthcare-providers/

The effect of vemurafenib 960 mg BID on QT interval was evaluated in a multicenter, open-label, single-arm study in 132 previously treated patients with *BRAF*^{V600} mutation–positive metastatic melanoma (Study NP22657). No large changes from baseline in mean QTc interval (i.e., >20 ms) were detected in the study. However, vemurafenib is associated with concentration-dependent QT prolongation.

Although nonclinical studies showed a low potential for QT-interval prolongation with cobimetinib, no additive effect on QT-interval prolongation was observed when patients were treated with cobimetinib in combination with vemurafenib in Study GO28141. A combined cobimetinib and vemurafenib concentration-QTcF model (for which 433 patients contributed 1031 cobimetinib and vemurafenib observations) provided no evidence that cobimetinib prolonged QTcF interval when co-administered with vemurafenib.

4.4.4.3 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.2) may be used during the study at the discretion of the investigator.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable. 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 5.1 for further information).

If a protocol-mandated study visit coincides with a holiday and/or weekend that preclude the visit, the visit should be scheduled on the nearest following feasible date.

4.5.1 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 randomized patients and for patients who are not subsequently randomized will be maintained at the study site.

BRAF 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 randomization. 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.

Standard-of-care screening assessments may be performed concurrently with the *BRAF*^{V600} mutation testing. The 28-day window begins at the time of the first standard-of-care screening assessment or the first study-specific screening assessment after the *BRAF*^{V600} mutation test result is available, whichever is earlier. Results of standard-of-care tests or examinations performed before obtaining informed consent and within 28 days prior to Run-In Day 1 may be used for screening assessments; such tests do not need to be repeated for screening.

Screening Window Extension

Every effort should be made to complete all assessments within the screening window. In exceptional circumstances when this is not possible, the screening window may be extended for an agreed upon and brief period (to allow re-evaluation of assessments) after discussion and agreement with the Medical Monitor. Not all requests will be granted, each request will be assessed.

Rescreening

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

4.5.2 Medical History and Demographic Data

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

4.5.3 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, dermatological, 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.

4.5.4 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 prior to 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).

4.5.5 Tumor and Response Evaluations

All measurable and non-measurable lesions must be documented at screening (within 28 days prior to initiation of study treatment). Previously irradiated lesions should not be selected as measurable (target) lesions. Evaluation of tumor response conforming to RECIST v1.1 must then be documented every 8 weeks (±1 week) (during the last week of every two treatment cycles) from the date of first study drug administration (Run-In Day 1) through 24 months (e.g., Weeks 8, 16, 24, 32, etc.) and then every 12 weeks (±1 week) thereafter, until investigator-determined disease progression (according to RECIST v1.1, that is confirmed 4–8 weeks after initial documentation of progression) or death, whichever occurs first. Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression. At the investigator's discretion, tumor assessments may be repeated at any time if disease progression is suspected.

Tumor assessments must be performed independently of changes to the study treatment administration schedule (i.e., when treatment is withheld). If a tumor assessment has to be performed early or late, subsequent assessments should be conducted according to the original schedule based on the date of first study treatment administration (Run-In Day 1).

Tumor assessments will include contrast-enhanced CT or MRI scans of the chest, abdomen, and pelvis. Imaging of the neck should be included if clinically indicated. In the event a positron emission tomography (PET)/CT scanner is used for tumor assessments, the CT portion of the PET/CT must meet criteria for diagnostic quality. A CT or MRI scan of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. Patients with untreated or actively progressing CNS metastases are not eligible for the study (see Section 4.1.2). Stable brain metastases (as defined in Section 4.1.2) must be evaluated at each tumor assessment 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 4) and [redacted] Objective response (complete or partial response) must be confirmed by repeat assessments ≥4 weeks after initial documentation. In the case of stable disease, tumor measurements must meet criteria for stable disease ≥6 weeks after initiation of study treatment.

4.5.6 Study-Specific Safety Monitoring Assessments

4.5.6.1 Monitoring for New Primary Neoplasms

All new primary neoplasms (benign or malignant), including new primary melanoma, will be reported until 6 months after the last dose of vemurafenib. Any new primary neoplasm other than cuSCC should be reported as a serious adverse event.

Dermatologic Evaluation

Evaluations of the skin by a dermatologist, or qualified equivalent medical specialist, will be performed at specified timepoints during the study. An unscheduled dermatology examination may be performed during treatment for investigation of any new skin lesions that are suspected of being cuSCC or another new primary cutaneous neoplasm.

The dermatologic evaluation should include the following:

- Complete history of prior dermatologic medications and cuSCC risk factors (i.e., radiation therapy, sun exposure, immunosuppression, prior cuSCC, use of tanning beds, precursor lesions, and phototherapy for psoriasis)

- Skin examination for cuSCC, BCC, actinic keratosis, keratoacanthoma (KA), and/or second primary melanoma
- Appropriate mapping of any suspicious lesions that may represent cuSCC, BCC, actinic keratosis, KA, or second primary melanoma
- Biopsy and/or excision of any suspicious lesions and submission of specimen blocks or sections for pathologic examination by the local laboratory *according to local standard of care*
- Treatment of identified skin neoplasms or conditions per local standard of care

Head and Neck Evaluation

To monitor for the occurrence of SCC in the upper aerodigestive tract, a head and neck examination will be performed by the investigator or his or her designee at screening, specified timepoints during the study, and as clinically indicated (e.g., if any new head and neck lesions are suspected of being non-cuSCC). Assessments will include (at a minimum) examination of the HEENT and neck, visual inspection of the oral mucosa, and lymph node palpation.

Any suspicious lesions that are identified will be evaluated*, biopsied, or excised if indicated and followed up* according to local standard of care.

Lung Examination

Patients will undergo CT or MRI scans of the chest to monitor for the occurrence of lung SCC. The chest CT or MRI scans performed as part of regularly scheduled tumor assessments may be used for lung SCC surveillance.

Anal Examination

To monitor for anal SCC, visual inspection and digital examination of the anus and anal canal will be performed by the investigator or his or her designee at specified timepoints during the study and as clinically indicated. Colonoscopy, sigmoidoscopy, or anoscopy is not required but may be performed if clinically indicated. Any suspicious lesions that are identified will need to be evaluated *and biopsied if indicated* according to local standard of care.

Gynecological Examination

To monitor for cervical carcinoma, all female patients will undergo a pelvic examination, including visual inspection of the uterine cervix and Papanicolaou (Pap) smear, at specified timepoints during the study and as clinically indicated.

4.5.6.2 Ophthalmologic Examinations

Patients will under ophthalmologic examinations at specified timepoints during the study. Patients will be evaluated at screening for risk factors for neurosensory retinal detachment, RVO, or neovascular macular degeneration. Risk factors for RVO include history of serous retinopathy, history of RVO, or evidence of ongoing serous retinopathy

or RVO at baseline. Patients with such conditions will be excluded from the study as detailed in Section 4.1.2.

Ophthalmologic examinations will include visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography (OCT). If spectral domain OCT is not available, time-domain OCT may be performed instead. Ophthalmologic examination must be performed by a qualified ophthalmologist.

4.5.6.3 Cardiac Monitoring

Electrocardiograms

ECG recordings will be obtained at screening and at specified subsequent timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated. ECG results will be evaluated by the investigator for determination of eligibility at screening and for the purposes of real-time cardiac safety monitoring and suitability for continued study treatment.

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

Electronic or paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

Guidelines for management of QT prolongation are provided in Section 5.1.3.6.

Evaluation of Left Ventricular Function

Patients will undergo evaluation of LVEF, either by ECHO or MUGA, at specified timepoints during the study, and as clinically indicated for new or worsening symptoms. Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF assessment. Evaluation of left ventricular function must be performed using the same method for each patient.

Guidelines for management of decreased LVEF (asymptomatic and symptomatic) are provided in Section 5.1.2.2 and Table 3.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

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, differential count (neutrophils, bands [if available], eosinophils, basophils, monocytes, lymphocytes)
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate (or total carbon dioxide), BUN or urea, creatinine, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, LDH, CPK, amylase, lipase, glucose (non-fasting)
- Fasting blood glucose (minimum of 8-hour fast), at screening only
- Fasting lipids: total cholesterol, LDL cholesterol, triglycerides (minimum of 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), free thyroxine
- HIV serology
- HBV serology: HBsAg, hepatitis B surface antibody, total HBcAb

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed at screening.
- 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 prior to initiation of study treatment (i.e., Run-In Day 1). Urine pregnancy tests will be performed on Day 1 of every cycle from Cycle 1. If a urine pregnancy test is not available, serum pregnancy test may be used. 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).

[redacted]

- [redacted]
- [redacted]

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[redacted]

4.5.8 Patient-Reported Outcomes

To more fully characterize disease burden and clinical benefit of atezolizumab plus cobimetinib and vemurafenib in patients with advanced melanoma, patient-reported

outcome (PRO) data will be obtained through use of the following instruments: EORTC QLQ-C30 and the [redacted]. The questionnaires will be translated as appropriate in the local language.

To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety by the patient before the patient receives any information on disease status and prior to the performance of non-PRO assessments and the administration of study treatment. Interviewer assessment is allowed but can only be conducted by a member of the clinic staff for patients who are unable to complete the measures on their own. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site.

Patients will use an electronic PRO (ePRO) device to capture PRO data. The ePRO device and/or instructions for completing the PRO questionnaires electronically will be provided by site staff. The data will be transmitted to a centralized database maintained by the ePRO vendor. The data will be available for access by appropriate study personnel. In the event that the device or the Web-based system is not readily available, paper questionnaires formatted for use as backup data collection forms should be used to minimize missing data. The paper PROs are entered into a Web Portal (i.e., not on the ePRO devices) by the site staff. Compliance with data collection will be documented throughout the study.

To minimize burden to patients and clinical research staff, only the [redacted] and select items of the EORTC QLQ-C30 to assess global health status (Questions 29 and 30) and physical functioning (Questions 1–5) and will be administered to patients after treatment discontinuation (due for instance to adverse event, loss of clinical benefit or confirmed disease progression) (see Appendix 1).

4.5.8.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) (see Appendix 7) that is commonly used in clinical trials involving patients with metastatic melanoma (Revicki et al. 2012; Schadendorf et al. 2015). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The EORTC QLQ-C30 module takes approximately 10 minutes to complete. A 10-point change is defined as a clinically meaningful difference for the EORTC QLQ-C30 (Osoba et al. 1998).

4.5.8.2 [redacted]

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation from Study

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

- Patient withdrawal of consent
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor
- Study termination or site closure
- Patients who develop a contraindication to atezolizumab therapy during the run-in period, which was not present at randomization and therefore are not eligible to receive atezolizumab, may continue in the study and receive cobimetinib and vemurafenib (960 mg BID). If the condition resolves or improves at a later date, the patient may be eligible to receive atezolizumab following discussion with the Medical Monitor. A week of the vemurafenib/placebo dosing as outlined the run-in period, Days 22–28, would be required prior to staring atezolizumab (see Table 2).

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. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

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

- Disease progression per investigator assessment according to RECIST v1.1 (confirmed as per Section 3.1)
- Clinical deterioration due to disease progression
- Use of an anti-cancer therapy (outside of study treatment per protocol)
- 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)
- Any adverse event that requires study treatment discontinuation per the guidelines in Section 5.1
- Intolerance of study treatment despite undergoing protocol-defined dose reduction
- In cases where discontinuation of one or two study drugs is required for toxicity, patients may continue on the remaining drug(s) per the guidelines in Section 5.1

Patients who discontinue all study drugs for any reason will be asked to return to the clinic for a treatment discontinuation visit 28 (±7) 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 28 (±7) 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.

If study treatment is discontinued prior to progressive disease, tumor assessments should continue according to the protocol schedule until investigator-assessed disease progression according to RECIST v1.1.

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.

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on 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 atezolizumab, cobimetinib, and vemurafenib in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections 5.1.1 [atezolizumab], 5.1.2 [cobimetinib], 5.1.3 [vemurafenib], and 5.1.4 [combination use]). Guidelines for dose modifications and treatment interruption, as well as management of patients who experience specific adverse events, are provided in Section 5.1.5.

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

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: infusion-related reactions and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, *and nephritis*. In addition, systemic immune activation (described below) is a potential risk associated with atezolizumab when given in combination with an immunomodulating agent. Refer to Section 5.1.1 and Appendix 10 of the protocol and to 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 given 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.

Guidelines for management of patients who develop specific adverse events associated with atezolizumab, vemurafenib, or cobimetinib are provided in Section 5.1.5.3 (see Table 3), and guidelines for events associated only with atezolizumab are provided in Appendix 10.

5.1.2 Risks Associated with Cobimetinib

The following adverse events are classified as identified risks associated with cobimetinib: serous retinopathy, left ventricular dysfunction, photosensitivity (when administered with vemurafenib), severe hemorrhage, rhabdomyolysis, and pneumonitis. The following adverse events are classified as potential risks for cobimetinib: severe hepatotoxicity (Grade $\geq$3), impaired female fertility, and teratogenicity and developmental toxicity. In addition, there is the possibility of drug-drug interactions in patients treated with cobimetinib (see Sections 4.4.2–4.4.4 for details). Refer to Section 6 of the Cobimetinib Investigator's Brochure for a detailed description of all anticipated risks for cobimetinib.

5.1.2.1 Serous Retinopathy

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

To address serous retinopathy with cobimetinib treatment, all patients are required to undergo a baseline ophthalmologic examination to evaluate for risk factors for

neurosensory retinal detachment. Patients will also undergo complete ophthalmologic examinations at specified timepoints throughout the study and as clinically indicated if a patient notes any visual disturbances. Details regarding baseline and subsequent ophthalmologic examinations are provided in Section 4.5.6.2.

Guidelines for management of patients who develop serous retinopathy are provided in Section 5.1.5.3 (see Table 3).

5.1.2.2 Left Ventricular Dysfunction

Decrease from baseline in left ventricular ejection fraction has been reported in patients receiving cobimetinib. Decreased left ventricular ejection fraction may be symptomatic or asymptomatic.

All patients will undergo evaluation of left ventricular ejection fraction, either by echocardiography or multigated acquisition scan at baseline, at specified timepoints during treatment, at the end of treatment, and as clinically indicated.

Guidelines for management of patients who have decreases in left ventricular ejection fraction (symptomatic or asymptomatic) are provided in Section 5.1.5.3 (see Table 3).

5.1.2.3 Photosensitivity (When Administered with Vemurafenib)

No evidence of photosensitivity has been observed with cobimetinib as a single agent. However, photosensitivity has been observed when cobimetinib was given in combination with vemurafenib.

Guidelines for management of patients who develop photosensitivity are provided in Section5.1.5.3 (see Table 3).

5.1.2.4 Pneumonitis

Events of pneumonitis have been reported in cobimetinib clinical studies. Most reported events were reported as non-serious and a lower severity (grade).

Guidelines for management of patients who develop pulmonary events (including pneumonitis) are provided in Section 5.1.5.3 (see Table 3).

5.1.2.5 Rhabdomyolysis

Elevations in CPK have been observed in patients who received cobimetinib monotherapy as well as when administered with other agents. The majority of CPK elevations reported were asymptomatic, non-serious, and resolved with or without study drug interruption. One event of rhabdomyolysis was reported in the Phase III study GO28141, and rhabdomyolysis has been reported in postmarketing experience. CPK will be monitored at baseline and monthly during treatment or as clinically indicated.

Guidelines for management of patients who develop CPK elevations or rhabdomyolysis are provided in Section 5.1.5.3 (see Table 3).

5.1.2.6 Hemorrhage

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

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 hemorrhage events are included in Section 5.1.5.3 (see Table 3).

5.1.2.7 Severe Hepatotoxicity (Grade ≥3)

Liver laboratory test abnormalities, including increases in ALT, AST, and alkaline phosphatase, have been reported as adverse events and serious adverse events in patients treated with cobimetinib and vemurafenib. Generally, elevations in liver laboratory tests have been managed effectively with dose modifications.

Guidelines for management of patients who develop elevations in ALT, AST, and/or bilirubin are provided in Section 5.1.5.3 (see Table 3).

5.1.2.8 Impaired Female Fertility

Results from nonclinical studies indicate that there is a potential for effects on female fertility. While no dedicated fertility studies have been conducted with cobimetinib in animals, degenerative changes were observed in reproductive tissues of dogs. These changes were reversible upon discontinuation of cobimetinib.

5.1.2.9 Teratogenicity and Developmental Toxicity

There are no data regarding the use of cobimetinib in pregnant women. When cobimetinib was administered to pregnant rats, cobimetinib caused embryolethality and fetal malformations of the great vessels and skull at similar systemic exposures to those observed in patients administered the 60 mg dose. Therefore, teratogenicity and developmental toxicity is a potential risk for cobimetinib, and cobimetinib use is not recommended during pregnancy.

5.1.3 Risks Associated with Vemurafenib

The following adverse events are classified as identified risks associated with vemurafenib: cutaneous squamous cell carcinoma, new primary melanoma, progression of *RAS*-mutant malignancy, photosensitivity and sunburn, liver injury, QT prolongation, hypersensitivity and severe cutaneous reactions, uveitis, VIIth nerve paralysis, radiation recall and radiation sensitization, and acute kidney injury. The following adverse events are classified as potential risks for vemurafenib: non-cutaneous squamous cell carcinoma, bone marrow toxicity, drug-drug interaction, second primary malignancy,

gastrointestinal polyps, and retinal vein occlusion. In addition, neutropenia, pancreatitis, Dupuytren's contracture, and plantar fascial fibromatosis have been identified as adverse drug reactions in the postmarketing setting. Descriptions of identified risks and selected other risks are provided below. Refer to Section 6 of the Vemurafenib Investigator's Brochure for a detailed description of all identified and potential risks for vemurafenib, including adverse drug reactions in the postmarketing setting.

5.1.3.1 Cutaneous Squamous Cell Carcinoma and New Primary Melanoma

Cases of cutaneous squamous cell carcinoma, which include those classified as keratoacanthomas or mixed keratoacanthoma subtype, have been reported in patients treated with vemurafenib, usually early in the course of treatment. Potential risk factors associated with cutaneous squamous cell carcinoma in three vemurafenib clinical trials included age (≥65 years), prior skin cancer, and chronic sun exposure. Cases of new primary malignant melanoma have also been reported in patients treated with vemurafenib. Cutaneous squamous cell carcinoma and new primary malignant melanoma were managed with excision, and patients were able to continue treatment without dose adjustment.

Evaluations of the skin by a dermatologist, or qualified equivalent medical specialist, will be performed at specified timepoints during the study (see Section 4.5.6.1 for details). All new primary neoplasms, including new primary melanoma, will be reported until 6 months after the last dose of vemurafenib.

Guidelines for management of patients who develop new skin lesions are provided in Section 5.1.5.3 (see Table 3).

5.1.3.2 Non-Cutaneous Squamous Cell Carcinoma

Cases of squamous cell carcinoma of the head and neck have been reported in patients treated with vemurafenib.

To monitor for the occurrence of squamous cell carcinoma, patients will undergo a head and neck examination, computed tomography or magnetic resonance imaging scans of the chest, and visual inspection and digital examination of the anus and anal canal at specified timepoints during the study (see Section 4.5.6.1 for details). To monitor for cervical carcinoma, all female patients will undergo a pelvic examination, including visual inspection of the uterine cervix and Papanicolaou smear, at specified timepoints during the study. All new primary neoplasms will be reported until 6 months after the last dose of vemurafenib.

5.1.3.3 *RAS*-Mutant Malignancies

On the basis of its mechanism of action, vemurafenib may cause progression of cancers associated with *RAS* mutations. In addition, progression of pre-existing RAS-mutant malignancies (chronic myelomonocytic leukemia, pancreatic cancer) have been reported in patients treated with vemurafenib. Vemurafenib should be used with caution in patients with a prior or concurrent cancer associated with *RAS* mutation.

5.1.3.4 Photosensitivity and Sunburn

Mild to severe skin photosensitivity has been reported in patients treated with vemurafenib. All patients should be advised to minimize sun exposure, wear protective clothing, and use a broad-spectrum ultraviolet A/ultraviolet B sunscreen and lip balm (SPF≥30), reapplied every 2 to 3 hours, when outdoors during vemurafenib treatment and for at least 5–10 days after discontinuing vemurafenib.

Guidelines for management of patients who develop photosensitivity are provided in Section 5.1.5.3 (see Table 3).

5.1.3.5 Liver Injury

Liver injury, including cases of severe liver injury, have been reported in patients treated with vemurafenib. Alkaline phosphatase, ALT, AST, and bilirubin will be monitored at specified timepoints throughout the study.

Guidelines for management of patients who develop elevations in ALT, AST, and/or bilirubin are provided in Section 5.1.5.3 (see Table 3).

5.1.3.6 QT Prolongation

Exposure-dependent QT prolongation was observed in an uncontrolled, open-label Phase II QT substudy in patients with metastatic melanoma. QT prolongation may lead to an increased risk of ventricular arrhythmias, including torsades de pointes.

Patients with a history of congenital long QT syndrome, QTc interval corrected using Fridericia's method ≥ 480 ms, or uncorrectable abnormalities in serum electrolytes will be excluded from study inclusion. ECG and electrolytes, including potassium, magnesium, and calcium, will be monitored throughout the study. In addition, investigators should closely monitor patients who are on medications or supplements that may affect the QT interval. Alternative treatment options for medications known to affect QT interval should be discussed with each patient prior to their randomization in this study.

Guidelines for management of patients who develop QT prolongation are provided in Section 5.1.5.3 (see Table 3).

5.1.3.7 Hypersensitivity and Severe Cutaneous Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with vemurafenib and upon re-initiation of treatment. Severe hypersensitivity reactions included generalized rash and erythema or hypotension. Drug reaction with eosinophilia and systemic symptoms has been reported in association with vemurafenib in the postmarketing setting. Severe dermatologic reactions have been reported in patients receiving vemurafenib, including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis.

Guidelines for management of patients who develop hypersensitivity reactions and dermatologic events are provided in Section 5.1.5.3 (see Table 3).

5.1.3.8 Uveitis and Retinal Vein Occlusion

Serious ophthalmologic reactions, including uveitis, have been reported in patients treated with vemurafenib. RVO has been observed and is a potential risk.

Patients will under ophthalmologic examinations at specified timepoints during the study (see Section 4.5.6.2). Patients will be evaluated at screening for risk factors for neurosensory retinal detachment, retinal vein occlusion, or neovascular macular degeneration. Risk factors for RVO include history of serous retinopathy or history of RVO, or evidence of ongoing serous retinopathy or RVO at baseline. Patients with such conditions will be excluded from the study as detailed in Section 4.1.2.

Guidelines for management of patients who develop uveitis or retinal vein occlusion are provided in Section 5.1.5.3 (see Table 3).

5.1.3.9 VIIth Nerve Paralysis

Cases of VIIth nerve paralysis have been observed in patients treated with vemurafenib. In clinical trials, these events resolved without sequelae.

5.1.3.10 Radiation Recall and Radiation Sensitization

An adverse drug reaction of potentiation of radiation treatment toxicity has been identified in patients treated with radiation prior to, during, or subsequent to vemurafenib treatment. The nature and severity were evaluated as worse than expected for the normal tissue tolerance to therapeutic radiation. The reaction was seen in the skin, esophagus, lung, liver, rectum, and urinary bladder. Most cases were cutaneous in nature, but some cases involving visceral organs had fatal outcomes. Vemurafenib should be used with caution when given concomitantly or sequentially with radiation treatment.

Radiotherapy is not permitted during the study.

5.1.3.11 Acute Kidney Injury and Renal Function Alterations

Acute kidney injury, including interstitial nephritis, has been observed in patients treated with vemurafenib. The majority of these cases have been characterized by mild to moderate increases in serum creatinine (some observed in the setting of dehydration events), with recovery after dose modification.

Serum creatinine will be monitored throughout the study. Vemurafenib acute kidney injury dose modification guidelines should be utilized when applicable and it is recommended to routinely monitor serum creatinine levels in all patients undergoing vemurafenib therapy.

5.1.3.12 Drug-Drug Interaction

Drug-drug interactions are a potential risk for vemurafenib. Prohibited therapies and food and cautionary therapies are described in Sections 4.4.2–4.4.4.

5.1.3.13 Gastrointestinal Polyps

Rare cases of colonic polyps have been reported in patients treated with vemurafenib for 2 or more years while enrolled in a clinical study (Chapman et al. 2012).

5.1.3.14 Neutropenia

Neutropenia has been identified as an uncommon adverse drug reaction associated with the use of vemurafenib, typically occurring during the first 6–12 weeks of treatment. It appears to be reversible usually within 2 weeks, with temporary interruption, dose reduction, or discontinuation of vemurafenib, and in some cases has been managed with granulocyte colony-stimulating factor.

5.1.3.15 Pancreatitis

Pancreatitis has been identified as an uncommon adverse drug reaction in patients being treated with vemurafenib. The clinical presentation in terms of severity, mild to moderate, was consistent with the clinical picture of drug-induced pancreatitis (Lankisch et al.1995).

The Sponsor recommends that serum amylase and lipase testing be conducted as part of the workup of any suspected case of pancreatitis in addition to other appropriate testing (e.g., abdomen computed tomography scan).

Guidelines for management of patients who develop pancreatitis are provided in Section 5.1.5.3 (see Table 3).

5.1.3.16 Dupuytren's Contracture and Plantar Fascial Fibromatosis

Dupuytren's contracture and plantar fascial fibromatosis have been reported with vemurafenib. The majority of cases were Grade 1 or 2, but severe, disabling cases of Dupuytren's contracture have also been reported.

5.1.4 [redacted]

[redacted]

5.1.4.1 [redacted]

[redacted]

5.1.4.2 [redacted]

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5.1.4.3

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5.1.4.6

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5.1.4.8 [redacted]

[redacted]

[redacted]

5.1.5 Management of Patients Who Experience Specific Adverse Events

5.1.5.1 Dose Modifications during the Run-In Period

Vemurafenib is blinded in this study. Following Days 1–21 of the run-in period, patients in Arm B will receive vemurafenib at a reduced dose (720 mg BID) compared with Arm A (960 mg BID). Thus, dose reductions will be managed via the IWRS system, and dose modifications will differ depending on the arm to which the patient is randomized. See Table 3 for additional details.

During the run-in period (Days 1–28), one dose-level reduction of cobimetinib and vemurafenib is permitted for management of drug-related toxicities. No further dose reductions are permitted in the run-in period. If toxicities do not improve within 28 days following the one level-dose reduction and or treatment interruption for either cobimetinib and or vemurafenib, study treatment should be discontinued, unless resumption of treatment is approved by the Medical Monitor. The run-in period may be extended to a total of 56 days to allow patients to recover from drug-related toxicities prior to proceeding to Cycle 1. Following a dose reduction in the run-in period, no escalation is permitted.

- During the run-in period, the dose of cobimetinib can be reduced by 20 mg QD (one dose level) from 60 mg daily to 40 mg daily during Days 1–21.

- If a vemurafenib dose reduction is required during Days 1–21, the dose of vemurafenib can be reduced from 960 mg BID to 720 mg BID. Patients who are taking 4 tablets from the large bottle during this period should reduce to 3 tablets from the large bottle. From Days 22–28, patients should take vemurafenib 720 mg/matching placebo (two tablets from the large bottle and one from the small bottle) BID.
- If an initial vemurafenib dose reduction to the 720 mg/matching placebo dose is required during Days 22–28, dose reduction will entail a change from dosing with three tablets from the large bottle and one from the small bottle BID to dosing with two tablets from the large bottle and one tablet from the small bottle BID. Drug-related toxicities presenting during Days 22–28 that require a vemurafenib dose reduction should be improving or have resolved (as outlined in Section 5.1.5.3 see Table 3) prior to Cycle 1 Day 1.

Patients must be receiving both study treatments in order to enter the triplet treatment period (Cycle 1 Day 1).

5.1.5.2 Dose Modifications during the Triplet Treatment Period

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

The dose of cobimetinib can be reduced by 20 mg QD (one dose level) decrements up to two times for management of drug-related toxicities (i.e., from 60 to 40 mg and then from 40 to 20 mg), except during run-in period when only one dose reduction is allowed. If further dose reduction is indicated after two dose reductions, the patient must discontinue cobimetinib but may continue treatment with atezolizumab and/or vemurafenib at the investigator's discretion. The dose of cobimetinib may be escalated by a maximum of one dose level (20 mg) from 20 mg QD to 40 mg QD at the investigator's discretion in patients who have previously undergone dose reduction, provided there are no safety concerns. Dose escalation from 40 mg QD to 60 mg QD is not permitted.

The dose of vemurafenib can be reduced by 240 mg/matching placebo BID (one dose level) decrements up to two times for management of drug-related toxicities (i.e., from 960 mg/matching placebo BID to 720 mg/matching placebo BID and then from 720 mg/matching placebo BID to 480 mg/matching placebo BID), except during the run-in period, when only one dose reduction is allowed. If further dose reduction is indicated after two dose reductions, the patient must discontinue vemurafenib but may continue treatment with atezolizumab and/or cobimetinib at the investigator's discretion. The dose of vemurafenib may be escalated by a maximum of one dose level (240 mg/matching placebo dose BID) from 480 mg/matching placebo dose BID to 720 mg/matching placebo BID at the investigator's discretion in patients who have previously undergone dose reduction, provided there are no safety concerns. Dose escalation from 720 mg/matching placebo BID to 960 mg/matching placebo BID is not permitted.

5.1.5.3 Treatment Interruption or Discontinuation

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

Cobimetinib and vemurafenib treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If either drug has been withheld for >28 days because of toxicity, the patient should be discontinued from that drug, unless resumption of treatment is approved following investigator discussion with the Medical Monitor. The Medical Monitor should be consulted for any major surgery (e.g., involving a body cavity), and cobimetinib and vemurafenib should generally be withheld for 2 days prior to the procedure and for 2 weeks afterwards. For interruptions required in the run-in period, refer to Section 5.1.5.1.

5.1.5.4 Management Guidelines

In general, toxicities should be managed with supportive care, dose modifications (if applicable), and treatment interruptions applied to the component of the study treatment judged to be the primary cause. Additional tests or procedures, such as autoimmune serology or biopsies to obtain tissue samples, may be performed to determine a possible immunogenic etiology. Patients should be monitored closely upon initiation of the third treatment component on Days 1 and 15 of Cycle 1 and Cycle 2, as well as the days immediately following these visits. Regular telephone contact and, if needed, unscheduled laboratory tests are strongly recommended.

Guidelines for management of patients who experience cobimetinib, vemurafenib, and atezolizumab specific adverse events are provided in Table 3. The table also includes general guidelines for dose modifications and treatment delays and discontinuation. The guidelines in Table 3 are not intended to replace clinical judgment or dictate care of individual patients.

Guidelines for management of cobimetinib and vemurafenib toxicities in Table 3 will not apply to reversible laboratory abnormalities with no clinical sequelae or no clinical significance as determined by the investigator in consultation with the Medical Monitor.

Risks associated with atezolizumab and guidelines for the management of adverse events associated with atezolizumab are provided in Section 5.1.1 and Appendix 10.

Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
General guidance for dose modifications and treatment delays and discontinuation	• The dose of cobimetinib and vemurafenib can be reduced by one dose level in the run-in period (see Section 5.1.5.1). • There will be no dose modifications for atezolizumab. • During the triplet combination period, Cycle 1 and beyond, 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 and/or vemurafenib at the investigator's discretion. • During the triplet combination period, in order to preserve the blind, two reductions in tablet number will be allowed in both Arm A and Arm B. The first dose reduction will be from 3 tablets in the large bottle plus 1 tablet in the small bottle BID to 2 tablets in the large bottle plus 1 tablet in the small bottle BID; this will represent a true dose reduction in Arm A (from 960 mg BID to 720 mg BID) and in Arm B (from 720 mg BID to 480 mg BID). If a second dose reduction is required, patients in both arms will reduce from 2 tablets in the large bottle plus 1 tablet in the small bottle BID to 2 tablets in the large bottle BID. This will represent a true dose reduction in Arm A (from 720 mg BID to 480 mg BID) whereas in Arm B, because the small bottle contains placebo tablets, it will represent a "false" dose reduction (with dosing maintained at 480 mg BID). If further dose reduction is indicated after two dose reductions, the patient must discontinue vemurafenib but may continue treatment with atezolizumab and/or cobimetinib at the investigator's discretion. • If atezolizumab is withheld and corticosteroids are initiated for treatment of a toxicity, corticosteroids must be tapered over ≥1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for >12 $weeks$, the patient should be discontinued from atezolizumab. Study treatment may be withheld for >12 $weeks$ to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >12 $weeks$ if the investigator and the Medical Monitor agree that the patient is likely to derive clinical benefit. • If either cobimetinib or vemurafenib is withheld for >28 days because of toxicity, the patient should be discontinued from that drug, unless resumption of treatment is approved by the Medical Monitor after discussion with the investigator. • After dose reduction, consideration may be given to allow for dose escalation of cobimetinib or vemurafenib by a maximum of one dose level following resolution of the adverse event that resulted in dose modification, provided there are no safety concerns (see Section 5.1.5.2). Escalation is not permitted during the run-in period (see Section 5.1.5.1).

BID = twice daily.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
IRRs, anaphylaxis, and hypersensitivity reaction	• Guidelines for management of IRRs are provided in Appendix 10. • For anaphylaxis precautions, see Appendix 6. • For severe hypersensitivity reactions, permanently discontinue all study treatment.
Gastrointestinal toxicity	
Gastrointestinal events: general guidance	• 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 CRP, 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.
Abdominal pain in combination with blood or mucus in stool **and/or** Grade ≥ 3 diarrhea with possible colitis (e.g., peritoneal signs, ileus, or fever)	• Withhold all study treatment. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS). • Initiate maximum supportive care and monitor patient closely. • Investigate etiology, ruling out bowel perforation. Refer patient to GI specialist. • If immune-related colitis is suspected, 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. Consider TNF antagonists for refractory diarrhea. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. [a,b,c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib and vemurafenib with doses reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib. • When study treatment is resumed, administer supportive care and/or prophylactic treatment.

CRP = C-reactive protein; GI = gastrointestinal; IV = intravenous; NSAID = non-steroidal anti-inflammatory drug; TNF = tumor necrosis factor.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea, Grade 1 or 2	• Continue all study treatment. • Initiate maximum supportive care and monitor patient closely. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis if appropriate.
Diarrhea, Grade 3	• Withhold all study treatment. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. • Initiate maximum supportive care and monitor patient closely. • 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 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. [a,b,c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib and vemurafenib with doses reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.
Diarrhea, Grade 4	• Permanently discontinue all study treatment and contact Medical Monitor. [c] • Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. • Initiate maximum supportive care and monitor patient closely. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if 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.

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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
New skin lesion	
Cutaneous primary malignancy or skin lesion suggestive of cutaneous primary malignancy	• Continue all study treatment. • Treat per institutional guidelines.
Dermatologic toxicity	
General guidance	• A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.
Photosensitivity, Grade 1	• Continue all study treatment. • Initiate supportive care.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Dermatologic toxicity (cont.)	
Photosensitivity, Grade 2	• Continue atezolizumab. • Initiate supportive care per institutional guidelines. **First episode:** • If event does not resolve to Grade 1 or better within 7 days, withhold cobimetinib and vemurafenib. • If treatment is withheld and event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. • If event does not resolve to Grade 1 or better within 28 days, permanently discontinue cobimetinib and vemurafenib. **Subsequent episodes:** • Withhold cobimetinib and vemurafenib. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. • If event does not resolve to Grade 1 or better within 28 days, permanently discontinue cobimetinib and vemurafenib.
Photosensitivity, Grade 3	• Withhold cobimetinib and vemurafenib. Continue atezolizumab. • Initiate supportive care per institutional guidelines. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.
Photosensitivity, Grade 4	• Initiate supportive care per institutional guidelines. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib. • Continue atezolizumab if clinically indicated.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Dermatologic toxicity (cont.)	
Dermatologic event, Grade 1	• Continue all study treatment. • Initiate maximum supportive care (e.g., antihistamines, topical corticosteroids).
Dermatologic event, Grade 2	• Continue all study treatment. • Consider patient referral to dermatologist. • Initiate maximum supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve, consider treatment with higher-potency topical corticosteroids.
Dermatologic event, Grade 3	• Refer patient to dermatologist. A biopsy should be performed if appropriate, and, if possible, photographs of the rash should be obtained and submitted to the Sponsor. **Acneiform rash:** • Withhold atezolizumab and cobimetinib. Continue vemurafenib. • Refer patient to dermatologist. • If event does not improve within 48–72 hours, consider treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event still does not improve. • If event resolves to Grade 2 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. [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. • When study treatment is resumed, consider treatment with topical corticosteroids and oral antibiotics. **Non-acneiform (e.g., maculo-papular) rash:** • Withhold vemurafenib. Continue atezolizumab and cobimetinib. • If event resolves to Grade 2 or better within 28 days, resume vemurafenib with dose reduced by one level. If not, permanently discontinue vemurafenib.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Dermatologic toxicity (cont.)	
Dermatologic event, Grade 4	• Permanently discontinue all study treatment and contact Medical Monitor. [c]
Elevations in ALT, AST, and/or bilirubin during run-in period	
Elevation in ALT, AST, and/or bilirubin, Grade 1 or 2 (run-in period)	• Continue cobimetinib and vemurafenib.
Elevation in ALT, AST, and/or bilirubin, Grade 3 (run-in period)	• Withhold vemurafenib. Continue cobimetinib. • If event resolves to Grade 1 or better within 28 days, resume vemurafenib with dose reduced by one level. If not, discontinue patient from study.
Elevation in ALT, AST, and/or bilirubin, Grade 4 (run-in period)	**First episode:** • Withhold cobimetinib and vemurafenib. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib and vemurafenib with doses reduced by one level. If not, discontinue patient from study. **Subsequent episodes:** • Discontinue patient from study.
Elevations in ALT, AST, and/or bilirubin during triple combination period	
ALT, AST, and bilirubin $\leq 3 \times$ ULN (triple combination period)	• Continue all study treatment. • Monitor ALT, AST, and bilirubin at least weekly.

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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin during triple combination period (cont.)	
ALT or AST > 3 × upper limit of normal (ULN) to 5 × ULN in combination with bilirubin ≤ 3 × ULN (triple combination period)	• Consider withholding all study treatment. • Monitor ALT, AST, and bilirubin at least weekly. If values worsen, monitor at least every other day. • If values have not worsened and have not resolved to ≤ 3 × ULN upon re-evaluation 1–20 days after event onset, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If values have not worsened and have not resolved to ≤ 3 × ULN upon re-evaluation ≥ 21 days after event onset, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If values have worsened upon re-evaluation, 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 values do not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If treatment is withheld and values resolve to ≤ 3 × ULN before or within 12 weeks after initiation of corticosteroids, resume atezolizumab at fixed dose. [a,b] • If values do not resolve to ≤ 3 × ULN within 12 weeks after initiation of corticosteroids, permanently discontinue atezolizumab. [a,b,c] • If treatment is withheld and values resolve to ≤ 3 × ULN before or within 28 days after initiation of corticosteroids, resume cobimetinib and vemurafenib as follows: – If values did not worsen prior to resolution, resume cobimetinib and vemurafenib at current doses. – If values worsened prior to resolution: First Episode: Resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. Second Episode: Resume cobimetinib and vemurafenib with doses reduced by one level. Third Episode: Resume cobimetinib with dose reduced by one level and permanently discontinue vemurafenib. Fourth Episode: Permanently discontinue cobimetinib. • If values do not resolve to ≤ 3 × ULN within 28 days after initiation of corticosteroids, permanently discontinue cobimetinib and vemurafenib.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin during triple combination period (cont.)	
ALT or AST > 5 × ULN to 10 × ULN in combination with bilirubin ≤ 1.5 × ULN (triple combination period)	• Withhold all study treatment. • Monitor ALT, AST, and bilirubin at least every other day. • If values do not improve within 48 hours, 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 values do not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If values improve within 48 hours but subsequently worsen or do not resolve to ≤ 3 × ULN within 14 days after event onset, 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 values do not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If values resolve to ≤ 3 × ULN before or within 12 weeks after initiation of corticosteroids, resume atezolizumab at fixed dose. [a,b] • If values do not resolve to ≤ 3 × ULN within 12 weeks after initiation of corticosteroids, permanently discontinue atezolizumab. [a,b,c] • If values resolve to ≤ 3 × ULN before or within 28 days after initiation of corticosteroids, resume cobimetinib and vemurafenib as follows: First Episode: Resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. Second Episode: Resume cobimetinib and vemurafenib with doses reduced by one level. Third Episode: Resume cobimetinib with dose reduced by one level and permanently discontinue vemurafenib. Fourth Episode: Permanently discontinue cobimetinib. • If values do not resolve to ≤ 3 × ULN within 28 days after initiation of corticosteroids, permanently discontinue cobimetinib and vemurafenib.

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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin during triple combination period (cont.)	
ALT or AST > 5 × ULN to 10 × ULN in combination with bilirubin > 1.5 × ULN to 3 × ULN **or** ALT or AST ≤ 10 × ULN in combination with bilirubin > 3 × ULN (triple combination period)	• Withhold all study treatment. • 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 values do not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • Monitor ALT, AST, and bilirubin at least every other day. • If values resolve to ≤ 3 × ULN within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. [a,b,c] • If values resolve to ≤ 3 × ULN within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.
ALT > 10 × ULN with or without elevation of AST or bilirubin **or** Confirmed cases of Hy's law with no identifiable cause other than study treatment (triple combination period)	• Permanently discontinue all study treatment and contact Medical Monitor. [c] • 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 values do not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.

IV = intravenous; 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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Pulmonary events	
Pulmonary event, Grade 1	• Continue all study treatment and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 2	• Withhold atezolizumab. Consider withholding cobimetinib and vemurafenib. • 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 within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a,b,c] • If cobimetinib and vemurafenib are withheld and event resolves to Grade 1 or better within 28 days, resume cobimetinib and vemurafenib at current doses. • If event does not resolve to Grade 1 or better within 28 days, permanently discontinue cobimetinib and vemurafenib. • 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] Withhold cobimetinib and vemurafenib. • 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. • If event resolves to Grade 1 or better within 28 days, cobimetinib and vemurafenib may be resumed with doses reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.

BAL = bronchoscopic alveolar lavage.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Endocrine disorders	
Asymptomatic hypothyroidism	• Continue all study treatment. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. Continue cobimetinib and vemurafenib. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • When symptoms are controlled and thyroid function is improving, resume atezolizumab.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue all study treatment. • Monitor TSH every 4 weeks. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. Continue cobimetinib and vemurafenib. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • When symptoms are controlled and thyroid function is improving, resume atezolizumab. • For life-threatening immune-related hyperthyroidism, permanently discontinue atezolizumab, withhold cobimetinib and vemurafenib, and contact Medical Monitor.[c] If event becomes clinically manageable within 28 days, resume cobimetinib and vemurafenib with doses reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.

TSH = thyroid-stimulating hormone.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Endocrine disorders (cont.)	
Adrenal insufficiency, Grade 2, 3, or 4	• Withhold atezolizumab. Continue cobimetinib and vemurafenib. • 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 within 12 weeks, resume atezolizumab at current dose. • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy within 12 weeks, permanently discontinue atezolizumab and contact Medical Monitor. [a,b,c]
Hyperglycemia, Grade 1 or 2	• Continue all study treatment. • Initiate treatment with insulin if needed. Consider cobimetinib dose modification per general guidelines as clinically indicated. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. Continue cobimetinib and vemurafenib. • Initiate treatment with insulin. • Monitor for glucose control. • When symptoms resolve and glucose levels are stable, resume atezolizumab.

IV = intravenous.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Pancreatic events	
Amylase and/or lipase elevation, Grade 1	• Continue all study treatment. • Monitor amylase and lipase prior to dosing.
Amylase and/or lipase elevation, Grade 2	• Continue all study treatment. • 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 and vemurafenib. Continue cobimetinib. • 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 within 12 weeks, resume atezolizumab. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a,b,c] • If event resolves to Grade 1 or better within 28 days, resume vemurafenib with dose reduced by one level. If not, permanently discontinue vemurafenib. • For recurrent events, permanently discontinue all study treatment and contact Medical Monitor. [c]

GI = gastrointestinal; IRR = infusion-related reaction; IV = intravenous.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Pancreatic events (cont.)	
Pancreatitis, Grade 2 or 3	• Withhold all study treatment. • 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 within 12 weeks, resume atezolizumab. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a,b,c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib. • For recurrent events, permanently discontinue all study treatment and contact Medical Monitor. [c]
Pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. Consider permanently discontinuing cobimetinib and vemurafenib. • 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. • If cobimetinib and vemurafenib are withheld and event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. If event does not resolve to Grade 1 or better within 28 days, permanently discontinue cobimetinib and vemurafenib.

GI = gastrointestinal; IRR = infusion-related reaction; IV = intravenous.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Neurologic disorders	
Neuropathy, Grade 1	• Continue all study treatment. • Investigate etiology.
Neuropathy, Grade 2	• Withhold atezolizumab. Continue cobimetinib and vemurafenib. • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a,b,c]
Neuropathy, Grade 3	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] Continue cobimetinib and vemurafenib. • Initiate treatment as per institutional guidelines.
Neuropathy, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] Withhold cobimetinib and vemurafenib. • Initiate treatment as per institutional guidelines. • If patient stabilizes within 28 days, consider resuming cobimetinib at current dose and vemurafenib with dose reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.
Myasthenia gravis or Guillain-Barre syndrome, Grades 1, 2, or 3	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] Continue cobimetinib and vemurafenib. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with 1–2 mg/kg/day oral or IV prednisone or equivalent.

IV = intravenous.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Neurological disorders (cont.)	
Myasthenia gravis or Guillain-Barré syndrome, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] Withhold cobimetinib and vemurafenib. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with 1–2 mg/kg/day oral or IV prednisone or equivalent. • If patient stabilizes within 28 days, resume cobimetinib and vemurafenib at current doses. If not, permanently discontinue cobimetinib and vemurafenib.
Immune-related meningoencephalitis, any grade	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] Withhold cobimetinib and vemurafenib. • 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. • If patient stabilizes within 28 days, resume cobimetinib and vemurafenib at current doses. If not, permanently discontinue cobimetinib and vemurafenib.
Ocular toxicity	
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 1	• Continue all study treatment. • 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.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Ocular toxicity (cont.)	
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 2	• Withhold atezolizumab and vemurafenib. Continue cobimetinib. • 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 within 12 weeks, resume atezolizumab. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a,b,c] • If event resolves to Grade 1 or better within 28 days, resume vemurafenib with dose reduced by one level. If not, permanently discontinue vemurafenib.
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] Withhold cobimetinib and vemurafenib. • 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. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Ocular toxicity (cont.)	
Other ocular toxicity (i.e., not immune related)	• Withhold cobimetinib and vemurafenib. Continue atezolizumab. • Refer patient to ophthalmologist. **Retinal vein occlusion:** • Permanently discontinue cobimetinib and vemurafenib. **Serous retinopathy, Grade 1:** • Resume cobimetinib and vemurafenib at current doses. • Continue ophthalmology follow-up. **Serous retinopathy, Grade 2 or 3:** • Resume vemurafenib at current dose. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. **Serous retinopathy, Grade 4:** • Permanently discontinue cobimetinib. Withhold vemurafenib. • If event resolves to Grade 1 or better within 28 days, reduce vemurafenib with dose reduced by one level. If not, permanently discontinue vemurafenib. **All other ocular events, Grade 1:** • Resume cobimetinib and vemurafenib at current doses. **All other ocular events, Grade 2, 3, or 4:** • If event resolves to Grade 1 or better within 28 days, resume cobimetinib and vemurafenib at current doses. If not, permanently discontinue cobimetinib and vemurafenib.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
QT interval prolongation	
QTcF ≤500 ms with change from baseline in QTcF of <60 ms	• Continue all study treatment.
QTcF >500 ms with change from baseline in QTcF of <60 ms **or** QTcF ≤500 ms with change from baseline in QTcF of ≥60 ms	• Withhold vemurafenib. Continue atezolizumab and cobimetinib. • Rule out other risk factors for arrhythmia (e.g., myocardial ischemia). Check for electrolyte disturbances (e.g., potassium, magnesium, and calcium). • Evaluate concomitant medications to determine if there is co-administration of drugs that prolong QT interval. • Refer patient to cardiologist. • Monitor ECG weekly. • If QTcF improves to ≤500 ms or baseline within 28 days, resume vemurafenib with dose reduced by one level. Repeat ECG at 2 and 4 weeks after resuming vemurafenib, on Day 15 of each subsequent cycle for three cycles, and then every 3 months thereafter. • If QTcF does not improve to ≤500 ms or baseline within 28 days, permanently discontinue vemurafenib.
QTcF >500 ms with change from baseline in QTcF of ≥60 ms	• Permanently discontinue vemurafenib. Continue atezolizumab and cobimetinib. • Rule out other risk factors for arrhythmia (e.g., myocardial ischemia). Check for electrolyte disturbances (e.g., potassium, magnesium, and calcium). • Evaluate concomitant medications to determine if there is co-administration of drugs that prolong QT interval. • Refer patient to cardiologist. • Monitor ECG weekly until QTcF improves to ≤500 ms or baseline.

QTcF = QT interval corrected using Fridericia's formula.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Asymptomatic LVEF decrease from baseline	
LVEF ≥ 50% **or** LVEF 40%–49% with < 10% absolute decrease from baseline	• Continue all study treatment.
LVEF < 40% **or** LVEF 40%–49% with ≥ 10% absolute decrease from baseline	• Withhold cobimetinib for at least 2 weeks. Continue atezolizumab and vemurafenib. • Re-evaluate LVEF at 14 days. If patient has a < 10% absolute decrease from baseline in LVEF, for the first occurrence resume cobimetinib with dose reduced by one level to 40 mg; for the second occurrence, resume cobimetinib at 20 mg; and for the third occurrence, permanently discontinue cobimetinib. [d] For all patients restarting treatment, re-evaluate LVEF at 2, 4, 10, and 16 weeks and then every 12 weeks (3 cycles as per protocol) or as clinically indicated until treatment discontinuation. If patient has an LVEF of < 40% or a ≥ 10% absolute decrease from baseline, permanently discontinue cobimetinib. For patients who permanently discontinue cobimetinib: • LVEF assessments should continue post-treatment every 6 weeks or as clinically indicated until the LVEF recovers to LLN or 50%.

LLN = lower limit of normal; LVEF = left ventricular ejection fraction.

[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 12 weeks 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.

[d] Patients on a cobimetinib dose less than 60 mg will reduce by one dose level reduction (a 20-mg daily reduction), from a 40-mg daily dose to a 20-mg daily dose, and patients on a 20-mg daily dose at the time of the interruption (for LVEF decline) should discontinue cobimetinib.

Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Symptomatic LVEF decrease from baseline	
	• Withhold cobimetinib for at least 4 weeks. Continue atezolizumab and vemurafenib. • Patient referral to cardiologist is strongly recommended. • Re-evaluate LVEF at 28 days. If the patient is **asymptomatic** following the treatment break: • If patient has a < 10% absolute decrease from baseline in LVEF, for the first occurrence resume cobimetinib with dose reduced by one level to 40 mg; for the second occurrence, resume cobimetinib at 20 mg; and for the third occurrence, permanently discontinue cobimetinib. [d] For all patients restarting treatment, re-evaluate LVEF at 2, 4, 10, and 16 weeks and then every 12 weeks (3 cycles as per protocol) or as clinically indicated until treatment discontinuation. • If patient has an LVEF of < 40% or a ≥ 10% absolute decrease from baseline, permanently discontinue cobimetinib. If the patient remains **symptomatic** following the treatment break: • Permanently discontinue cobimetinib. For patients (asymptomatic and symptomatic) who permanently discontinue cobimetinib: • LVEF assessments should continue post-treatment every 6 weeks or as clinically indicated until the LVEF recovers to LLN or 50% and or symptoms resolve.

LLN = lower limit of normal; LVEF = left ventricular ejection fraction.

[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 12 weeks 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.

[d] Patients on a cobimetinib dose less than 60 mg will reduce by one dose level reduction (a 20-mg daily reduction), from a 40-mg daily dose to a 20-mg daily dose, and patients on a 20-mg daily dose at the time of the interruption (for LVEF decline) should discontinue cobimetinib.

Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Rhabdomyolysis or CPK elevation	
General guidance	• Consider withholding cobimetinib while investigating etiology. Continue atezolizumab and vemurafenib. • Assess patient for any history of strenuous physical activity, blunt trauma, or recent intramuscular injections. • Evaluate for cardiac injury and rhabdomyolysis. If evidence of clinically significant cardiac injury or rhabdomyolysis, consider permanent discontinuation of cobimetinib.
Asymptomatic CPK elevation, Grade 1, 2, or 3	• Continue all study treatment.
Rhabdomyolysis or symptomatic CPK elevation, Grade 1, 2, or 3	• Withhold cobimetinib. Continue atezolizumab and vemurafenib. • If event improves by at least one grade within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.
Rhabdomyolysis or CPK elevation (symptomatic or asymptomatic), Grade 4	• Withhold cobimetinib. Continue atezolizumab and vemurafenib. • If event improves to Grade ≤3 within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.
Grade 3 or 4 or intolerable Grade 2 treatment-related toxicities not described above	• Withhold all study treatment. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. [a,b,c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib and vemurafenib with doses reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.

CPK = creatine phosphokinase.

[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 12 weeks 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 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Hemorrhage	
Grade 3 events	• Interrupt cobimetinib treatment. There is no data on the effectiveness of cobimetinib dose modifications for hemorrhage events. • Clinical judgment should be applied when considering restarting cobimetinib treatment. • Vemurafenib dosing can be continued when cobimetinib treatment is interrupted, if clinically indicated. • Continue atezolizumab treatment.
Grade 4 events or cerebral hemorrhage (all grades)	• Interrupt cobimetinib treatment. • Permanently discontinue cobimetinib for hemorrhage events attributed to cobimetinib. • Interrupt vemurafenib and restart if event improves within 28 days. • Continue atezolizumab unless clinically indicated.

[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 12 weeks 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 [redacted], 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 NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

5.2.3 [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]morrhage
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
  - [redacted]
  - [redacted]
- [redacted]

[redacted]

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 treatment**, 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 treatment, adverse events will be reported as follows:

- All adverse events will be reported until 30 days after the last dose of study treatment or until initiation of subsequent anti-cancer therapy, whichever occurs first
- Serious adverse events and [redacted] will continue to be reported until 90 days after the last dose of study treatment or until initiation of subsequent anti-cancer therapy, whichever occurs first.
- All new primary neoplasms (benign or malignant), including new primary melanoma, will be reported until 6 months after the last dose of vemurafenib. Any new primary malignant neoplasm other than cutaneous squamous cell carcinoma should be reported as a serious adverse event.

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 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 5):

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

Table 5 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

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

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

based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

A recurrent adverse event is one that resolves between patient evaluation 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 $\times$ 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 [redacted] (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). The iDMC will monitor the frequency of deaths from all causes.

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

be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Melanoma

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer

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

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

5.3.5.12 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).

No safety data related to overdosing of atezolizumab, cobimetinib, or vemurafenib are available.

5.3.5.13 Patient-Reported Outcome Data

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (see Section 5.4.2 for further details)
- [redacted]
- 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

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

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, 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 and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information and List of Investigators").

5.4.2 Reporting Requirements for Serious Adverse Events and [redacted]

5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/[redacted] 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 Treatment Initiation

After initiation of study treatment, serious adverse events and [redacted] will be reported until 90 days after the last dose of study treatment (or until initiation of subsequent anti-cancer therapy, whichever occurs first). New primary neoplasms other than cutaneous squamous cell carcinoma (which qualify as serious adverse events) will continue to be reported until 6 months after the last dose of vemurafenib. 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/[redacted] 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 6 months after the last dose of study treatment. 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 treatment 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 6 months after the last dose of study treatment. 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 treatment. 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 investigator 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 treatment or the female partner of a male patient exposed to study treatment 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 treatment 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, [redacted], 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 for deaths (defined as 90 days after the last dose of study treatment), 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 exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/[redacted] Reporting Form using the fax number or email address provided to investigators.

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

The Sponsor will promptly evaluate all serious adverse events and [redacted] 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:

- Atezolizumab Investigator's Brochure
- Cobimetinib Investigator's Brochure
- Vemurafenib 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.

An iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

6.1.1 Progression-Free Survival

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

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

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

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

6.1.2 Overall Survival

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

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

6.2 SUMMARIES OF CONDUCT OF STUDY

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

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables, stratification factors, and other baseline and disease characteristics will be summarized.

6.4 EFFICACY ANALYSES

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

6.4.1 Primary Efficacy Endpoint

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

The statistical hypothesis of this study is as follows:

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

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

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

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

6.4.2 Secondary Efficacy Endpoints

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

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

Objective response will be presented as objective response rate (ORR), defined as the total number of patients whose objective response is CR or PR, divided by the number of patients in the ITT population. Objective response is defined as a CR or CR on two consecutive occasions ≥4 weeks apart, as determined by the investigators using RECIST v1.1. A 95% Clopper-Pearson CI will be calculated for the ORR.

For patients who achieve an objective response, DOR is defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first. The censoring method for DOR will be the same as that for PFS. The Kaplan-Meier approach will be used to estimate median DOR. The 95% CI of the median DOR will be estimated using the Brookmeyer and Crowley method.

OS is defined as the time from randomization to death from any cause. For patients who are alive at the time of analysis data cut-off, OS time will be censored at the date the patient was last known to be alive. Survival time for patients with no post-baseline survival information will be censored at randomization. The Kaplan-Meier approach will be used to estimate median OS and 2-year landmark survival rate. The 95% CI of the median OS will be estimated using the Brookmeyer and Crowley method. The 95% CI of landmark survival rate will be calculated using the standard error derived from Greenwood's formula.

The EORTC QLQ-C30 data will be scored according to the EORTC scoring manual (Fayers et al. 2001). The data from the ITT population will be used to assess time to deterioration (TTD) in global health status (Items 29 and 30 of the EORTC QLQ C30) and TTD in physical functioning (Items 1–5 of the EORTC QLQ C30) for each treatment arm. TTD in global health status is defined as the time from randomization to first observed ≥10-point decrease in EORTC QLQ-30 linearly transformed global health status scale score that is sustained for two consecutive assessments or followed by death while the patient is on treatment. TTD in physical functioning is defined as the time from randomization to first observed ≥10-point decrease in EORTC QLQ-30 linearly transformed physical functioning scale score that is sustained for two consecutive assessments or followed by death while the patient is on treatment. Data for patients who do not achieve a 10-point decrease will be censored at the last time PRO data are available. Only patients with a EORTC QLQ-C30 assessment at randomization plus at least one post-randomization assessment will be included in the analysis. Data for patients without at least one post-randomization assessment will be censored at randomization.

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

6.4.3 Exploratory Efficacy Endpoints

[redacted]

6.5 SAFETY ANALYSES

Safety analyses will be performed on the safety population and will include all randomized patients who received at least one dose of study drug. For safety analyses, patients will be grouped based on receipt of at least one dose of any study drug, including when atezolizumab, cobimetinib, or vemurafenib was received in error (for example, if a patient assigned to Arm A received atezolizumab in error, this patient will be grouped to Arm B and vice versa).

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

Verbatim description of adverse events will be summarized by mapped terms and appropriate thesaurus levels and graded according to NCI CTCAE v4.0. All adverse events that occur during or after the first study drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grades 3, 4, and 5), [redacted], and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. The proportion of patients who experience at least one adverse event will be reported by toxicity term and treatment arm.

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

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

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

6.6 PHARMACOKINETIC ANALYSES

PK samples will be collected in this study as outlined in Appendix 2. Cobimetinib, vemurafenib, and atezolizumab concentration-time data will be overlaid with typical concentration-time profiles for each molecule using existing population PK models to determine if exposures in this study are consistent with previously characterized pharmacokinetics. In addition, individual patient PK parameters will be determined using the non-linear mixed-effects modeling. The results of PK analyses may be reported in a standalone report and may not be reported in the Clinical Study Report for this study.

Additional PK and exposure-response analyses will be conducted, as appropriate, based on the availability of data.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include all patients randomized, with patients grouped according to treatment received.

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

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported descriptively via subgroup analyses.

6.8 BIOMARKER ANALYSES

[redacted]

6.9 INTERIM ANALYSES

6.9.1 Planned Interim Analysis of the Primary Efficacy Endpoint

[redacted]

6.9.2 Interim Efficacy Analysis of Secondary Efficacy Endpoint

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

[redacted]

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

PRO data will be collected through the use of an electronic device provided by a vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The electronic data are available for view access only via a secure Web portal provided by the ePRO vendor. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patients will use an electronic device to capture PRO data. The data will be transmitted via a pre-specified transmission method (e.g. Web or wireless) automatically after entry to a centralized database at the electronic device vendor. Appropriate study personnel will be able to access the data securely via the Internet.

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

7.4 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, PROs, 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 on the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

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

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

7.5 USE OF COMPUTERIZED SYSTEMS

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

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 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.

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 (see definition of end of study in Section 3.2).

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 trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately [redacted] sites globally will participate to randomize approximately 500 patients. Screening and enrollment will occur through an IWRS system.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

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

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

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).

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Appendix 1
Schedule of Activities

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

Appendix 1
Schedule of Activities (cont.)

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

Appendix 1
Schedule of Activities (cont.)

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

Appendix 1
Schedule of Activities (cont.)

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

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

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

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

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

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

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

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

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

Appendix 1
Schedule of Activities (cont.)

[redacted]

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

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

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

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

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

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

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

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

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

Appendix 1
Schedule of Activities (cont.)

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

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

[t] If a patient develops a new skin lesion that is suspected of being cuSCC or another new primary cutaneous neoplasm during the study or up to 6 months after the last dose of vemurafenib, *dermatologic evaluation (as described in Section 4.5.6.1) should be performed.* All new primary neoplasms (benign or malignant), including new primary melanoma, will be reported until 6 months after the last dose of vemurafenib. Any new primary neoplasm other than cuSCC should be reported as a serious adverse event.

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

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

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

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

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

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

Appendix 1
Schedule of Activities (cont.)

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

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

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

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

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

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

Appendix 1
Schedule of Activities (cont.)

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

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

[redacted]

[jj] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to signing of the Informed Consent Form through 30 days after the last dose of study treatment.

[kk] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, adverse events will be reported as follows: All adverse events will be reported until 30 days after the last dose of study treatment or until initiation of subsequent anti-cancer therapy, whichever occurs first. Serious adverse events and [redacted] will continue to be reported until 90 days after the last dose of study treatment or until initiation of subsequent anti-cancer therapy, whichever occurs first. All new primary neoplasms (benign or malignant), including new primary melanoma, will be reported until 6 months after the last dose of vemurafenib. After the 6 month safety follow-up period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

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

Appendix 1
Schedule of Activities (cont.)

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

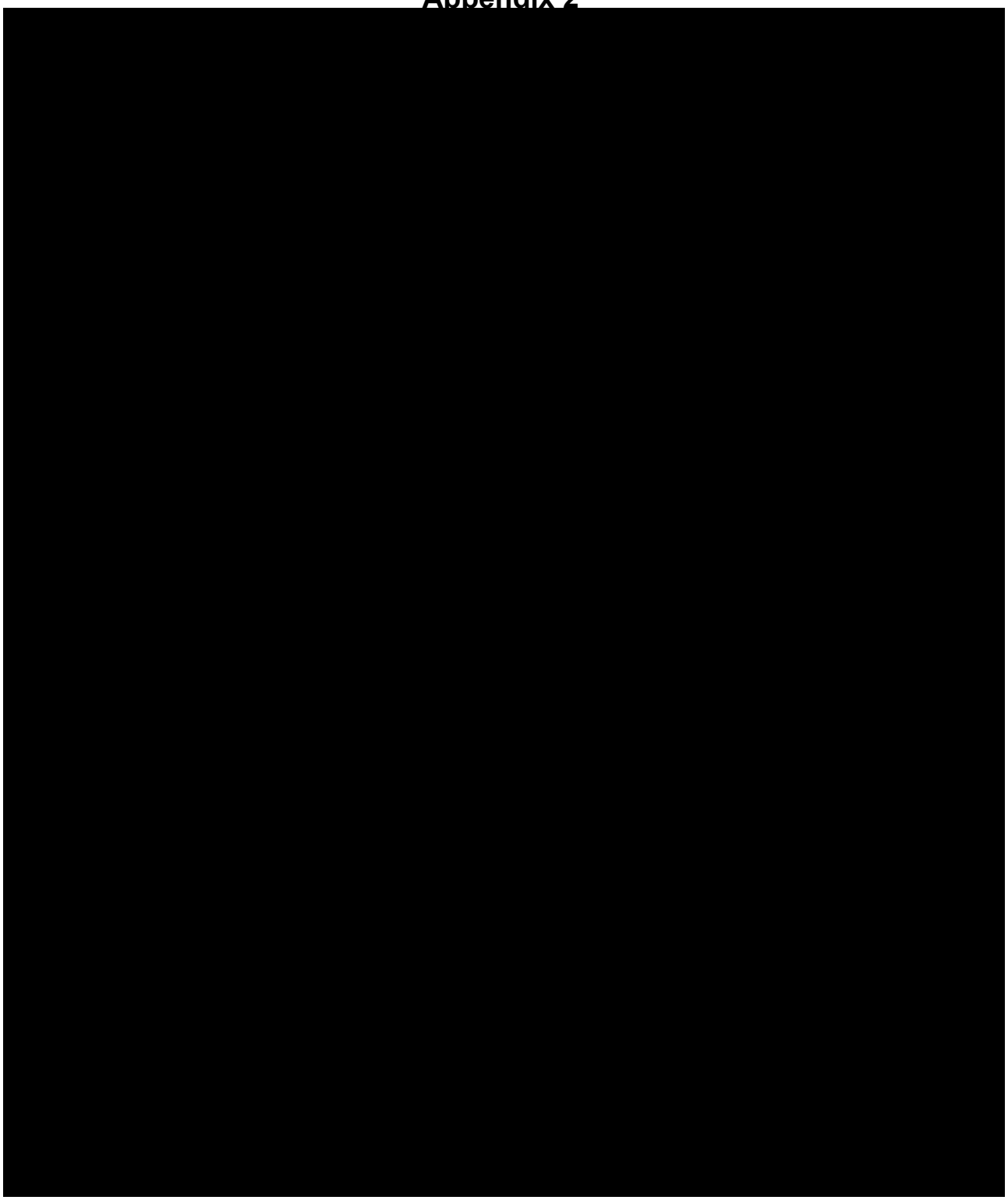
[nn] All patients will receive vemurafenib at a dose of 960 mg (four 240-mg tablets) PO BID on Days 1–21 of the run-in period. Patients in Arm A will continue to receive vemurafenib at a dose of 960 mg PO BID on Days 22–28 of the run-in period and Days 1–28 of each 28-day cycle during the triple combination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

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

[pp] Atezolizumab 840 mg or placebo will be administered by IV infusion on Days 1 and 15 of Cycle 1 and Days 1 and 15 of subsequent cycles. The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. The morning dose of vemurafenib and the once daily dose of cobimetinib may occur prior to the atezolizumab infusion.

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

Appendix 2



Appendix 3
ECOG Performance Status Scale

Grade	Description
0	Fully active; able to carry on all pre-disease 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 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1),[1] are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[2]

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 ≤ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

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

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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 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

DEFINITION OF NON-MEASURABLE LESIONS

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

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

Cystic Lesions:

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

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

METHODS FOR ASSESSING LESIONS

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

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

CLINICAL LESIONS

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

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 $\leq$ 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 randomization 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, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

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

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

ASSESSMENT OF TUMOR BURDEN

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

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

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

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

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

CALCULATION OF SUM OF DIAMETERS

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

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

Measuring Lymph Nodes

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

Measuring Lesions That Become Too Small to Measure

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

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

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

Measuring Lesions That Split or Coalesce on Treatment

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

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

EVALUATION OF NON-TARGET LESIONS

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

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

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

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

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

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

CRITERIA FOR NON-TARGET LESIONS

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

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

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

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

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

NEW LESIONS

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

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

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

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

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

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

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

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

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

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

SPECIAL NOTES ON RESPONSE ASSESSMENT

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

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

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.

Appendix 5

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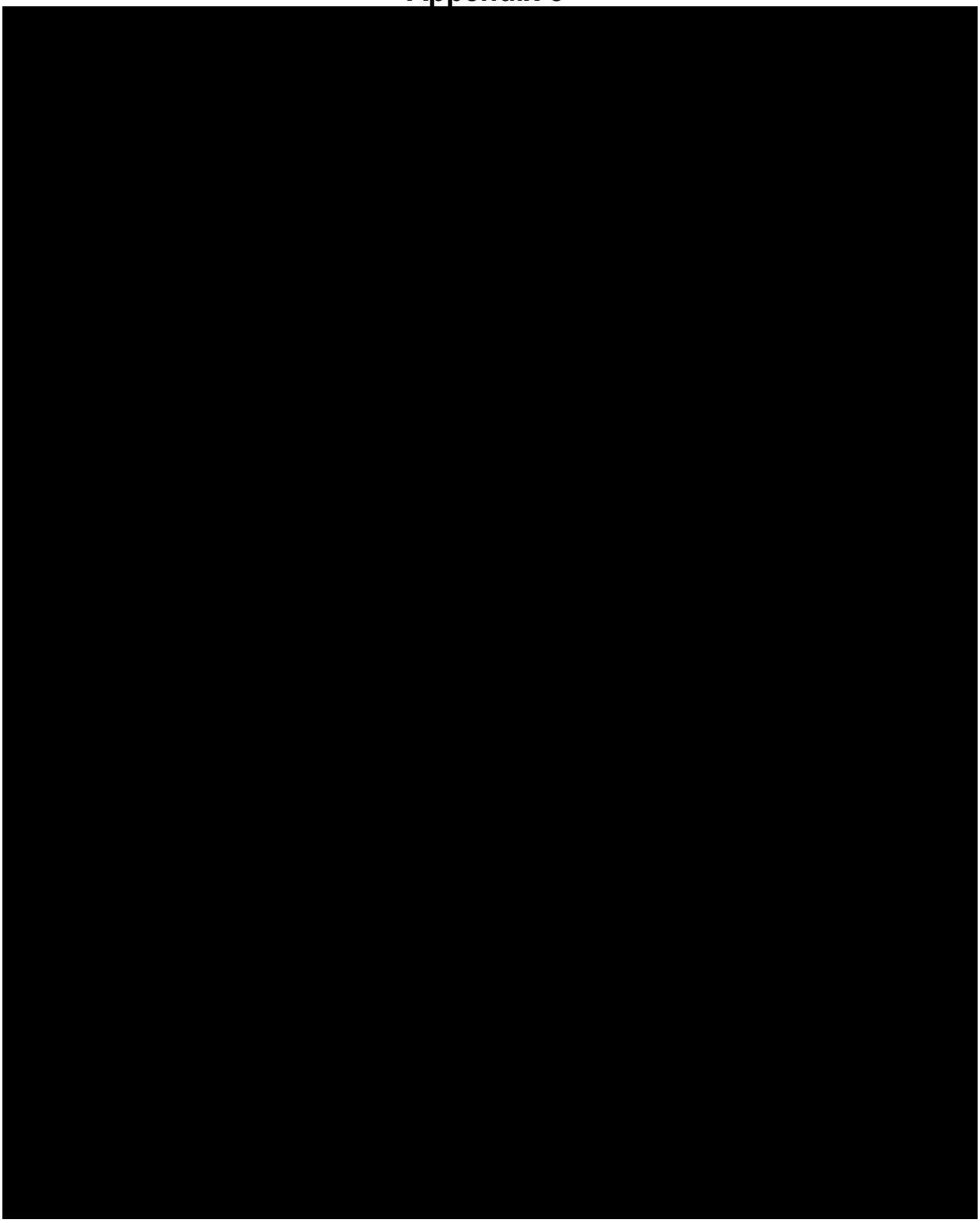
Appendix 5



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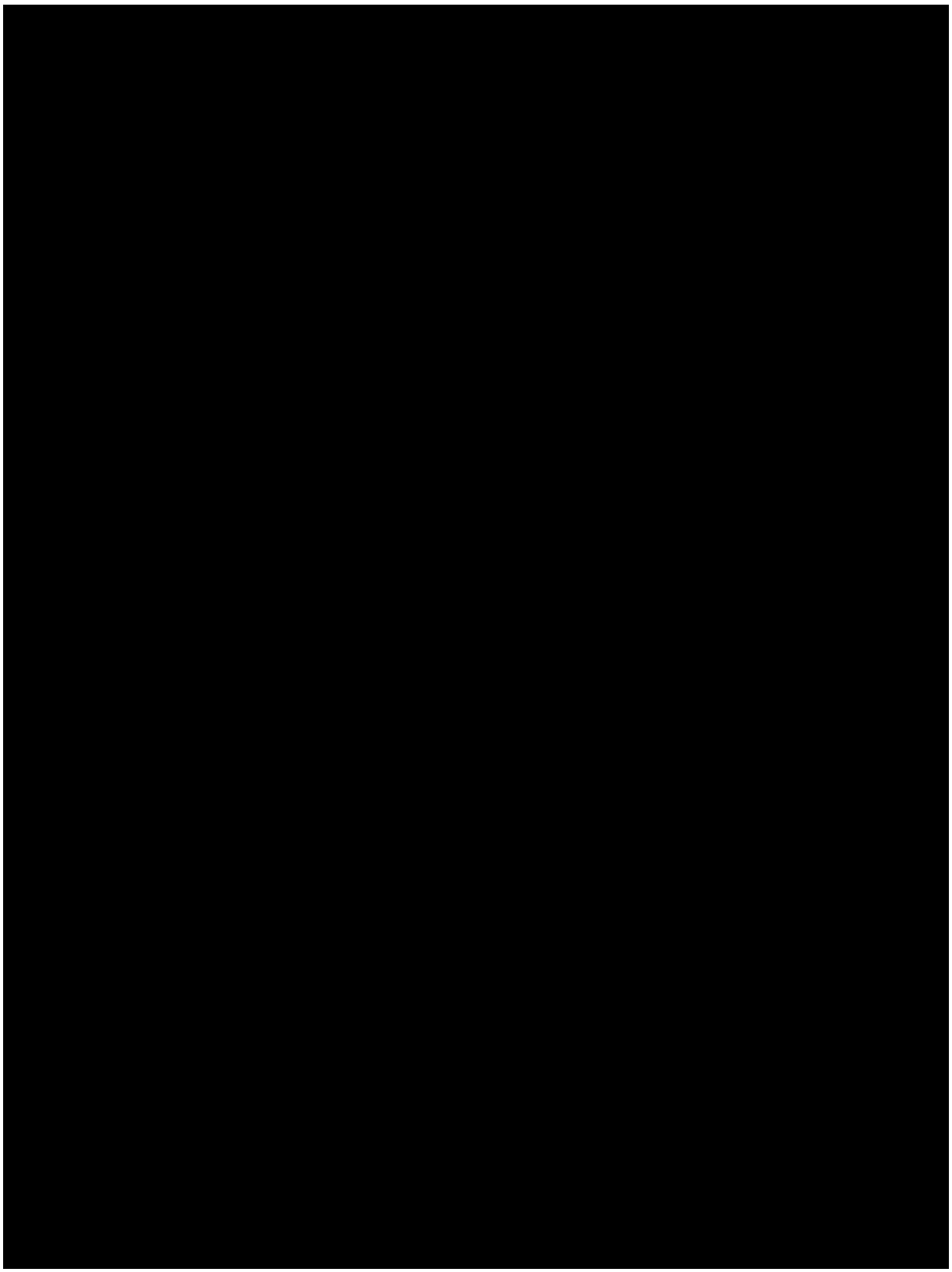

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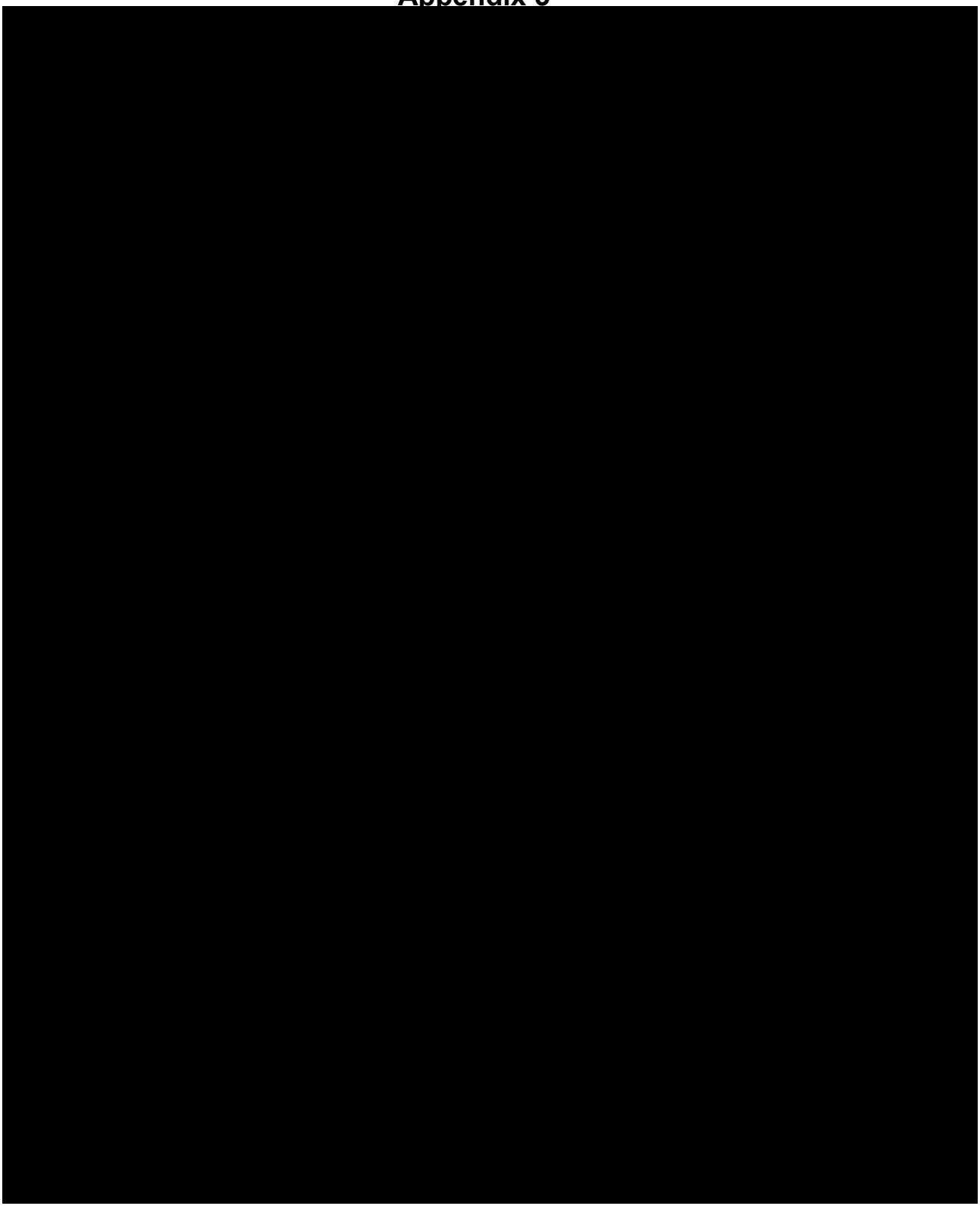

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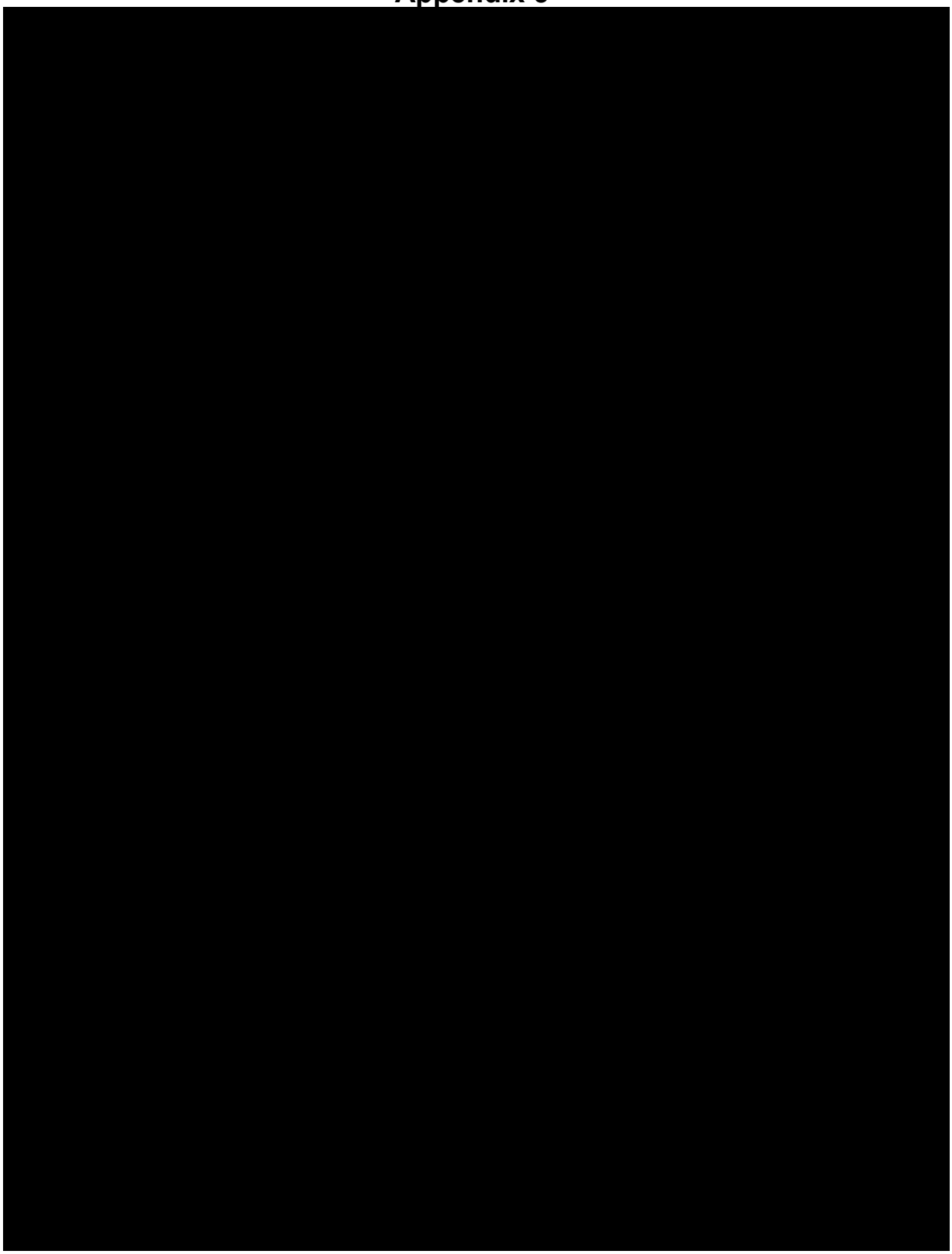

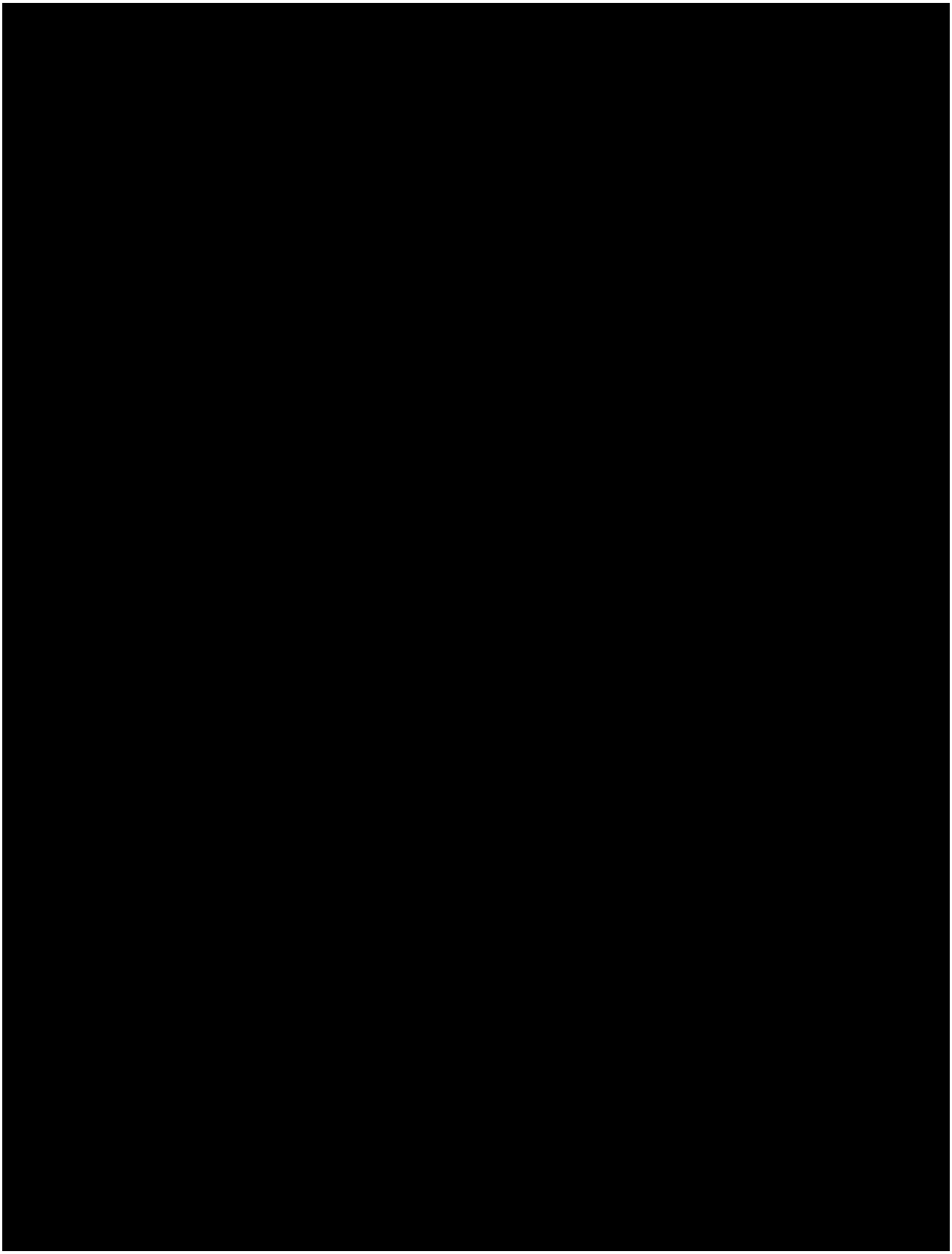

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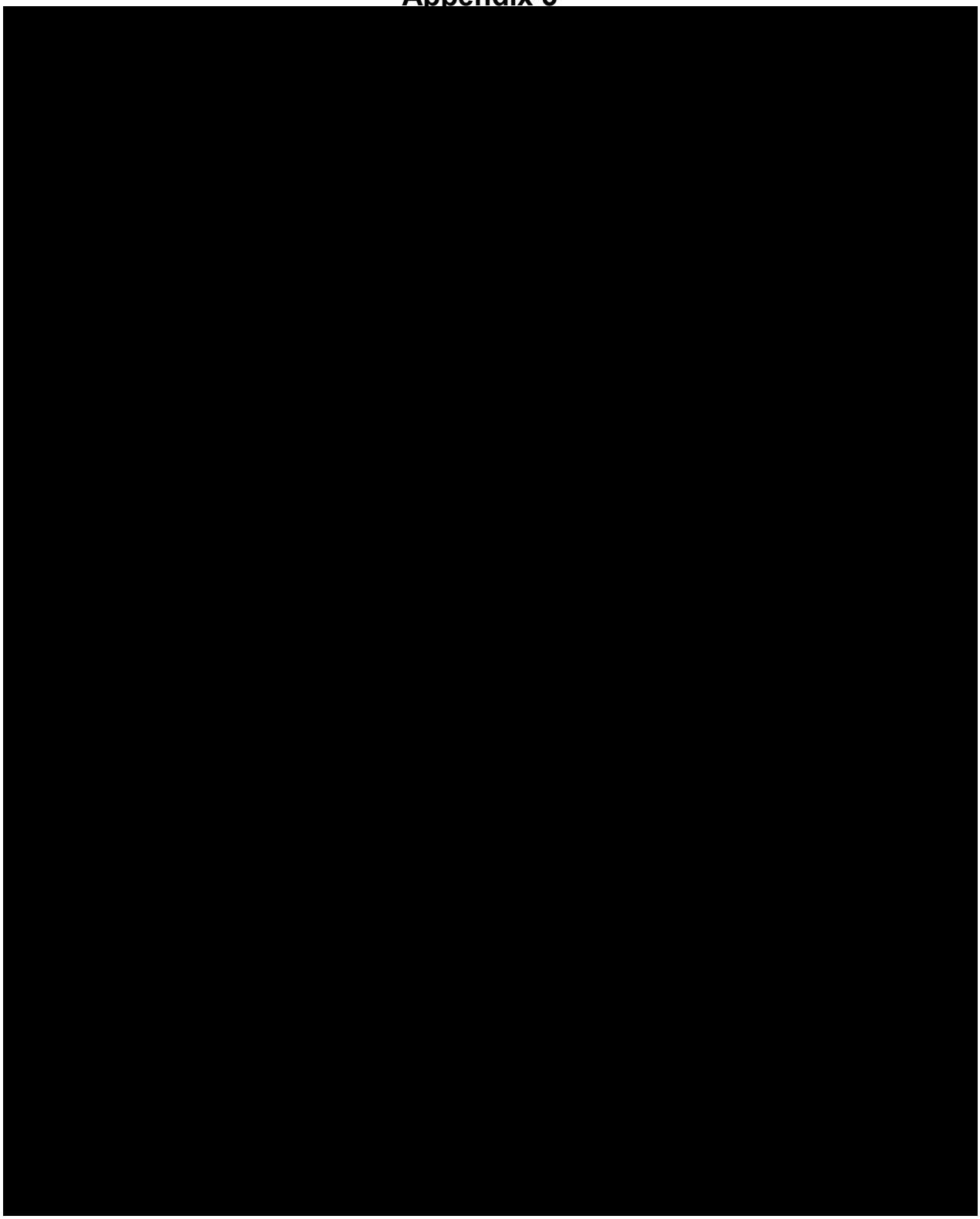


Appendix 6
Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

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

Appendix 7
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

EORTC QLQ-C30 (version 3)

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

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

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

Please go on to the next page

Appendix 7
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (cont.)

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

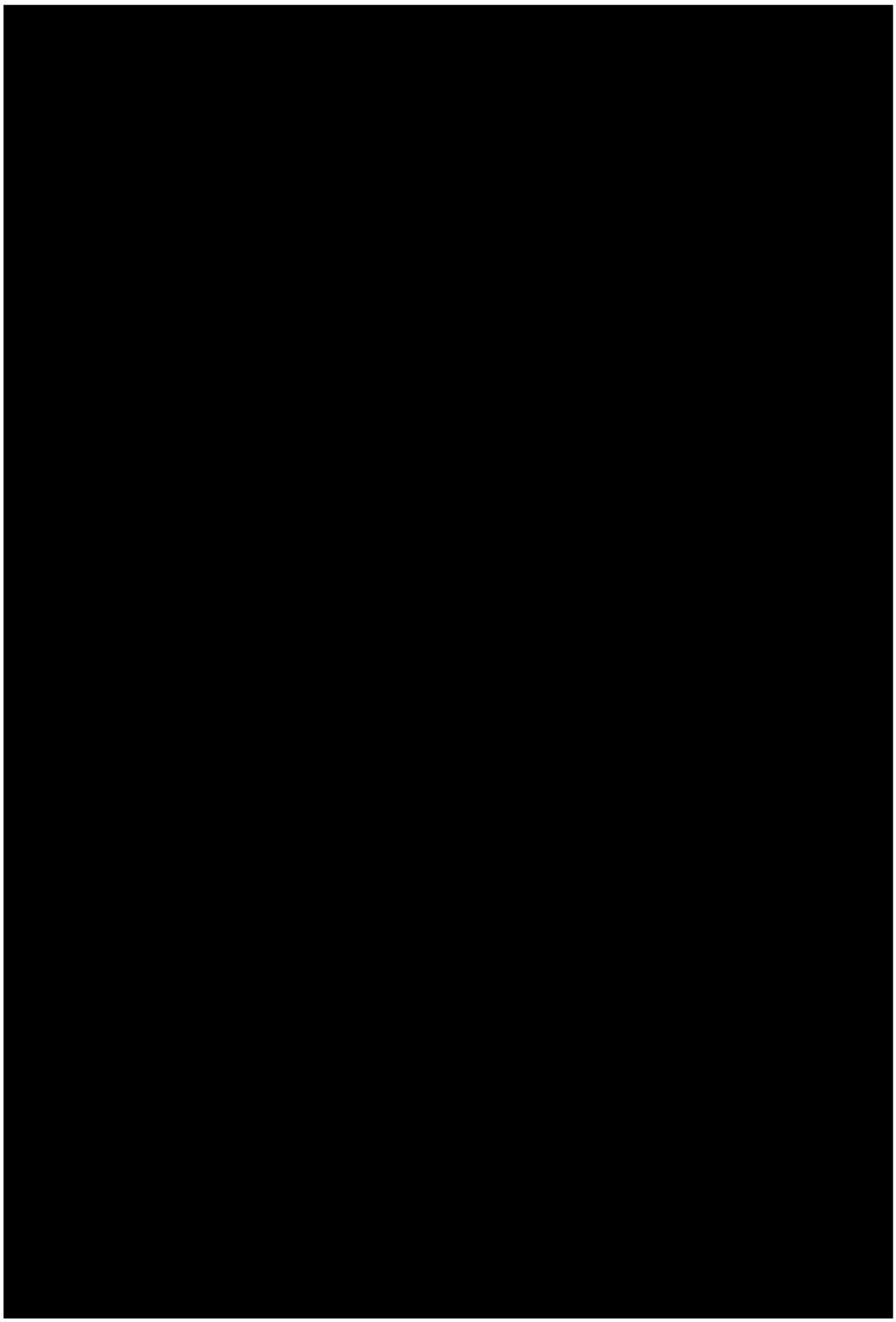
For the following questions please circle the number between 1 and 7 that best applies to you

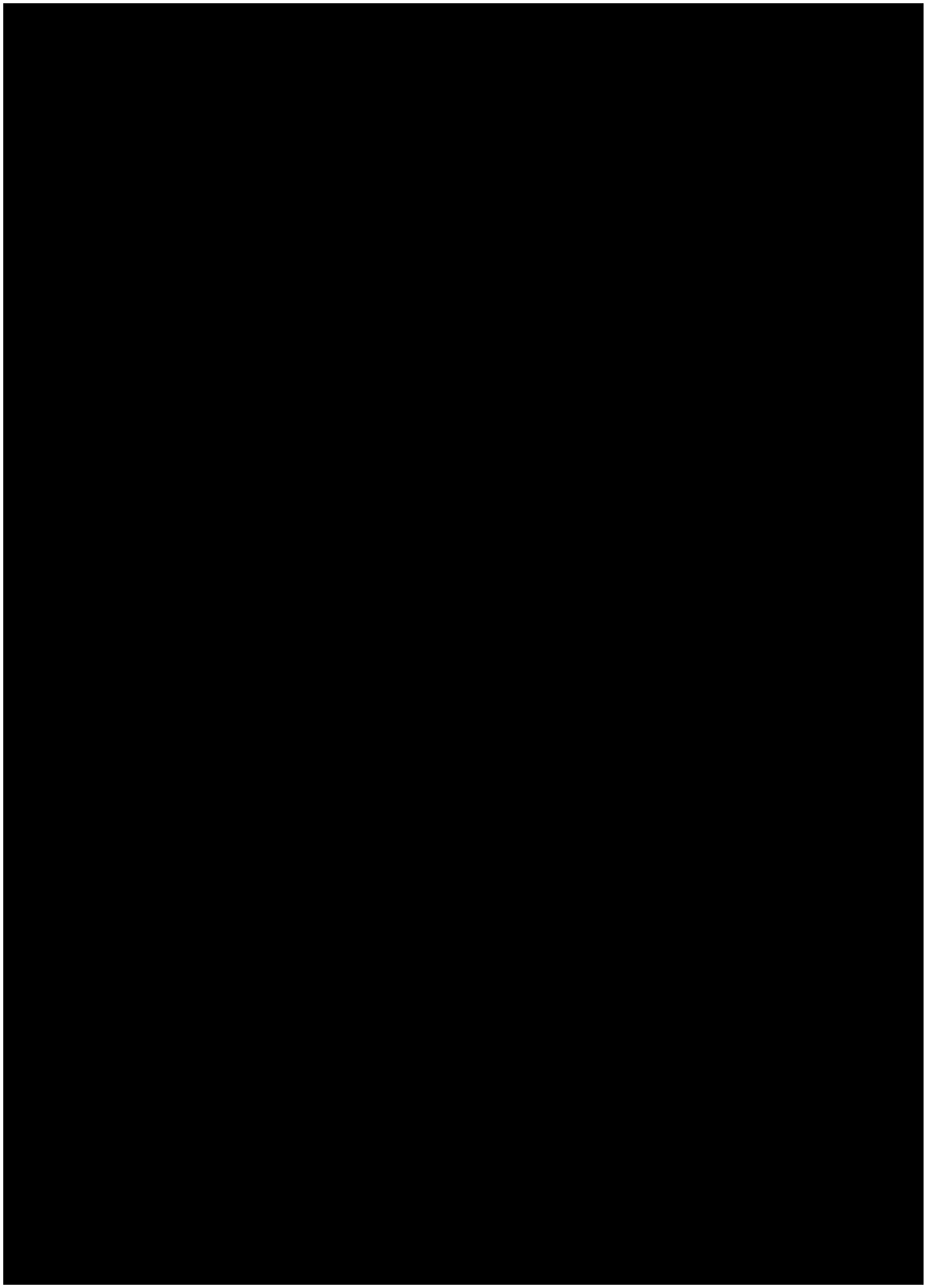
29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent





Appendix 9
Pre-existing 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 10
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.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Management guidelines for pulmonary events are provided in Section 5.1.5.4.

HEPATIC EVENTS

Management guidelines for hepatic events are provided in Section 5.1.5.4.

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Section 5.1.5.4.

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab.

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.

Management guidelines for endocrine events are provided in Section 5.1.5.4, with the exception of hypophysitis (see Table 1).

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 1 Management Guidelines for Endocrine Events

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.

[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 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

OCULAR EVENTS

Management guidelines for ocular events are provided in Section 5.1.5.4.

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 2.

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 2 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 or 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 10
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 3. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table 3 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 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

PANCREATIC EVENTS

Management guidelines for pancreatic events, including pancreatitis, are provided in Section 5.1.5.4.

DERMATOLOGIC EVENTS

Management guidelines for dermatologic events are provided in Section 5.1.5.4.

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 Section 5.1.5.4.

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 Section 5.1.5.4.

Appendix 10
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 4.

Table 4 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]

[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.*

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Renal Events ***(cont.)***

Event	*Management*
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.*