PROTOCOL

TITLE:	**A PHASE Ib/II STUDY OF COBIMETINIB ADMINISTERED AS SINGLE AGENT AND IN COMBINATION WITH VENETOCLAX, WITH OR WITHOUT ATEZOLIZUMAB, IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA**
PROTOCOL NUMBER:	BO39813
VERSION NUMBER:	7
EUDRACT NUMBER:	2017-000830-68
IND NUMBER:	Not applicable
NCT NUMBER:	NCT03312530
TEST PRODUCTS:	Cobimetinib (RO5514041) Venetoclax (GDC-0199, ABT-199, RO5537382) Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
18-Feb-2021 20:55:24	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
7	See electronic date stamp on title page
6	24 January 2020
5	27 March 2019
4	20 September 2018
3	2 March 2018
2	10 August 2017
1	18 April 2017

PROTOCOL AMENDMENT, VERSION 7:
RATIONALE

Protocol BO39813 has been amended to implement changes to align the cobimetinib and atezolizumab risk language with the current Cobimetinib Investigator's Brochure and Atezolizumab Investigator's Brochures, respectively. Changes to the protocol, along with a rationale for each change, are summarized below:

- The list of approved indications for atezolizumab has been updated to include hepatocellular carcinoma and melanoma (Section 1.7.1).
- Language has been added to clarify the use of investigational medicinal product accountability. Language has been added to indicate that sites can confirm that appropriate temperature conditions have been maintained during investigational medicinal product transit either by time monitoring (shipment arrival date and time) or temperature monitoring (Section 4.3.3).
- Immunosuppressive medications have been removed from the prohibited therapy section (4.4.5) and added to the cautionary therapy for atezolizumab-treated patients section (4.4.2) to align with atezolizumab management guidelines in Appendix 7 that permit use of immunosuppressive medications for the treatment of corticosteroid-refractory immune-mediated adverse events.
- Photosensitivity (when administered with vemurafenib) and pneumonitis have been re-added as identified risks associated with cobimetinib (Section 5.1.1.1). Additionally, diarrhea classification has been updated to an identified risk associated with cobimetinib (Section 5.1.1.1).
- The list of identified risks for atezolizumab have been revised to include severe cutaneous adverse reactions (SCARs; Section 5.1.3).
- Guidelines for the management of atezolizumab-associated dermatologic adverse events have been revised to provide guidance SCARs of Stevens-Johnson syndrome and toxic epidermal necrolysis in Section 5.1.5.5 (and Table 10) of the protocol.
- To address a request by the [redacted] the management guidelines for infusion-related reactions (IRRs) associated with atezolizumab have been updated to include guidelines for cytokine release syndrome (CRS) to align with the definition, grading, and management of CRS reflected in a recent publication (Lee et al. 2019) (Section 5.1.5.15 and Table 4 of Appendix 8).
- To address a request by the [redacted], hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) have replaced systemic inflammatory response syndrome on the list of atezolizumab-associated adverse events of special interest (Section 5.2.3).
- Language has been added to indicate that the Informed Consent Form will instruct female patients to inform the investigator if they become pregnant (Section 5.4.3.1).
- Language regarding investigator reporting of pregnancies has been clarified (Section 5.4.3.2).

- The name of a Roche policy on data sharing has been corrected (Section 9.5).
- Appendix 7 has been revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent.
- The adverse event management guidelines for IRR and CRS have been updated to ensure COVID-19 is included in the differential diagnosis (Appendix 8).
- To address a request by the [redacted], the management guidelines for HLH and MAS have been modified to indicate that HLH should be considered when CRS presentation is atypical or prolonged, to add anticytokine therapy as an option for treating HLH or MAS, and to suggest that published guidelines should be followed for HLH or MAS events that do not respond to treatment within 24 hours (Table 10 of Appendix 8).

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

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

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PHASE:	Phase Ib/II
INDICATION:	Multiple Myeloma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will assess the efficacy, safety, tolerability, and pharmacokinetics of cobimetinib administered as a single agent, cobimetinib plus venetoclax, and cobimetinib plus venetoclax plus atezolizumab in patients with relapsed and refractory multiple myeloma (R/R MM). Specific objectives and corresponding endpoints are outlined below.

Primary Objective	Corresponding Endpoints
• To evaluate the preliminary safety and tolerability and the preliminary efficacy of cobimetinib administered as single agent (Arm A), cobimetinib+ venetoclax (Arm B), and cobimetinib + venetoclax + atezolizumab (Arm C)	• Incidence, nature, and severity of adverse events, graded according to NCI CTCAE, v4.0; laboratory data • ORR (sCR, CR, VGPR, PR) as determined by the investigator using the IMWG response criteria in the safety population and biomarker-selected population
Secondary Efficacy Objective	**Corresponding Endpoints**
• To further evaluate the efficacy of cobimetinib administered as single agent (Arm A), cobimetinib+venetoclax (Arm B), and cobimetinib+venetoclax + atezolizumab (Arm C)	• CBR defined as MR or better • PFS defined as the time from randomization to the first occurrence of disease progression or relapse as determined by the investigator using the IMWG criteria or death from any cause during the study, whichever occurs first • DOR applies to patients achieving at least a PR, and is measured from the first observation of PR to the time of disease progression; deaths not due to progression will be censored • OS defined as the time from randomization until death from any cause

Exploratory Efficacy Objective	Corresponding Endpoint
• To evaluate the time elapsed before requiring the start of further anti-myeloma treatment	• Time to next treatment defined as the time between the start date of the current treatment line and the start date of the next treatment line, death or last follow-up
Pharmacokinetic Objective	**Corresponding Endpoints**
• To characterize the pharmacokinetics of cobimetinib (Arm A), to characterize the pharmacokinetics of cobimetinib and venetoclax when administered together (Arm B), and to characterize the pharmacokinetics of cobimetinib, venetoclax, and atezolizumab when administered together (Arm C)	• Plasma concentration of cobimetinib and venetoclax at specified timepoints • Serum concentration of atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to atezolizumab administered in Arm C	• Incidence of ADAs during the study relative to the prevalence of ADAs at baseline
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the potential effects of ADAs	• Correlation between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objectives	**Corresponding Endpoints**
• To identify biomarkers that are predictive of response to cobimetinib, venetoclax, and atezolizumab, such as RAS mutation, t(11;14) translocation, Bcl-2 family proteins, and pretreatment immune contexture • Identification and profiling of biomarkers associated with disease biology; the mechanisms of action of cobimetinib alone (Arm A), cobimetinib + venetoclax (Arm B), or cobimetinib + venetoclax + atezolizumab (Arm C); mechanism of resistance to drugs in all the arms; pharmacodynamics; prognosis and improvement of diagnostic assays • Determine impact of MRD measurements with patient response and survival	• The effect of treatment with cobimetinib, venetoclax, and atezolizumab on markers of MAPK pathway activity, apoptosis, immune infiltration and activation • Determine impact of MRD measurements with patient responses and survival • Relationship between biomarkers in blood and bone marrow (may include somatic mutations) and efficacy, safety, pharmacokinetics, immunogenicity, or other biomarker endpoints.

ADA = anti-drug antibody; CBR = clinical benefit rate; CR=complete response; DOR = duration of response; IMWG = International Myeloma Working Group; MAPK = mitogen-activated protein kinase; MR = minimal response; MRD = minimal residual disease; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.

Study Design

Description of Study

This is an open-label, randomized, multicenter, triple-arm Phase Ib/II study designed to assess the efficacy, safety, tolerability, and pharmacokinetics of cobimetinib administered as a single agent (Arm A), cobimetinib plus venetoclax (Arm B), and cobimetinib plus venetoclax plus atezolizumab (Arm C) in patients with R/R MM.

Two successive cohorts will evaluate the safety of cobimetinib plus venetoclax (n = 6) and that of cobimetinib plus venetoclax plus atezolizumab (n = 6) in the selected population during the

safety run-in phase of the study. Once the dose levels have demonstrated acceptable safety during this phase, randomization will begin for all treatment arms (Arms A, B, and C).

Safety Run-In Phase

Cobimetinib plus Venetoclax Safety Run-In Cohort

The cobimetinib plus venetoclax safety run-in cohort will enroll 6 patients with a starting dose of cobimetinib 40 mg orally (PO) daily on Days 1–21, plus venetoclax 800 mg PO daily on Days 1–28 of each 28-day cycle. This combination is currently being evaluated in an ongoing Phase Ib/II study (Study GH29914, a multi-arm study with venetoclax in combination with cobimetinib and venetoclax in combination with idasanutlin in patients aged ≥ 60 years with R/R acute myeloid leukemia (AML) who are not eligible for cytotoxic therapy). In that study, cobimetinib 40 mg plus escalating doses of venetoclax (400, 600, and 800 mg) have been explored as part of the dose-escalation phase.

The study team will evaluate the safety and tolerability data from the first cycle of treatment for patients in the cobimetinib plus venetoclax safety run-in cohort in accordance with the following rules:

- If < 2 of 6 (< 33%) evaluable patients experience a dose-limiting toxicity (DLT), cobimetinib 40 mg plus venetoclax 800 mg will be considered to have acceptable safety.
- If ≥ 2 of 6 (≥ 33%) evaluable patients experience a DLT, then one or more sequential cohorts of 6 additional evaluable patients will be enrolled and treated with cobimetinib 40 mg plus lower doses of venetoclax (600 mg → 400 mg → 200 mg) until < 2 of 6 evaluable patients experience a DLT.

This same approach with respect to the management of patients treated with cobimetinib 40 mg plus venetoclax 800 mg will be used for the evaluation of cohorts of patients treated with cobimetinib at 40 mg and lower doses of venetoclax at (600 mg → 400 mg → 200 mg). If the dose of venetoclax reaches 200 mg, then if necessary, the dose of cobimetinib may be reduced to a final dose of 20 mg. After the last patient has been enrolled and completed the DLT period in the safety run-in cohort of the cobimetinib plus venetoclax combination, patient enrolment in the cobimetinib plus venetoclax plus atezolizumab safety run-in cohort can start provided that the treatment is considered to have acceptable safety.

Cobimetinib plus Venetoclax plus Atezolizumab Safety Run-In Cohort

Once the dose level of cobimetinib plus venetoclax is considered safe in the safety run-in cohort, a cohort of 6 evaluable patients will then be treated with cobimetinib plus venetoclax plus atezolizumab. Cobimetinib PO and venetoclax PO will be administered at the selected dose for the randomization phase of the study with atezolizumab IV at the fixed dose of 840 mg on Day 1 and Day 15 (± 3 days) of each 28-day cycle (note: Cycle 1 of the safety run-in phase does not include the 3-day window). For this cohort, a staggered design will be adopted for the first 3 patients. One patient will be enrolled and dosed in the initial dose cohort. Afterwards, patients will be enrolled sequentially once the prior patient has completed the first cycle with an acceptable safety. If no DLTs are observed in the first 3 patients, 3 more patients will be enrolled simultaneously. If a DLT is observed in 1 of the first 3 patients, the following 3 patients will be enrolled consecutively after the completion of the first cycle of the prior patient.

Once the last patient has completed the first cycle of therapy, patient enrollment will be put on hold until the study team has completed the evaluation of the safety and tolerability data of the cobimetinib plus venetoclax plus atezolizumab safety run-in phase of the study in accordance with the following rules:

- Cobimetinib plus venetoclax plus atezolizumab will be considered safe if < 2 evaluable patients experience a DLT during the first cycle of treatment.
- If ≥ 2 of 6 (≥ 33%) evaluable patients experience a DLT, then one or more sequential cohorts of 6 additional evaluable patients will be enrolled and treated with cobimetinib 40 mg plus lower doses of venetoclax (600 mg → 400 mg → 200 mg) until < 2 of 6 evaluable patients experience a DLT.

- If < 2 of 6 (< 33%) evaluable patients experience a DLT with the new lower dose level, this would be the selected dose for the randomization phase of the study.
- If ≥ 2 of 6 (≥ 33%) evaluable patients experience a DLT, 6 additional patients will be enrolled and assessed for DLTs at lower dose levels.

For initial dose reductions at the starting dose, cobimetinib and atezolizumab will remain fixed with dose reductions for venetoclax if needed in sequential decrements of 200 mg. If the dose of venetoclax reaches 200 mg, then if needed, the dose of cobimetinib may be reduced from the starting dose of 40 mg to a final dose of 20 mg.

Definition of Evaluable Patients in the Safety Run-In Cohorts

During the safety run-in phase of the study, patients will be evaluable if they have completed at least 70% of the protocol-planned dose for each individual drug. If a significant decrease (< 70%) in the intended relative dose intensity is due to safety reasons, the toxicity will be considered a DLT. If the significant decrease (< 70%) in the intended relative dose intensity is due to unrelated adverse events or to progressive disease (PD), then the patient will be replaced.

An interim analysis for safety will be performed prior to the randomization phase to assess data from all safety run-in cohorts. The analysis will assess the DLTs during the DLT period and the tolerability of the study treatments for patients who have received more than one cycle of study therapy. The interim analysis will be completed after the last evaluable patient in Arm C (triplet regimen) has concluded the first cycle.

Randomization Phase

After the safety run-in phase and prior to patient randomization (1:2:2 for Arms A:B:C), a biomarker assessment for the translocation t(11;14) will be performed to allow randomization of a representative MM population and to ensure that approximately 20% of patients in each arm have MM with a t(11;14). See the protocol for patient assignment to study arms.

Approximately 12 patients will be randomized to the cobimetinib single-agent arm (Arm A) and will receive the standard single-agent cobimetinib dose of 60 mg PO daily on Days 1–21 of each 28-day cycle. Upon progression, patients will be allowed to receive treatment with cobimetinib and atezolizumab at the recommended Phase II dose of cobimetinib 60 mg PO from Day 1 to Day 21 plus atezolizumab IV at a fixed dose of 840 mg on Day 1 and Day 15 (± 3 days) of each 28-day cycle. This combination at the above-indicated doses is currently being explored in multiple clinical studies including a Phase III clinical trial in patients with metastatic colorectal cancer (CRC; Study GO30182).

Arm B (cobimetinib plus venetoclax) will randomize approximately 24 patients to receive cobimetinib plus venetoclax at the dose level identified in the safety run-in phase.

Arm C will randomize approximately 24 patients to receive cobimetinib plus venetoclax at the dose level identified in the safety run-in phase plus atezolizumab IV at a fixed dose of 840 mg on Day 1 and Day 15 (± 3 days) of each 28-day cycle.

The study drugs will be administered on 28-day cycles as follows:

Arm A: Cobimetinib

- Cobimetinib 60 mg PO daily on Days 1–21
- Upon progression, patients in Arm A are allowed to receive treatment with:
  - Cobimetinib 60 mg PO daily on Days 1–21
  - Atezolizumab 840 mg IV infusion on Day 1 and Day 15 (± 3 days)

Arm B: Cobimetinib + Venetoclax

- Cobimetinib 40 mg PO daily on Days 1–21
- Venetoclax 800 mg PO daily on Days 1–28

Arm C: Cobimetinib + Venetoclax + Atezolizumab

- Cobimetinib (dose to be determined in Arm B) PO daily on Days 1–21
- Venetoclax (dose to be determined in Arm B) PO daily on Days 1–28
- Atezolizumab 840 mg IV on Day 1 and Day 15 (± 3 days)

Treatment will continue until the patient has disease progression as defined by the International Myeloma Working Group (IMWG) consensus criteria, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurs first.

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at the treatment discontinuation visit, and during the follow-up period. A treatment discontinuation visit will take place within 30 (± 7) days after the last dose of study drug. After PD and study treatment discontinuation, the required follow-up information will be collected via telephone calls and/or clinic visits every 3 months until death, withdrawal of consent, the patient is lost to follow-up, or study termination by the Sponsor, whichever occurs first.

Any toxicity associated with, or possibly associated with cobimetinib and/or venetoclax administration should be managed with supportive care and/or dose interruptions (maximum allowable length of treatment interruption is 28 days) and/or dose reductions. If the investigator considers that the patient could derive clinical benefit from the study treatment after an interruption longer than 28 days, study treatment may continue after discussion with the Medical Monitor. Toxicity due to atezolizumab administration will be managed by supportive care and/or dose interruptions. No dose modification of atezolizumab is allowed in this study.

A DLT will be defined as any of the following adverse events related to study treatment occurring during the DLT period which corresponds to the first cycle of study treatment (from Cycle 1 Day 1 to Cycle 1 Day 28):

- Any treatment-related death
- Grade 4 hematologic toxicity lasting ≥ 7 days or higher (except leukopenia or lymphopenia)
- Treatment-related non-hematologic toxicity Grade ≥ 3 (according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 [NCI CTCAE v4.0]) except for the following:
  - Grade 3 fatigue, asthenia, fever, anorexia, or constipation
  - Grade 3 nausea, vomiting, or diarrhea that responds to maximal supportive care within 72 hours
  - Grade 3 rash that resolves to Grade 1 within 7 days with maximal supportive care
  - Grade 3 laboratory abnormality that is asymptomatic and deemed to be not clinically significant by the investigator
- A patient who receives less than 70% of the protocol-planned dose for each individual drug due to drug-related toxicity

If any of the DLT toxicities occur and are assessed as related to study treatment by the investigator, the study treatment will be halted immediately for the individual patient, and a thorough investigation and safety analysis will be conducted.

NCI CTCAE v4.0 will be used to characterize the toxicity profile of the study treatments on all patients.

Anti-myeloma response will be evaluated according to IMWG criteria. Disease evaluations will include biochemical disease assessments, skeletal survey, bone marrow aspirate, and biopsy. Investigators will assess anti-myeloma response every cycle, regardless of any dose delays. Patients who discontinue treatment for reasons other than disease progression (e.g., for toxicity) will continue to have tumor assessments as scheduled until confirmed disease progression per IMWG criteria, withdrawal of consent, initiation of a new anti-cancer therapy, study termination by the Sponsor, or death, whichever occurs first.

Number of Patients

Approximately 72 patients with R/R MM (across the three arms) will be recruited into this study, from approximately 25 centers worldwide.

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
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
- Life expectancy of at least 12 weeks
- Documented MM as defined by the below criteria:
  - Monoclonal plasma cells in the bone marrow ≥ 10% or presence of a biopsy-proven plasmacytoma
  - Measurable disease as defined by any of the following:

    Serum M-protein level ≥ 1.0 g/dL or urine monoclonal protein (M-protein) level ≥ 200 mg/24 hours; or

    Light chain MM: Serum Ig free light chain (FLC) ≥ 10 mg/dL and abnormal serum Ig kappa/lambda FLC ratio
- Received 3 to 5 prior lines of therapy for MM, including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD)
  - A line of therapy consists of ≥ 1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various drugs (e.g., induction therapy followed by stem cell transplantation [SCT] is considered 1 line of therapy)
- Achieved a response (minimal response [MR] or better) to at least one prior regimen
- Documented evidence of PD (as defined by the IMWG criteria) on or after their last prior therapy, or patients who were intolerant to their last prior therapy

  Note: There is no required time period between last prior therapy and documented evidence of PD.
- Toxicities resulting from previous therapy (including peripheral neuropathy) that must be resolved or stabilized to Grade 1
- Laboratory values as follows:
  - Hemoglobin level ≥ 7.5 g/dL (≥ 5 mmol/L) (without growth factor support)
  - Platelet count ≥ 50,000/mm^3 or ≥ 30,000 if bone marrow plasma cell > 50% (without transfusion support)
  - Absolute neutrophil count ≥ 1000/mm^3 (without growth factor support)
  - AST and ALT ≤ 2.5 × the upper limit of normal (ULN)
  - Total bilirubin ≤ 1.5 × ULN
  - Adequate renal function as demonstrated by a calculated creatinine clearance of ≥ 40 mL/min; determined via urine collection for 24-hour creatinine clearance or by the Cockcroft-Gault formula
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use <u>two</u> contraceptive measures, and agreement to refrain from donating eggs, as defined below:
  - A woman is considered to be of childbearing potential if she is post-menarcheal, 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).
  - Women must remain abstinent or use <u>two</u> contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 3 months after the final dose of cobimetinib, 1 month after the final dose of venetoclax, and 5 months after the final dose of atezolizumab. Women must refrain from donating eggs during this same period.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- 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.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:
  - With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of cobimetinib to avoid exposing the embryo. Men must refrain from donating sperm during this same period.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

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

- Anti-myeloma treatment within 14 days or 5 pharmacokinetic (PK) half-lives of the treatment, whichever is longer, before the date of randomization
- Completion of autologous stem cell transplant within 100 days prior to the date of randomization
- Prior allogeneic stem cell transplant as well as prior solid organ transplant
- Spinal cord compression not definitively treated with surgery and/or radiation
- Prior treatment with MEK inhibitors, Bcl-2 inhibitors, or immune checkpoint inhibitor therapies including anti–CTLA-4, anti–PD-1 or anti–PD-L1
- Treatment with systemic immunostimulatory agents (including, but not limited to, CD137 agonists or interferon and interleukin 2) within 28 days or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF–α agents) within 14 days prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions:
  - Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor approval has been obtained.
- Surgical procedure (including open biopsy, surgical resection, or any other major surgery) or significant traumatic injury within 28 days prior to enrollment, or anticipation of need for major surgical procedure during the course of the study
- Prior radiation therapy within 14 days prior to study enrollment and/or persistence of radiation-related adverse effects
- Minor surgical procedure within 7 days (including placement of a vascular access device)
- History or evidence of retinal pathology on ophthalmic examination that is considered a risk factor for neurosensory retinal detachment/central serous chorioretinopathy, retinal vein occlusion (RVO), or neovascular macular degeneration:
  - History of serous retinopathy
  - History of RVO
  - Evidence of ongoing serous retinopathy or RVO at baseline
- Left ventricular ejection fraction below institutional lower limit of normal
- History of clinically significant cardiovascular dysfunction including the following:
  - Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg that is treated or untreated)

- Prior history of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months of study enrollment
- History of stroke or transient ischemic attack within 6 months prior to enrollment
- History of myocardial infarction within 6 months prior to first dose of study drug in Cycle 1
- New York Heart Association Class III or IV cardiac disease
- Unstable arrhythmias, or unstable angina
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

- Any previous venous thromboembolism Grade $>$ 3 within 12 months of study enrollment
- INR $>$ 1.5 and aPTT $>$ 1.5 $\times$ upper limit of normal within 7 days prior to study enrollment
- History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins (for patients in Arm C only)
- History of other malignancy that could affect compliance with the protocol or interpretation of results
  - Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix are allowed.
- 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's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see the protocol for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism who are on thyroid replacement hormone are eligible for the study.
  - Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

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

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

    There is 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
- Uncontrolled serious medical or psychiatric illness
- History of malabsorption or other condition that would interfere with absorption of study drugs
- Active tuberculosis
- Severe infection within 28 days prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 14 days 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.

- Positive test results for hepatitis B (hepatitis B surface antigen and/or total hepatitis B core antibody [HBcAb]) or hepatitis C virus (HCV) antibody
  - Patients positive for HBcAb are eligible only if polymerase chain reaction (PCR) is negative for hepatitis B virus DNA.
  - Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
- Known history of HIV seropositivity
- Treatment with a live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to Cycle 1 Day 1, at any time during the study, and for at least 5 months after the last dose of study drug (for patients in Arm C only)
- Received strong CYP3A inhibitors (such as ketoconazole and clarithromycin), moderate CYP3A inhibitors (such as fluconazole, ciprofloxacin, and verapamil) strong CYP3A inducers (such as carbamazepine and phenytoin), and moderate CYP3A inducers (such as efavirenz, modafinil) within 7 days prior to the initiation of study treatment
- The following foods/supplements are prohibited at least 7 days prior to initiation of and during study treatment:
  - St John's wort or hyperforin (potent CYP3A enzyme inducer)
  - Grapefruit juice (potent CYP3A enzyme inhibitor)
- Pregnant or lactating, or intending to become pregnant during the study
  - Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to initiation of study drug

End of Study

The end of this study is defined as when all patients randomized have been followed until death, withdrawal of consent, lost to follow-up, or the Sponsor decides to end the trial, whichever occurs first.

Length of Study

The total length of the study, from first patient in until end of follow-up, is expected to be approximately 24 months.

Investigational Medicinal Products

Test Products (Investigational Drugs)

The investigational medicinal products for this study are cobimetinib, venetoclax, and atezolizumab.

Cobimetinib will be supplied by the Sponsor as tablets. The 20-mg cobimetinib drug product is a film-coated, white, round, immediate-release tablet. Cobimetinib will be packaged in blister packs. Cobimetinib should not be stored above 25°C (77°F). If the study drug is stored outside of the permitted temperature ranges, quarantine the affected supply and contact the study monitor.

Venetoclax (GDC-0199/ABT-0199) is manufactured by AbbVie, Inc. and will be supplied by the Sponsor as oral film-coated tablets of 100-mg strength. Venetoclax tablets will be packaged in high-density polyethylene plastic bottles to accommodate the study design. Venetoclax tablets must be stored at 15°C–25°C (59°F–77°F).

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

Statistical Methods

Primary Analysis

The primary efficacy objective of this study is to evaluate the anti-myeloma activity of cobimetinib administered as a single agent (Arm A), cobimetinib in combination with venetoclax (Arm B), and cobimetinib in combination with venetoclax and atezolizumab (Arm C) based on the overall response rate (ORR) as determined by the investigator using the IMWG response criteria. ORR is defined as a stringent complete response, complete response, very good partial response, or partial response and will be analyzed in the efficacy population and in biomarker-selected sub-populations (e.g., MAPK activation, t[11;14]). For Arm A, ORR will also be analyzed separately in the cobimetinib single-agent arm and for those patients who are treated with cobimetinib plus atezolizumab upon disease progression.

Descriptive statistics will be used to evaluate the incidence, nature and severity of adverse events, graded according to the NCI CTCAE v4.0.

Determination of Sample Size

Design considerations were not made with regard to power or to control the type I error, but to obtain preliminary efficacy, safety, tolerability, and PK information of cobimetinib as a single agent (Arm A), cobimetinib plus venetoclax (Arm B), and cobimetinib plus venetoclax plus atezolizumab (Arm C) in patients with R/R MM.

Approximately 72 patients are anticipated to be recruited in this study: approximately 12 patients in the safety run-in cohorts, 12 patients in Arm A, 24 patients in Arm B, and 24 patients in Arm C.

If patients must be replaced or additional cohorts are enrolled during the safety run-in, the total sample size for this study may increase and the study team may enroll 6 additional patients (in each safety run-in cohort, if necessary) at a reduced dose level. Depending on the outcome of the review of the clinical data from the additional 6 patients, the study team will determine if the expansion stage can initiate with this lower combination dose.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
14/14	14 days on/14 days off
21/7	21 days on/7 days off
ACTH	*adrenocorticotropic hormone*
ADA	anti-drug antibody, also known as anti-therapeutic antibody (ATA)
ALP	alkaline phosphatase
AML	acute myeloid leukemia
AUC	area under the concentration–time curve
BCRP	breast cancer resistance protein
BH	Bcl-2 homologue
BOR	best overall response
CL	*clearance*
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed concentration at steady state
C_{min}	*minimum concentration under steady-state conditions within a dosing interval*
CR	complete response
CRC	colorectal cancer
CT	computed tomography
C_{trough}	target trough concentration
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
ERK	extracellular signal-regulated kinase
FDA	(U.S.) Food and Drug Administration
FISH	fluorescence in situ hybridization
FLC	free light chain
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Definition
HLH	*hemophagocytic lymphohistiocytosis*
IC	*immune cell*
ICH	International Council for Harmonisation
IL-2	interleukin 2
IMiD	immunomodulatory drug
IMP	investigational medicinal product
IMWG	International Myeloma Working Group
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRR	infusion-related reaction
K_i	inhibitor constant
LFT	liver function test
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MAS	*macrophage activation syndrome*
MHC	major histocompatibility complex
MM	multiple myeloma
M-protein	monoclonal protein
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
mUC	*metastatic urothelial carcinoma*
MUGA	multiple-gated acquisition (scan)
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NSCLC	non–small cell lung cancer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival

Abbreviation	Definition
Pgp	P-glycoprotein 1
PI	proteasome inhibitor
PK	pharmacokinetic
PO	oral
popPK	*population pharmacokinetics*
PR	partial response
Q2W	every 2 weeks
Q3W	every 3 weeks
QD	once per day
RBR	Research Biosample Repository
R/R	relapsed and refractory
RVO	retinal vein occlusion
sCR	stringent complete response
SCT	stem cell transplant
SD	stable disease
sFLC	serum free light chain
SIFE	serum immunofixation electrophoresis
SLL	small lymphocytic leukemia
SPEP	serum protein electrophoresis
$t_{1/2}$	*elimination half-life*
T4	thyroxine
T3	triiodothyronine
TC	*tumor cell*
TGFβ	transforming growth factor-β
TIL	tumor-infiltrating lymphocyte
TLS	tumor lysis syndrome
Tregs	T regulatory cells
TSH	thyroid-stimulating hormone
UC	urothelial carcinoma
UIFE	urine immunofixation electrophoresis
ULN	upper limit of normal
UPEP	urine protein electrophoresis
VGPR	very good partial response
V_{ss}	*volume of distribution under steady-state conditions*
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON MULTIPLE MYELOMA

Multiple myeloma (MM) is a B-cell neoplasm characterized by the clonal expansion of malignant plasma cells in the bone marrow leading often to an excessive production of monoclonal proteins (M-proteins). The expansion of malignant plasma cells and the accumulation of the M-protein lead to the end-organ damage that characterizes evolution of the disease. MM represents 15% of all hematologic cancers. There are approximately 86,000 new cases of MM annually worldwide (Becker 2011).

Treatment of MM consists of combination regimens based on proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and corticosteroids administered in different lines of therapy. Recent advances in the treatment of MM have included a new generation of PIs (e.g., carfilzomib) and IMiDs (e.g., pomalidomide), and more recently, monoclonal antibodies such as daratumumab and elotuzumab, which target the CD38 and the signaling lymphocytic activation molecule F7 (SLAMF7) (Nooka et al. 2015). These new therapeutic options have prolonged the life expectancy of patients with MM. However despite these advances, MM is still an incurable disease, and new combinations with novel mechanisms of action are necessary.

Several drugs that target central mechanisms of malignant plasma cell biology (such as the mitogen-activated protein kinase [MAPK] pathway and the prosurvival protein Bcl-2) and the immune system, such as the PD-L1 antibody, are currently being explored in nonclinical and clinical settings.

1.2 THE MAPK SIGNALING PATHWAY AND REGULATION OF THE IMMUNE TUMOR MICROENVIRONMENT

The MAPK signaling cascade is a key intracellular signaling network that transduces multiple proliferative and differentiating signals from the extracellular environment to the nucleus of cells to activate cellular growth and differentiation. Signaling through the MAPK pathway plays a significant role in normal cellular regulation (Johnson and Lapadat 2002; Roberts and Der 2007). Given the central role played by the MAPK pathway in normal cellular proliferation, abnormal regulation of this pathway could lead or contribute to uncontrolled proliferation, invasion, metastasis, and angiogenesis as well as diminished apoptosis. Constitutive activation of the MAPK pathway occurs frequently in solid tumors as well as in MM (Heuck et al. 2016) because of somatic mutations that activate additional downstream pathways. This is the case for RAS or RAF mutations, which activate the MAPK pathway and thereby perpetuate uncontrolled proliferative signals.

The MAPK pathway has also been implicated in regulation of the tumor microenvironment. Blocking the MAPK pathway in in vitro cell lines has shown to increase antigen expression and enhance reactivity to antigen–specific T lymphocytes (Boni et al. 2010). In patients with melanoma treated with a combination of BRAF and

MEK inhibitors, an increased number of intra-tumoral lymphocytes (CD4+ and CD8+ T cells) were observed compared to pretreatment biopsy samples (Kakavand et al. 2015). Furthermore, pretreatment biopsies with increased tumor-infiltrating lymphocytes (TILs) demonstrated a larger increase in TILs and PD-1 expression after treatment with a BRAF inhibitor and a MEK inhibitor (Cooper et al. 2015; Kakavand 2015; Liu et al. 2015).

Additionally, up-regulation of the MAPK pathway inhibits the immune cell function through the down-expression of major histocompatibility complex (MHC) antigens that impairs the tumor antigen presentation to the immune effector cells. MAPK inhibition upregulates the expression of cell-surface MHC antigens (Liu et al. 2015) and increases immune effector cells in the tumor, thus enabling the immune system to attack the tumor.

The MAPK pathway is also associated with the production of transforming growth factor-beta (TGFβ) by malignant cells, which through paracrine signaling has been linked to the induction of CD4+ CD25+ FoxP3+ T regulatory cells (Tregs) implicated in the tumor immune escape mechanism. Although not essential for the generation of Tregs, there is accumulating evidence that the TGFβ proteins are essential for the function and survival of induced Treg cells (Hossain et al. 2015).

Inhibition of the MAPK pathway has focused on the suppression of targets, such as MEK1 and MEK2, within this signaling network. There are multiple upstream activating signals but multiple pathways exist to bypass their inhibition and still activate extracellular signal-regulated kinase 1 and 2 (ERK1 and ERK2). ERK1 and ERK2 can only be activated and phosphorylated by MEK1 and MEK2, which therefore render MEK1 and MEK2 as key signaling nodes for therapeutic inhibition of the MAPK pathway.

Cobimetinib is a potent and highly selective non-ATP competitive inhibitor of MEK. Cobimetinib inhibits the phosphorylation of ERK1/2 and causes inhibition of proliferation and induction of apoptosis in BRAF mutant melanoma cell lines.

1.3 THE ANTI-APOPTOTIC SIGNALLING PATHWAY

Resistance to cell death is a hallmark of the cancer cell and a relevant biological feature that gives the tumor cells a competitive advantage over normal cells. The equilibrium of pro- and anti-apoptotic signals is disrupted in malignant diseases. Bcl-2, along with closely related proteins (Bcl-xL, Bcl-w, Mcl-1, A1) are inhibitors of apoptosis, acting in large part by binding to and thereby suppressing the proapoptotic triggering Bcl-2 homologue (BH)3 proteins (Bid, Bad, Bim, Bik, Bmf, Noxa, Puma, and Hrk; Taylor et al. 2008).

Bcl-2 family proteins are crucial regulators of MM cell survival and therefore represent attractive therapeutic targets (Punnoose et al. 2016). Venetoclax is a potent and selective small-molecule Bcl-2-selective BH3 mimetic. Venetoclax induces cell death in

MM cell lines in vitro and primary MM samples ex vivo. Certain genetic subtypes of MM cells are particularly sensitive to venetoclax, including those bearing the recurrent chromosomal translocation t(11;14), which results in a high ratio of Bcl-2 to Mcl-1 and resistance to apoptosis (Kumar et al. 2015).

1.4 THE PROGRAMMED T-CELL DEATH LIGAND PATHWAY

Encouraging clinical data in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against malignant diseases can result in significant survival benefit in patients with disseminated disease (Hodi and Dranoff 2010; Kantoff et al. 2010). Therefore, immune modulation represents a promising new strategy for cancer therapy that may result in improved anti-tumor activity.

PD-L1 is commonly expressed in many human tumors (e.g., lung, ovarian, melanoma, and colon carcinoma), and its overexpression has been associated with poor prognosis in some cancers (Thompson et al. 2006; Hamanishi et al. 2007; Ozaki and Honjo 2007; Hino et al. 2010). In a large number of patients with plasma cell dyscrasias including MM it has been shown that PD-L1 is commonly and broadly expressed on the patients' plasma cells (Yousef et al. 2015), while the expression of the PD-L1 receptor, PD-1, is upregulated on T cells isolated from patients with MM (Rosenblatt et al. 2011). These results indicate the importance of the PD-L1/PD-1 pathway in the biology of plasma cell dyscrasias including MM.

PD-L1 is one of two ligands (PD-L1 and PD-L2) that bind PD-1. The PD-1 receptor is an inhibitory receptor expressed on T cells following T-cell activation in states of chronic activation, such as chronic infection or cancer (Blank et al. 2005; Keir et al. 2008). Binding of PD-L1 to PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity thus leads to functional inactivation of T cells. Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, which results in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to enhance tumor-specific T-cell immunity.

Therapeutic targeting of PD-L1 or PD-1 results in strong and often rapid anti-tumor effects in several mouse tumor models (Iwai et al. 2002; Strome et al. 2003) and also demonstrates clinical activity with drugs such as atezolizumab (Besse et al. 2015; Rosenberg et al. 2015; Vansteenkiste et al. 2015).

Atezolizumab is a humanized IgG1 monoclonal antibody (mAb) that targets PD-L1 by altering interaction with its receptors, PD-1 and B7-1 (also known as CD80). Both of these interactions provide inhibitory signals to T cells. Atezolizumab was engineered with a modified Fc domain to eliminate the antibody–dependent cellular cytotoxicity at clinically relevant doses, which prevents the depletion of activated T cells (Herbst et al. 2014).

1.5 BACKGROUND ON COBIMETINIB

Cobimetinib is a potent and selective inhibitor of MEK1 and MEK2. Cobimetinib (Cotellic®) is approved for use with vemurafenib for the treatment of advanced BRAF V600 mutated melanoma in the European Union, United States, and Switzerland, as well as other countries.

1.5.1 Summary of Nonclinical Studies with Cobimetinib

Cobimetinib inhibits proliferation of a variety of human tumor cell lines through inhibition of MEK1 and MEK2. In addition, cobimetinib inhibits ERK1 and ERK2 phosphorylation and induces apoptosis in xenograft tumor models. Cobimetinib accumulates in tumor xenografts and remains at high concentrations in the tumor after plasma concentrations have declined. The activity of cobimetinib to inhibit ERK1 phosphorylation is more closely correlated with its concentration in tumor tissue than in plasma; in general, there is a good correlation between reduced ERK1 phosphorylation and efficacy in tumor xenograft models. Tumor regression has been observed in several human tumor xenograft models. This regression was dose dependent with up to 100% regression at the highest doses tested. The models studied included colorectal cancer (CRC), malignant melanoma, breast carcinoma, and lung carcinoma.

A characterization of the pharmacologic and pharmacokinetic (PK) properties of cobimetinib was performed in a series of nonclinical studies. The nonclinical toxicity of cobimetinib was characterized in single- and repeat-dose toxicology studies in rats and dogs, in vitro genotoxicity studies, embryolethality/teratogenicity studies in rats, and nonclinical cardiovascular, neuro-behavioral, and respiratory safety pharmacology studies. Additional information on nonclinical studies is summarized in the Cobimetinib Investigator's Brochure.

1.5.2 Summary of Clinical Study with Cobimetinib Monotherapy

As of August 2016, cobimetinib had been administered alone or in combination with other agents to more than 1000 adult patients with cancer and approximately 120 healthy volunteers in 24 clinical trials; the vast majority of patients had been treated with cobimetinib plus other agents, such as vemurafenib. These included 2 trials of cobimetinib as a single agent, 7 clinical pharmacology studies, and 15 trials of cobimetinib in combination with other agents.

Cobimetinib monotherapy was assessed in Study MEK4592g, a Phase I, non-randomized, open-label, safety and PK dose-escalation study. The study was conducted in patients with metastatic or unresectable solid tumors for which standard curative or palliative measures did not exist or were no longer effective. A total of 115 patients were treated, and the study has been completed.

The study consisted of five treatment stages:

- Stage I: Dose-escalation cohorts; patients were treated on a 21-days-on, 7-days-off (21/7) schedule to determine the maximum-tolerated dose (MTD).
- Stage IA: Dose-escalation cohorts; patients were treated on a 14-days-on, 14-days-off (14/14) schedule to determine the MTD on an alternate dosing regimen.
- Stage II: Expansion cohort with the MTD determined in Stage I (60 mg once a day [QD] 21/7) in patients who harbored a BRAF, NRAS, or KRAS mutation.
- Stage IIA: Expansion cohort with the MTD determined in Stage IA (100 mg QD 14/14) in patients harboring a BRAF, NRAS, or KRAS mutation.
- Stage III: A dedicated drug-drug interaction study at the MTD determined in Stage I (60 mg QD 21/7) in approximately 20 patients with solid tumors.

Adverse Events

All patients in Study MEK4592g experienced an adverse event. The most frequent adverse events were diarrhea (67.0%), fatigue (50.4%), rash (49.6%), nausea and vomiting (33.9% each), and peripheral edema (28.7%). Other events that occurred in $\geq$10% of patients included anemia, abdominal pain, constipation, hypokalemia, decreased appetite, headache, dizziness, back pain, increased AST, dermatitis acneiform, pruritus, and dry skin. Among the patients who received cobimetinib 60 mg QD 21/7, the most frequent treatment-emergent adverse events were diarrhea (64.4%), rash (53.3%), fatigue (48.9%), nausea and peripheral edema (31.1% each), and vomiting (28.9%).

Grade $\geq$ 3 Adverse Events

Among all cobimetinib-treated patients, 5 patients (4.3%) experienced a Grade 4 adverse event, and 53 patients (46.1%) experienced a Grade 3 adverse event. The most frequent Grade 3 and Grade 4 adverse events were hyponatremia (9.6%), fatigue (8.7%), anemia (7.8%), and diarrhea (6.1%) and hypokalemia (6.1%).

Serious Adverse Events

A total of 49 patients (42.6%) experienced a serious adverse event. The most common types of serious adverse events were gastrointestinal disorders (n = 17), but there were no trends in specific preferred terms. The gastrointestinal serious adverse events, such as intestinal obstructions and gastrointestinal hemorrhages, occurred in patients with gastrointestinal malignancies. Serious adverse events reported for more than 2 patients among all patients in the study were anemia, bile duct obstruction, dehydration, syncope, and respiratory arrest (3 patients each [2.6%]).

Efficacy

Best overall response (BOR) was assessed for 74 of 97 patients in Stages I, IA, II, and IIA. Overall 6 patients (all of whom had melanoma; 6.2%) had a confirmed partial response (PR), 28 patients (28.9%) had stable disease (SD), and 40 patients (41.2%) had progressive disease (PD). Out of the 14 CRC patients, all patients experienced PD.

In Stage III of Study MEK4592g, 18 patients were enrolled and BOR was assessed for 14 of 18 patients. Four patients (22.2%) had SD as their BOR, and 2 patients (11.1%) had unconfirmed tumor responses.

A recent case report refers to a young patient with a highly resistant MM harboring the BRAF V600E mutation in Exon 15 (c.1799T>A) who was treated with the combination of vemurafenib and cobimetinib. The patient achieved at least a very good partial response (VGPR) but declined bone marrow biopsy to confirm complete response (CR) and remained in remission at the time of the publication (Mey et al. 2016).

For additional data, including the complete safety profile of cobimetinib and data from clinical studies with cobimetinib administered as a single agent or in combination with other anti-cancer agents, refer to the Cobimetinib Investigator's Brochure.

1.5.2.1 Clinical Pharmacokinetics of Cobimetinib

The pharmacokinetics of cobimetinib administered as a single agent have been characterized in patients with cancer following oral (PO) administration after single and multiple dosing in the Phase Ia dose-escalation Study MEK4592g. Additionally, clinical pharmacology studies have been conducted in healthy volunteers to determine the absolute bioavailability, effect of food, and effect of proton-pump inhibitor on cobimetinib pharmacokinetics.

Cobimetinib has a mean terminal elimination half-life of 43.6 hours. Cobimetinib exposure (area under the concentration–time curve [AUC] at steady state and maximum observed concentration at steady state [C_{max}]) was dose-proportional across the dose range of 0.05 mg/kg (3.5 mg for a 70-kg adult) to 100 mg (clinically relevant dose range) following PO administration. Cobimetinib binds to plasma proteins (95%) in a concentration-independent manner.

Cobimetinib is extensively metabolized by CYP3A, and to a lesser extent by UGT2B7, and eliminated in feces with minimal renal elimination. In vitro data showed that cobimetinib is a CYP3A and CYP2D6 inhibitor; however, clinical studies showed no PK interaction with probe substrates of CYP3A or CYP2D6. Cobimetinib can be administered without regard to food, proton-pump inhibitors, or other acid-reducing agents. Concomitant administration of strong CYP3A inhibitors with cobimetinib should be avoided if possible and may require dose reduction for cobimetinib. Cobimetinib may be co-administered with weak CYP3A inhibitors without any dose adjustment, while caution should be exercised when administering moderate inducers and inhibitors with cobimetinib.

Cobimetinib is a substrate of the efflux transporter P-glycoprotein but does not appear to inhibit P-glycoprotein or the uptake transporters (OATP1B1, OATP1B3, or OCT1) at clinically relevant concentrations.

Cobimetinib monotherapy did not result in prolongation of the corrected QT interval. Cobimetinib pharmacokinetics were not affected in patients with mild (n151) and moderate (n=48) renal impairment based on population PK analysis.

For details on the cobimetinib clinical pharmacokinetics or further clinical information on cobimetinib as monotherapy or with other anti-cancer agents, see the Cobimetinib Investigator's Brochure.

1.6 BACKGROUND ON VENETOCLAX

1.6.1 Summary Nonclinical Studies with Venetoclax

Venetoclax is a potent and selective small-molecule inhibitor of Bcl-2 that binds with >1,000-fold higher affinity for Bcl-2 (inhibitor constant [K_i] < 0.010 nM) than for Bcl-XL (K_i = 48 nM) or Mcl-1 (K_i > 444 nM) (Souers et al. 2013). In vitro, venetoclax has demonstrated activity against patient-derived chronic lymphocytic leukemia (CLL) cells and a variety of lymphoma and leukemia cell lines (Souers et al. 2013).

A characterization of the pharmacologic and PK properties of venetoclax was performed in a series of nonclinical studies. The nonclinical toxicity of venetoclax was characterized in single- and repeat-dose toxicology studies in rat and dog, in vitro genotoxicity studies, and nonclinical cardiovascular, neuro-behavioral, and respiratory safety pharmacology studies.

Venetoclax demonstrated high protein binding to human, rat, dog, and monkey plasma proteins (> 99.9%). Blood to plasma ratios showed that venetoclax does not partition preferentially into the RBCs. Following PO administration of venetoclax to nonclinical species and humans, parent compound and metabolites were cleared mainly via biliary excretion and fecal elimination, with minimal renal clearance. In humans, M27 was identified to be a major human disproportionate metabolite.

In vitro, venetoclax is metabolized by CYP3A. It is a weak inhibitor of UGT1A1, CYP2C9, and CYP2C8 in vitro, but it is not predicted to cause clinically relevant inhibition due to high plasma protein binding. Venetoclax is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP3A4 at clinically relevant concentrations. Venetoclax is a substrate of the efflux transporters P-glycoprotein 1 (Pgp) and breast cancer resistance protein (BCRP). Venetoclax is a Pgp, BCRP, and weak OATP1B1 inhibitor in vitro. Venetoclax does not appear to be an in vitro substrate for the human OATP isoforms, 1B1 or 1B3, or OCT1. Venetoclax is not an inhibitor of UGT1A4, UGT1A6, UGT1A9, or UGT2B7.

Additional information on nonclinical studies for venetoclax is summarized in the Venetoclax Investigator's Brochure.

1.6.2 Summary of Clinical Data for Venetoclax

As of 28 November 2016, on the basis of data available in the AbbVie and Genentech/Roche clinical databases, a total of 2759 patients have been exposed to at least one dose of venetoclax in the oncology and immunology development programs.

A total of 2534 oncology patients had data available in AbbVie and Genentech/Roche studies as of 28 November 2016. Of the 2534 patients, 1435 patients had CLL/small lymphocytic leukemia (SLL), 626 patients had non-Hodgkin lymphoma (NHL), 178 patients had MM, and 295 patients had acute myeloid leukemia (AML). An additional 127 participants were healthy volunteers. A total of 663 oncology patients received the drug as monotherapy, 1871 patients received the drug in combination with other therapies, and 1 patient received venetoclax as a single dose in a drug-drug interaction study and did not re-enroll in a subsequent monotherapy study. Additionally, 98 patients had been exposed to at least one dose of venetoclax in the AbbVie immunology study, M13-093, as of 28 November 2016.

Two clinical studies for venetoclax have been conducted in the MM indication, one with venetoclax as single agent and the other study with venetoclax in combination with bortezomib and dexamethasone. Two additional venetoclax studies are currently ongoing: a Phase II study in combination with carfilzomib and dexamethasone, and a Phase III in combination with bortezomib and dexamethasone.

Study M14-031 (BELLINI) is an ongoing Phase III, multicenter, randomized, double-blind study of bortezomib and dexamethasone in combination with either venetoclax or placebo in patients with relapsed and refractory (R/R) MM who are sensitive or naive to PIs. The study has been unblinded, as per protocol, for the final analysis of the primary efficacy endpoint. As of the data cut-off date of 26 November 2018, 194 patients were randomly assigned to the venetoclax arm and 97 patients to the placebo arm (2:1 randomization). The study met its primary endpoint of progression-free survival (PFS) (median 22.4 versus 11.5 months, HR 0.63, 95% CI: 0.44 to 0.90) and showed statistically significant improvements in overall response rate (ORR) (82% versus 66%) and very good partial response or better (59% versus 36%) in the venetoclax arm compared with the control arm. However, there were 51 deaths in the safety analysis set, 40 (20.7%) in the venetoclax arm and 11 (11.5%) in the placebo arm (median ~~OS~~ overall survival [OS] has not been reached in either arm). The imbalance was predominantly seen in the treatment-emergent deaths, i.e., those occurring on therapy or within 30 days after the last dose of therapy. Among the 14 treatment-emergent deaths reported, 13 (6.7%) were in the venetoclax arm and 1 (1.0%) in the placebo arm. Of the 13 treatment-emergent deaths in the venetoclax arm, 8 were attributed by investigator to an event of infection, with $>$ 50% also in the setting of refractory or progressive disease. Although the majority of infection-related deaths occurred within 180 days of starting study treatment, some have occurred later, even after a year or more on treatment.

A higher rate of Grade 3 or 4 neutropenia was observed in the venetoclax arm compared with the placebo arm, but an association of infection-related deaths with neutropenia has not been established at this point. Among the 37 non–treatment-emergent deaths (those occurring more than 30 days after the last dose of study treatment), 27 (14.0%) were in the venetoclax arm (6 deaths attributed to infection, 3.1%), and 10 (10.4%) in the placebo arm (2 deaths attributed to infection, 2.1%). Additional deaths were reported in the BELLINI study after the data cut-off of 26 November 2018. As of 1 March 2019, there were 65 deaths in the safety analysis set, 48 (24.7%) in the venetoclax arm and 17 (17.5%) in the placebo arm.

Summarized data on venetoclax studies in the MM indication are shown in Table 1. For more detailed clinical information on venetoclax, refer to the Venetoclax Investigator's Brochure.

Table 1 Summary of Clinical Studies with Venetoclax in Patients with Multiple Myeloma

Study	Study Title	Dosage Regimen	No. of Patients
M13-367	A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects with Relapsed or Refractory Multiple Myeloma	Escalating doses of venetoclax were given daily at 300, 600, 900, or 1200 mg. The 1200-mg dose is being evaluated in the in the safety expansion cohort.	66 (enrolled)
		A combination cohort is exploring venetoclax and dexamethasone in subjects with R/R MM positive for t(11;14).	9 (enrolled)
M12-901	A Phase 1b Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Relapsed or Refractory Multiple Myeloma Subjects Who Are Receiving Bortezomib and Dexamethasone as Their Standard Therapy	Escalating doses of daily venetoclax (50–1200 mg), combined with bortezomib (1.3 mg/m^2 SC) and dexamethasone (20 mg PO)	66 (enrolled)
M14-031	A Phase 3, Multicenter, Randomized, Double-Blind Study of Bortezomib and Dexamethasone in Combination with Either Venetoclax or Placebo in Subjects with Relapsed or Refractory Multiple Myeloma Who Are Sensitive or Naïve to Proteasome Inhibitors	Oral daily dose of either venetoclax 800 mg plus bortezomib 1.3 mg/m^2 and dexamethasone 20 mg or placebo plus bortezomib and dexamethasone	194 (venetoclax arm), and 97 (placebo arm)
M15-538	A Phase 2, Open-Label, Dose-Escalation Study to Evaluate the Safety and Efficacy of Venetoclax in Combination with Carfilzomib-Dexamethasone (Kd) in Participants with Relapsed or Refractory MM and Have Received 1 to 3 Prior Lines of Therapy.	Venetoclax tablet administered orally once daily during Cycles 1–18. Two dose levels of venetoclax 400 mg once daily or 800 mg once daily.	NA

NA = not applicable. PO = orally; R/R MM = relapsed/refractory multiple myeloma.

1.6.3 Venetoclax Clinical Pharmacology and Pharmacokinetics

Venetoclax clinical pharmacology is being evaluated in several Phase I to III clinical trials, and preliminary data are available from three Phase I studies (M12-175, M13-367, M12-630), four Phase Ib studies (M13-365, M12-901, GO29440, GP28331), one Phase II study (M14-212), and five dedicated clinical pharmacology studies (M13-364, M14-497, M13-363, M14-253, M15-101).

The venetoclax formulation being used in clinical trials is a tablet formulation in strengths of 10, 50, and 100 mg. After a single dose in CLL/SLL patients, after a low-fat meal, venetoclax plasma concentrations peaked at approximately 6 hours after dosing. The mean harmonic terminal-phase elimination half-life ($t_{1/2}$) of venetoclax was approximately 17 hours, and the mean oral clearance was approximately 13 L/hr. No accumulation was seen after repeated QD administration of venetoclax over the 100- to 800-mg QD dose range in CLL/SLL patients. Preliminary data from CLL/SLL patients suggested that venetoclax AUC was approximately dose-proportional across the 150- to 1200-mg dose levels at steady state. Preliminary data did not suggest apparent PK differences among patients with CLL/SLL, NHL, MM, or AML. Low-fat and high-fat meals increased the venetoclax exposure compared with fasting in healthy volunteers by approximately 3.4- and 5.1-fold, respectively. Venetoclax should always be given after a low-fat meal.

Venetoclax is eliminated almost entirely through the hepatic route via metabolism by CYP3A enzymes. Specific recommendations are provided for co-administration of venetoclax with moderate and strong inhibitors and inducers of CYP3A (see Section 4.4.4). Venetoclax does not appear to be a clinically significant inhibitor of CYP2C9.

Preliminary results from a dose- and exposure-response analysis based on Study M12-175 data indicate that there is no relationship between venetoclax dose or exposure and QT interval corrected using Fridericia's formula for doses up to 1200 mg (8 μg/mL plasma concentrations) of venetoclax.

For details on the clinical pharmacokinetics of venetoclax, see the Venetoclax Investigator's Brochure.

1.6.4 Clinical Safety Data for Venetoclax

As of the clinical data cutoff date of 28 November 2016, data on venetoclax monotherapy in patients with R/R MM come from Study M13-367. This study includes a dose-escalation portion and an expanded safety cohort portion. Sixty-six patients have been enrolled in Study M13-367 in the dose-escalation and safety expansion cohorts of venetoclax monotherapy, and 9 patients were enrolled in the combination with dexamethasone cohort.

Most patients (96.0%) in Study M13-367 experienced at least one treatment-emergent adverse event. The most common treatment emergent adverse events were nausea (41.3%), diarrhea (34.7%), fatigue (24.0%), and anemia and platelet count decreased (21.3% each). Over half (62.7%) of patients experienced events Grade 3 or above; the most common events were platelet count decreased (16.0%), and anemia and neutrophil count decreased (13.3% each).

Serious adverse events were reported in 26 (34.7%) patients, including events of pneumonia and malignant neoplasm progression (6 patients each), sepsis (3 patients), and anemia, pain, pyrexia, cough, and hypotension (2 patients each). All other events occurred in 1 patient each.

In Study M12-901 escalating doses of venetoclax are administered with bortezomib and dexamethasone in patients with R/R MM. Most (98.5%) patients experienced at least one treatment-emergent adverse event. The most common adverse events were diarrhea (45.5%); constipation (42.2%); thrombocytopenia (39.4%); nausea (36.4%); neuropathy peripheral and insomnia (33.3% each); anemia; edema peripheral and peripheral sensory neuropathy (27.3% each); and asthenia, fatigue, and dyspnea (24.2% each).

Fifty-five (83.3%) patients experienced events Grade 3 or above; the most common event was thrombocytopenia in 20 (30.3%) patients.

Serious adverse events were reported in 36 (54.5%) patients, including pneumonia (5 patients); pyrexia (4 patients); febrile neutropenia, influenza, and sepsis (3 patients); and thrombocytopenia, cardiac failure, disease progression, lower respiratory tract infection, respiratory failure, hypoxia, hypotension and pulmonary embolism (2 patients each). All other events occurred in 1 patient each.

Tumor lysis syndrome (TLS) is an important risk identified particularly in patients with R/R CLL but has not been observed in patients with MM.

Refer to the Venetoclax Investigator's Brochure for further information on the clinical safety of venetoclax.

1.7 BACKGROUND ON ATEZOLIZUMAB

1.7.1 Summary of Nonclinical Studies with Atezolizumab

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

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

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

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

1.7.2 Clinical Experience with Atezolizumab Monotherapy

1.7.2.1 Ongoing Clinical Studies

Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as a single agent and in combination with several anti-cancer therapies (see the Atezolizumab Investigator's Brochure for study descriptions). Much of the safety and efficacy data summarized below is from the Phase I Study PCD4989g, a multicenter, first-in-patient, open-label, dose-escalation study to evaluate the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence for biological activity of atezolizumab administered as a single agent by IV infusion to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.

1.7.2.2 Clinical Safety of Atezolizumab

As of 17 May 2017, approximately 11,000 patients with solid tumor and hematologic malignancies have received atezolizumab in clinical studies as a single agent or in combination with cytotoxic chemotherapy and/or targeted therapy.

Safety findings of single-agent atezolizumab across multiple tumor types in the clinical development program are consistent with the known mechanism of action of atezolizumab and the underlying disease. Overall, treatment with atezolizumab is well tolerated, with a manageable adverse event profile. Currently, no MTD has been determined, no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of adverse events have been observed. Among 2160 patients treated with single-agent atezolizumab for whom pooled safety data are available, the most commonly reported adverse events (i.e., ≥10%) include fatigue, decreased appetite, cough, nausea, dyspnea, constipation, diarrhea, pyrexia, vomiting, arthralgia, back pain, asthenia, anemia, pruritus, rash, headache, and peripheral edema.

The adverse events observed with atezolizumab in combination with chemotherapy and/or targeted therapies are consistent with the known risks of each study treatment.

Adverse events were comparable between patients who received atezolizumab monotherapy and those who were treated with atezolizumab in combination with targeted therapy and/or chemotherapy. For example, the percentage of patients who experienced an adverse event among a pooled population of 2160 patients with metastatic urothelial carcinoma (mUC) and NSCLC, who received single-agent atezolizumab, was 95.4%, compared with 98.7% in Study GP28328, in which atezolizumab is used in combination with chemotherapy. Similarly, serious adverse

events occurred at rates of 38.5% among the mUC/NSCLC pool and 45.0% among patients in GP28328, and rates of adverse events leading to discontinuation of atezolizumab due to any adverse event were 6.6% among the UC/NSCLC, and 8.3% in Study GP28328. Rates of treatment-related Grade 5 adverse events were also similar in these populations (0.2% in the pooled UC/NSCLC population and 0.9% in Study GP28328).

Immune-Mediated Adverse Events

Immune-mediated adverse events are consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance. Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated adverse events are closely monitored during the atezolizumab clinical program. Immune mediated adverse events associated with atezolizumab include hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, and meningoencephalitis.

Refer to the Atezolizumab Investigator's Brochure for additional details on the safety profile of the agent.

1.7.3 Atezolizumab Clinical Pharmacology and Pharmacokinetics

The key PK findings from the above-listed atezolizumab monotherapy clinical studies are summarized below:

- The pharmacokinetics of atezolizumab monotherapy have been characterized in patients in Study PCD4989g at doses 0.01 mg/kg to 20 mg/kg every 3 weeks (Q3W), including the fixed dose 1200 mg (equivalent to 15 mg/kg). Exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg. While a subset of ATA-positive patients in Study PCD4989g receiving 0.3 to 3 mg/kg atezolizumab Q3W experienced a reduction of atezolizumab *minimum concentration under steady-state conditions within a dosing interval* (C_{min}) to below the PK assay lower limit of quantification, patients receiving 10 to 20 mg/ kg atezolizumab, including the fixed 1200 mg dose, maintained geometric mean C_{min} that was in excess of both the lower limit of quantification and the target serum concentration of 6 μg/mL (Deng et al. 2016).
- A Phase I *population pharmacokinetics* (popPK) analysis that included 472 patients from Studies PCD4989g and JO28944 described atezolizumab pharmacokinetics for the dose range 1–20 mg/kg with a linear two-compartment disposition model with first-order elimination. The popPK analysis indicated that central compartment volume of distribution (V_1) was 3.28 L and the volume of distribution under steady–state conditions (V_{ss}) was 6.91 L in the typical patient. Further, the *clearance* (CL) of atezolizumab was 0.20 L/day and the $t_{1/2}$ was 27 days. Steady–state was obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in AUC, C_{max}, and C_{min} was 1.91, 1.46, and 2.75-fold, respectively.

- Based on an analysis of exposure, safety, and efficacy data, the following factors had no clinically relevant effect: age (21–89 years), body weight, gender, positive ADA status, albumin levels, tumor burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or Eastern Cooperative Oncology Group (ECOG) performance status.
- The effect of moderate or severe hepatic impairment (bilirubin > *upper limit of normal* [ULN] and AST > ULN or bilirubin ≥ 1.0 to 1.5 × ULN and any AST elevation) on the pharmacokinetics of atezolizumab is unknown.
- No formal PK drug-drug interaction studies have been conducted with atezolizumab. The drug interaction potential of atezolizumab is unknown.

For more information, refer to the Atezolizumab Investigator's Brochure.

1.7.3.1 Clinical Activity of Atezolizumab

As of 17 May 2017, efficacy data were most extensive for patients with NSCLC (1651 patients enrolled in Studies GO28754 [BIRCH], GO28753 [POPLAR], GO28915 [OAK], GO28625 [FIR], and the NSCLC cohort of PCD4989g) and patients with mUC (524 efficacy-evaluable patients in studies PCD4989g and GO29293 [IMvigor 210]) who were administered atezolizumab as a single agent.

Efficacy parameters ORR in Cohort 1 and ORR, PFS, and OS in Cohort 2 observed in the Phase II IMvigor 210 study as of the clinical cutoff date of 4 July 2016 after an additional 10 months, and 14 months of follow-up (Cohorts 1 and 2, respectively) were consistent with those obtained at primary analyses of each cohort. Similar response rates and consistency between primary and updated analyses were seen in the mUC cohort of Study PCD4989g. In both studies, higher ORR results in the *immune cell* (IC) 2/3 expression group suggest that higher levels of PD-L1 expression on ICs may be associated with increased benefit.

The results from the five studies evaluating atezolizumab as monotherapy in patients with locally advanced or metastatic NSCLC (PCD4989g, FIR, OAK, POPLAR, and BIRCH, single-agent treatment with atezolizumab resulted in clinically meaningful OS improvement in the 2L/3L NSCLC ITT population, compared with standard of care, in both non-squamous and squamous histologies, and across all PD-L1 expression subgroups. Higher PD-L1 expression on *tumor cell* (TC)s or ICs was associated with higher ORRs and longer median PFS and OS duration. Responses were highly durable across all PD-L1 expression groups.

On 18 May 2016, atezolizumab (Tecentriq®) was granted accelerated *(U.S.)* Food and Drug Administration (FDA) approval for the treatment of patients with locally advanced or metastatic UC who have received prior platinum-containing chemotherapy. On 18 October 2016, FDA approved atezolizumab for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy.

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

1.8 CLINICAL EXPERIENCE OF COBIMETINIB PLUS ATEZOLIZUMAB

Study GP28363 is a Phase Ib, open-label, multicenter study designed to assess the safety, tolerability, and pharmacokinetics of cobimetinib plus atezolizumab in patients with advanced solid tumors.

The study has two stages: Stage 1 (dose escalation) and Stage 2 (expansion). Stage 1 is designed to establish the combination MTD for cobimetinib plus atezolizumab. In Stage 2, the recommended Phase II dose and schedule were investigated in tumor-specific expansion cohorts: KRAS-mutant metastatic CRC, NSCLC, and metastatic melanoma.

In the Stage 1 dose-escalation phase, there were no DLTs, and the combination of 60 mg cobimetinib 21/7 and 800 mg atezolizumab every 2 weeks (Q2W) was determined to be the recommended Phase II dose.

As of 17 January 2017, a total of 150 patients were accrued and evaluable for safety. The most frequently observed adverse events (≥30%) were diarrhea (70.7%), fatigue (56%), rash (48%), vomiting (42%), nausea (36%), pruritus (35.3%), decreased appetite (34.7%), and constipation (29.3%). Adverse events assessed as related to atezolizumab were reported in 117 patients (78%). The most common such adverse events (i.e., ≥10%) were fatigue (30.7%), diarrhea (28%), pruritus (14%), rash (13.3%), nausea (12.7%), and pyrexia (10%).

These findings are consistent with the known adverse event profiles for atezolizumab and cobimetinib and did not represent additive toxicity.

Grade 3-4 adverse events were observed in 96 (64%) of the patients, and the most common (≥ 2.7% or ≥ 4 patients) included fatigue (10%), anemia (9.3%), diarrhea (8%), abdominal pain (5.3%), rash and blood creatinine phosphokinase increased (4.7% each), dyspnea and aspartate aminotransferase increased (4% each), amylase increased and hypertension (3.3% each), and ascites, vomiting, peripheral edema, asthenia, pleural effusion, pulmonary embolism, blood bilirubin increased, neutrophil count decreased, and hypophosphatemia (2.7% each). Most of the Grade 3-4 adverse

events considered related to atezolizumab were single reports except for rash and fatigue (2.7% each), asthenia, diarrhea, amylase increased, and lipase increased (2% each), and nausea, vomiting, dermatitis acneiform, aspartate aminotransferase increased, neutrophil count decreased, and dyspnea (1.3% each).

Seven patients (4%) were reported to have had Grade 5 adverse events. The following events led to death in 7 patients (4.7%): pneumonia, large intestine perforation, small intestinal perforation, sepsis, road traffic accident, and respiratory failure. The event of sepsis was the only Grade 5 event considered related to atezolizumab. In this case, the patient had a medical history of infectious disease (right temporal lobe abscess).

Refer to the Cobimetinib and Atezolizumab Investigator's Brochures for details on safety data from Study GP28363.

1.9 CLINICAL DATA OF COBIMETINIB PLUS VENETOCLAX

Study GH29914 is an ongoing, Phase Ib/II multi-arm study in which venetoclax is combined with either cobimetinib or idasanutlin as first-line therapy for patients with R/R AML who are ≥65 years of age and not eligible for standard induction therapy.

As of 21 June 2019, the Phase Ib dose-escalation stage for the venetoclax plus cobimetinib arm is fully accrued, and 30 patients have safety data available across the four venetoclax plus cobimetinib treatment cohorts.

Of the 30 patients treated with venetoclax plus cobimetinib, all patients (100%) reported at least one treatment emergent adverse event. The most frequent treatment emergent adverse events (reported in ≥30% of patients overall) included diarrhea (76.7%), nausea (60.0%), febrile neutropenia (40.0%), vomiting (36.7%), fatigue (36.7%), constipation (33.3%), and edema peripheral (30.0%). All, except 1 patient experienced treatment emergent adverse events considered related to study treatment (venetoclax, cobimetinib, or both).

Grade 3 or 4 treatment emergent adverse events reported in ≥10% of patients treated with venetoclax plus cobimetinib included febrile neutropenia (40.0%); diarrhea (36.7%); anemia and pneumonia (16.7% each); lung infection, sepsis, hypokalemia, and thrombocytopenia (13.3% each); and ejection fraction decreased and decreased appetite (10.0% each). Of these, diarrhea was considered related to treatment in all patients (36.7%).

Serious adverse events were reported in 24 patients (80.0%) treated with venetoclax plus cobimetinib, of which 9 patients (30.0%) experienced serious adverse events considered related to study treatment (venetoclax, cobimetinib, or both). The most frequently reported serious adverse events (reported in ≥15% of patients overall) included febrile neutropenia (30.0%), and lung infection and sepsis (20.0% each).

Overall, 26 deaths (86.7%) have been reported as of the cutoff date of 21 June 2019. Of these, deaths due to adverse events were reported in 6 patients and included events of sepsis and lung infection (24 events, 6.7% each), and respiratory failure and lung disorder (1 event, 3.3% each). The event of lung disorder was considered by the investigator to be related to both venetoclax and cobimetinib. Twenty patients died due to disease progression.

The combination of venetoclax and cobimetinib will not proceed to the Phase II expansion stage due to unfavorable benefit–risk profile in this population of patients with AML who are not eligible for cytotoxic therapy. This was driven by Grade ≥ 3 events of diarrhea, which were noted to be higher than that reported for either study drug as a single agent, and higher overall mortality rate due to adverse events.

Caution should be given to the interpretation of the safety data generated in study GH29914, which should be analyzed in the context of the study population. Patients with R/R AML who are not eligible for cytotoxic therapy constitute a very fragile population. A high proportion of patients with acute leukemia invariably present with severe myelosuppression and cytopenias associated with infections that affect organ function and require hospitalization. The high frequency of clinical complications related to AML is an essential problem in clinical studies evaluating the toxicities of new agents in acute leukemias (Atallah et al. 2007; Avvisati et al. 2007).

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

1.10 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Despite recent advances, MM remains an incurable disease. Most patients eventually relapse and have shorter remissions with each additional line of therapy until refractory disease develops and the patient succumbs to the consequences of bone marrow failure or end-organ damage.

The estimated median survival is 6–7 years for patients with standard risk myeloma and 2–3 years for patients with high-risk disease (Kumar et al. 2014). The outcome for patients with MM after becoming refractory to PI or IMiD is quite poor with survival ≤ 1 year (Kumar et al. 2012; Usmani et al. 2016).

Therefore, there is a significant unmet medical need for patients with R/R MM, and new regimens with innovative mechanisms of action are highly needed.

1.10.1 Rationale for Evaluating Cobimetinib in Relapsed and Refractory Multiple Myeloma

The RAS/MAPK pathway is a key signaling pathway that regulates cell proliferation, cell-cycle regulation, cell survival, angiogenesis, and cell migration (Friday and Adjei 2008). The MEK1/2 proteins are central components of the MAPK pathway and MEK

inhibition is particularly efficacious in tumors harboring oncogenic mutations in the BRAF, KRAS, and NRAS genes.

The RAS/MAPK pathway is frequently dysregulated in MM, with NRAS, KRAS, or BRAF mutations being present in up to 50% of newly diagnosed MM cases (Heuck et al. 2016). Notably, there is no difference in the frequency of altered RAS/MAPK pathway genes between newly diagnosed and relapsed patients, in whom there is an increased average mutant allele frequency, indicating clonal selection (Heuck et al. 2015).

Recent reports have demonstrated that MM cases with BRAF V600E mutations can respond to the BRAF inhibitor vemurafenib, even in the autologous stem cell transplant double-refractory setting, suggesting that blocking the MAPK pathway can be effective, even in end-stage, genetically complex cases (Andrulis et al. 2013).

Heuck et al. (2016) reported a retrospective analysis of 58 patients with MM who were treated on a compassionate basis with the MEK inhibitor trametinib, as a single agent or in combination with other drugs. Patients were selected based on MAPK hyperactivation identified by comprehensive genomic profiling using the FoundationOne Heme assay. The median number of prior treatments was five.

In most cases, trametinib was started as a single agent and other agents were added during the course of the treatment. Of the 40 patients with measurable disease at time of trametinib initiation, 16 patients (40%) experienced a reduction of the measurable M-protein by at least 50%. This number (16 patients) was reduced to 4 patients when only considering the time on single-agent trametinib. The most significant adverse events were rash, diarrhea and cardiac toxicities (Heuck et al. 2016).

Selumetinib, a MEK1/2 inhibitor, was administered to patients with MM with a median number of prior therapies of 5 (range: 2–11). The most common toxicities included anemia, neutropenia, thrombocytopenia, diarrhea, and fatigue. The response rate (CR+PR) was 5.6% and the median PFS of 3.52 months. One patient with a multiple myeloma SET domain translocation had a VGPR, 1 patient had a PR, 17 patients had SD, 13 patients had PD, and 4 patients could not be assessed for response (Holkova et al. 2016).

Despite limited activity of previous MEK inhibitors administered as single agents in heavily pretreated patients, the anti-MM activity seems to be improved with the combination strategy even in the refractory setting. In this study, cobimetinib will be investigated for patients with MM, both as a single agent and in combination with either venetoclax or venetoclax plus atezolizumab.

1.10.2 Rationale for Evaluating Cobimetinib and Venetoclax, and Cobimetinib with Venetoclax and Atezolizumab in Relapsed/Refractory Multiple Myeloma

The Bcl-2 family protein members interact to prevent or induce apoptosis. "Activator" BH3-only proteins (Bid, Bad, Bim, Bik, Bmf, Noxa, Puma, and Hrk) directly interact with "effector" Bax and/or Bak, inducing the assembly of Bak/Bax multimeric pores in the mitochondrial membrane and triggering cellular apoptosis. Anti-apoptotic Bcl-2 family members (Bcl-2, Bcl-xL, Mcl-1, Bcl-w, BFL-1/A1) inhibit apoptosis by sequestering the activators and preventing engagement of Bax and Bak (Certo et al. 2006).

In the clinical setting, venetoclax administered as monotherapy has an acceptable safety profile in R/R MM. Preliminary efficacy shows significant anti-myeloma activity of venetoclax, particularly for MM harboring chromosomal translocation t(11;14) (Kumar et al. 2015; Punnoose et al. 2016). Bcl-2 inhibition is overcome by the overexpression of other pro-survival proteins such as Mcl-1 (Cragg et al. 2008; Punnoose et al. 2016). Antagonism of the action of pro-survival Bcl-2 proteins with a Bcl-2 inhibitor and enrichment of pro-apoptotic BH3-only proteins like Bim may be an effective strategy for overcoming the high levels of Bcl-2 and Mcl-1 to promote apoptosis and overcome resistance of tumor cells (Cragg et al. 2008). MEK inhibition prevents the phosphorylation of Bim by ERK, facilitating increased Bim expression. Thus, MEK inhibition offsets the prosurvival effect of Bcl-2 (VanBrocklin et al. 2009) and the combination of a MEK inhibitor and a Bcl-2 inhibitor potentially shifts the apoptotic and pro-survival signaling equilibrium in favor of apoptosis. Furthermore, this synergism is relevant in MM because hematologic malignancies are highly dependent on Bcl-2 overexpression and its anti-apoptotic effects.

Hence, the combination of cobimetinib plus venetoclax represents a strategy for inducing MM cell apoptosis by increasing Bim expression via MEK inhibition and by venetoclax-induced inhibition of Bcl-2. In preclinical models of acute leukemia, MEK inhibition synergizes with Bcl-2/Bcl-xL family inhibitors to suppress proliferation and induce apoptosis in leukemic cells. That synergism is mediated by the pro-apoptotic factor Bim, which is dephosphorylated as a result of MEK inhibition, allowing it to bind and neutralize MCL-1, thereby enhancing Bcl-2 inhibitor-induced cell death (Korfi et al. 2016). Cobimetinib plus venetoclax is being explored in a R/R AML clinical trial (Study GH29914) (see Section 1.9).

Historically, ERK signaling downstream MEK was synonymous with cell proliferation but it is now clear that deregulation of this pathway is linked to many other aspects of the tumor phenotype. MEK inhibition potentially enhances the anti-tumor activity of atezolizumab since the MAPK pathway plays an important role in immune evasion. Clinical and nonclinical data show a negative association between MEK activity and both active antigen presentation (MHC antigen expression) and PD-L1 expression (Ebert et al. 2016; Loi et al. 2016). Consistently, MEK inhibition results in an increased number of tumor-infiltrating CD8+ T lymphocytes and both enhanced PD-L1 and MHC

antigen expression (Ebert et al. 2016; Loi et al. 2016). These effects are responsible for the enhanced anti-tumor immune response observed with the combination of MEK inhibitors with agents targeting PD-L1/PD-1 (Loi et al. 2016). Additionally, induction of CD4+ CD25+ FoxP3+ Treg cells (which are implicated in tumor immune escape) depend on MAPK activity. Pharmacological inhibitors of MEK/ERK signaling inhibit the production of TGFβ, which induces the differentiation of CD4+ T-cells into Treg (Hossain et al. 2015). Consequently, the hyperactivated MAPK pathway has been identified as a potential target for increasing the CD8+ lymphocyte tumor infiltration, enhancing PD-L1 and MHC antigen expression, and reversing the Treg cell augmentation in patients with malignant diseases.

In the context of a pro-apoptotic state and a primed tumor microenvironment, the addition of atezolizumab to cobimetinib plus venetoclax may further enhance anti-tumor activity. Myeloma cells have preserved adaptive mechanisms of regulating PD-L1 expression in response to inflammatory cytokines (Liu et al. 2007). Moreover, direct interaction with stromal cells also upregulates PD-L1 expression in myeloma cells (Tamura et al. 2013). Notably, PD-L1 expression appears to be higher not only after relapse but also in more advanced disease (Stages 2–3 vs. Stage 1) (Tamura et al. 2013).

The triple combination of cobimetinib, venetoclax, and atezolizumab targets key features of cancer cell biology including proliferation, resistance to programmed cell death, and immune evasion (Hanahan and Weinberg 2011). The combination of a MEK inhibitor and a Bcl-2 inhibitor is supported by emerging insights into the molecular pathogenesis of MM, and the addition of atezolizumab may potentially further enhance the anti-myeloma immune response. Based on the significant unmet medical need for patients with R/R MM and the safety/efficacy profile of each agent, the Sponsor considers this study to have a favorable benefit-to-risk assessment for patients.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, tolerability, and pharmacokinetics of cobimetinib administered as a single agent, cobimetinib plus venetoclax, and cobimetinib plus venetoclax plus atezolizumab in patients with R/R MM. Specific objectives and corresponding endpoints are outlined below.

Table 2 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoints
• To evaluate the preliminary safety and tolerability and the preliminary efficacy of cobimetinib administered as single agent (Arm A), cobimetinib + venetoclax (Arm B), and cobimetinib + venetoclax + atezolizumab (Arm C)	• Incidence, nature, and severity of adverse events, graded according to NCI CTCAE, v4.0; laboratory data • ORR (sCR, CR, VGPR, PR) as determined by the investigator using the IMWG response criteria (Kumar et al. 2016) in the safety population and biomarker-selected population
Secondary Efficacy Objective	**Corresponding Endpoints**
• To further evaluate the efficacy of cobimetinib administered as single agent (Arm A), cobimetinib + venetoclax (Arm B), and cobimetinib + venetoclax + atezolizumab (Arm C)	• CBR defined as MR or better • PFS defined as the time from randomization to the first occurrence of disease progression or relapse as determined by the investigator using the IMWG criteria or death from any cause during the study, whichever occurs first • DOR applies to patients achieving at least a PR, and is measured from the first observation of PR to the time of disease progression; deaths not due to progression will be censored • OS defined as the time from randomization until death from any cause

Table 2 Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objective	Corresponding Endpoint
To evaluate the time elapsed before requiring the start of further anti-myeloma treatment	Time to next treatment defined as the time between the start date of the current treatment line and the start date of the next treatment line, death or last follow-up
Pharmacokinetic Objective	**Corresponding Endpoints**
• To characterize the pharmacokinetics of cobimetinib (Arm A), to characterize the pharmacokinetics of cobimetinib and venetoclax when administered together (Arm B), and to characterize the pharmacokinetics of cobimetinib, venetoclax, and atezolizumab when administered together (Arm C)	• Plasma concentration of cobimetinib and venetoclax at specified timepoints • Serum concentration of atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to atezolizumab administered in Arm C	• Incidence of ADAs during the study relative to the prevalence of ADAs at baseline
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the potential effects of ADAs	• Correlation between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objectives	**Corresponding Endpoints**
• To identify biomarkers that are predictive of response to cobimetinib, venetoclax, and atezolizumab, such as RAS mutation, t(11;14) translocation, Bcl-2 family proteins, and pretreatment immune contexture • Identification and profiling of biomarkers associated with disease biology; the mechanisms of action of cobimetinib alone (Arm A), cobimetinib + venetoclax (Arm B), or cobimetinib + venetoclax + atezolizumab (Arm C); mechanism of resistance to drugs in all the arms; pharmacodynamics; prognosis and improvement of diagnostic assays • Determine impact of MRD measurements with patient response and survival	• The effect of treatment with cobimetinib, venetoclax, and atezolizumab on markers of MAPK pathway activity, apoptosis, immune infiltration and activation • Determine impact of MRD measurements with patient responses and survival • Relationship between biomarkers in blood and bone marrow (may include somatic mutations, listed in Section 4.5.6) and efficacy, safety, pharmacokinetics, immunogenicity, or other biomarker endpoints.

ADA = anti-drug antibody; CBR = clinical benefit rate; CR=complete response; DOR = duration of response; IMWG = International Myeloma Working Group; MAPK = mitogen-activated protein kinase; MR = minimal response; MRD = minimal residual disease; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.

3. STUDY DESIGN

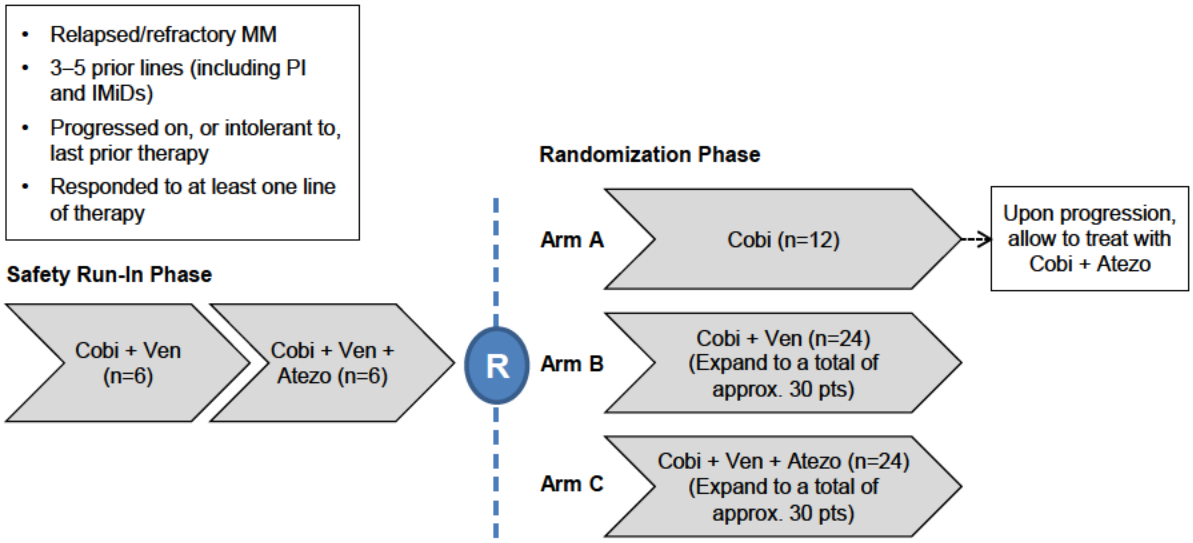
3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of the Study Design

This is an open-label, randomized, multicenter, triple-arm Phase Ib/II study designed to assess the efficacy, safety, tolerability, and pharmacokinetics of cobimetinib administered as a single agent (Arm A), cobimetinib plus venetoclax (Arm B), and cobimetinib plus venetoclax plus atezolizumab (Arm C) in patients with R/R MM.

Two successive cohorts will evaluate the safety of cobimetinib plus venetoclax (n=6) and that of cobimetinib plus venetoclax plus atezolizumab (n=6) in the selected population during the safety run-in phase of the study. Once the dose levels have demonstrated acceptable safety during this phase, randomization will begin for all treatment arms (Arms A, B, and C; see Figure 1).

Figure 1 Study Design Schema



Note: The numbers depicted for each part of the study are provided for the purposes of illustration and are therefore approximate only.
Atezo=atezolizumab; Cobi=cobimetinib; IMiD=immunomodulatory drug; MM=multiple myeloma; PI=proteasome inhibitors; pts=patients; R=randomization; Ven=venetoclax.

After written informed consent has been obtained, patients will undergo screening procedures as specified in Appendix 1 and described in Section 4.5. The schedule of activities to be performed during the study is provided in Appendix 1.

3.1.1.1 Safety Run-In Phase

Cobimetinib plus Venetoclax Safety Run-In Cohort

The cobimetinib plus venetoclax safety run-in cohort will enroll 6 patients with a starting dose of cobimetinib 40 mg PO daily on Days 1–21, plus venetoclax 800 mg PO daily on Days 1–28 of each 28-day cycle. This combination is currently being evaluated in an ongoing Phase Ib/II study (Study GH29914, a multi-arm study with venetoclax in combination with cobimetinib and venetoclax in combination with idasanutlin in patients aged ≥60 years with R/R AML who are not eligible for cytotoxic therapy). In that study, cobimetinib 40 mg plus escalating doses of venetoclax (400, 600, and 800 mg) have been explored as part of the dose-escalation phase.

The study team will evaluate the safety and tolerability data from the first cycle of treatment for patients in the cobimetinib plus venetoclax safety run-in cohort in accordance with the following rules:

- If <2 of 6 (<33%) evaluable patients experience a DLT (as defined in Section 3.1.1.2), cobimetinib 40 mg plus venetoclax 800 mg will be considered to have acceptable safety.
- If ≥2 of 6 (≥33%) evaluable patients experience a DLT, then one or more sequential cohorts of 6 additional evaluable patients will be enrolled and treated with cobimetinib 40 mg plus lower doses of venetoclax (600 mg → 400 mg → 200 mg) until <2 of 6 evaluable patients experience a DLT.

This same approach with respect to the management of patients treated with cobimetinib 40 mg plus venetoclax 800 mg will be used for the evaluation of cohorts of patients treated with cobimetinib at 40 mg and lower doses of venetoclax at (600 mg → 400 mg → 200 mg). If the dose of venetoclax reaches 200 mg, then if necessary, the dose of cobimetinib may be reduced to a final dose of 20 mg. After the last patient has been enrolled and completed the DLT period in the safety run-in cohort of the cobimetinib plus venetoclax combination, patient enrolment in the cobimetinib plus venetoclax plus atezolizumab safety run-in cohort can start provided that the treatment is considered to have acceptable safety.

Cobimetinib plus Venetoclax plus Atezolizumab Safety Run-In Cohort

Once the dose level of cobimetinib plus venetoclax is considered safe in the safety run-in cohort, a cohort of 6 evaluable patients will then be treated with cobimetinib plus venetoclax plus atezolizumab. Cobimetinib PO and venetoclax PO will be administered at the selected dose for the randomization phase of the study with atezolizumab IV at the fixed dose of 840 mg on Day 1 and Day 15 (±3 days) of each 28-day cycle (note: Cycle 1 of the safety run-in phase does not include the 3-day window). For this cohort, a staggered design will be adopted for the first 3 patients. One patient will be enrolled and dosed in the initial dose cohort. Afterwards, patients will be enrolled sequentially once the prior patient has completed the first cycle with an acceptable safety. If no DLTs are observed in the first 3 patients, 3 more patients will be enrolled

simultaneously. If a DLT is observed in 1 of the first 3 patients, the following 3 patients will be enrolled consecutively after the completion of the first cycle of the prior patient.

Once the last patient has completed the first cycle of therapy, patient enrollment will be put on hold until the study team has completed the evaluation of the safety and tolerability data of the cobimetinib plus venetoclax plus atezolizumab safety run-in phase of the study in accordance with the following rules:

- Cobimetinib plus venetoclax plus atezolizumab will be considered safe if <2 evaluable patients experience a DLT during the first cycle of treatment.
- If ≥ 2 of 6 ($\geq 33\%$) evaluable patients experience a DLT, then one or more sequential cohorts of 6 additional evaluable patients will be enrolled and treated with cobimetinib 40 mg plus lower doses of venetoclax (600 mg → 400 mg → 200 mg) until <2 of 6 evaluable patients experience a DLT.
- If <2 of 6 ($<33\%$) evaluable patients experience a DLT with the new lower dose level, this would be the selected dose for the randomization phase of the study.
- If ≥ 2 of 6 ($\geq 33\%$) evaluable patients experience a DLT, 6 additional patients will be enrolled and assessed for DLTs at lower dose levels.

For initial dose reductions at the starting dose, cobimetinib and atezolizumab will remain fixed with dose reductions for venetoclax if needed in sequential decrements of 200 mg. If the dose of venetoclax reaches 200 mg, then if needed, the dose of cobimetinib may be reduced from the starting dose of 40 mg to a final dose of 20 mg.

Definition of Evaluable Patients in the Safety Run-In Cohorts

During the safety run-in phase of the study, patients will be evaluable if they have completed at least 70% of the protocol-planned dose for each individual drug. If a significant decrease ($<70\%$) in the intended relative dose intensity is due to safety reasons, the toxicity will be considered a DLT. If the significant decrease ($<70\%$) in the intended relative dose intensity is due to unrelated adverse events or to PD, then the patient will be replaced.

An interim analysis for safety will be performed prior to the randomization phase to assess data from all safety run-in cohorts. The analysis will assess the DLTs during the DLT period and the tolerability of the study treatments for patients who have received more than one cycle of study therapy. The interim analysis will be completed after the last evaluable patient in Arm C (triplet regimen) has concluded the first cycle.

3.1.1.2 Randomization Phase

After the safety run-in phase and prior to patient randomization (1:2:2 for Arms A:B:C), a biomarker assessment for the translocation t(11;14) will be performed to allow randomization of a representative MM population and to ensure that approximately 20% of patients in each arm have MM with a t(11;14) (Avet-Loiseau et al. 2007). See Section 3.3 for patient assignment to study arms.

Approximately 12 patients will be randomized to the cobimetinib single-agent arm (Arm A) and will receive the standard single-agent cobimetinib dose of 60 mg PO daily on Days 1–21 of each 28-day cycle. Upon progression, patients will be allowed to receive treatment with cobimetinib and atezolizumab at the recommended Phase II dose of cobimetinib 60 mg PO from Day 1 to Day 21 plus atezolizumab IV at a fixed dose of 840 mg on Day 1 and Day 15 (±3 days) of each 28-day cycle. This combination at the above-indicated doses is currently being explored in multiple clinical studies including a Phase III clinical trial in patients with metastatic CRC (Study GO30182).

Arm B (cobimetinib plus venetoclax) will randomize approximately 24 patients to receive cobimetinib plus venetoclax at the dose level identified in the safety run-in phase.

Arm C will randomize approximately 24 patients to receive cobimetinib plus venetoclax at the dose level identified in the safety run-in phase plus atezolizumab IV at a fixed dose of 840 mg on Day 1 and Day 15 (±3 days) of each 28-day cycle.

The study drugs will be administered on 28-day cycles as follows:

Arm A: Cobimetinib

- Cobimetinib 60 mg PO daily on Days 1–21
- Upon progression, patients in Arm A are allowed to receive treatment with:
  - Cobimetinib 60 mg PO daily on Days 1–21
  - Atezolizumab 840 mg IV infusion on Day 1 and Day 15 (±3 days)

Arm B: Cobimetinib + Venetoclax

- Cobimetinib 40 mg PO daily on Days 1–21
- Venetoclax 800 mg PO daily on Days 1–28

Arm C: Cobimetinib + Venetoclax + Atezolizumab

- Cobimetinib (dose to be determined in Arm B) PO daily on Days 1–21
- Venetoclax (dose to be determined in Arm B) PO daily on Days 1–28
- Atezolizumab 840 mg IV on Day 1 and Day 15 (±3 days)

Treatment will continue until the patient has disease progression as defined by the International Myeloma Working Group (IMWG) consensus criteria (Kumar et al. 2016), unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurs first.

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at the treatment discontinuation visit, and during the follow-up period. A treatment discontinuation visit will take place within 30 (±7) days after the last dose of study drug. After PD and study treatment discontinuation, the required follow-up information will be collected via telephone calls and/or clinic visits every 3 months until death, withdrawal of consent, the patient is lost to follow-up, or study termination by the Sponsor, whichever occurs first.

Any toxicity associated with, or possibly associated with cobimetinib and/or venetoclax administration should be managed with supportive care and/or dose interruptions (maximum allowable length of treatment interruption is 28 days) and/or dose reductions. If the investigator considers that the patient could derive clinical benefit from the study treatment after an interruption longer than 28 days, study treatment may continue after discussion with the Medical Monitor. Toxicity due to atezolizumab administration will be managed by supportive care and/or dose interruptions. No dose modification of atezolizumab is allowed in this study.

A DLT will be defined as any of the following adverse events related to study treatment occurring during the DLT period which corresponds to the first cycle of study treatment (from Cycle 1 Day 1 to Cycle 1 Day 28):

- Any treatment-related death
- Grade 4 hematologic toxicity lasting ≥7 days or higher (except leukopenia or lymphopenia)
- Treatment-related non-hematologic toxicity Grade ≥3 (according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 [NCI CTCAE v4.0]) except for the following:

– Grade 3 fatigue, asthenia, fever, anorexia, or constipation

– Grade 3 nausea, vomiting, or diarrhea that responds to maximal supportive care within 72 hours

– Grade 3 rash that resolves to Grade 1 within 7 days with maximal supportive care

– Grade 3 laboratory abnormality that is asymptomatic and deemed to be not clinically significant by the investigator

- A patient who receives less than 70% (Postel-Vinay 2015) of the protocol-planned dose for each individual drug due to drug-related toxicity

If any of the DLT toxicities occur and are assessed as related to study treatment by the investigator, the study treatment will be halted immediately for the individual patient, and a thorough investigation and safety analysis will be conducted.

NCI CTCAE v4.0 will be used to characterize the toxicity profile of the study treatments on all patients.

Anti-myeloma response will be evaluated according to IMWG criteria (Kumar et al. 2016; Appendix 5). Disease evaluations will include biochemical disease assessments, skeletal survey, bone marrow aspirate, and biopsy (see Section 4.5 for details and Appendix 1 for the schedule of activities). Investigators will assess anti-myeloma response every cycle, regardless of any dose delays. Patients who discontinue treatment for reasons other than disease progression (e.g., for toxicity) will continue to have tumor assessments as scheduled until confirmed disease progression per IMWG criteria, withdrawal of consent, initiation of a new anti-cancer therapy, study termination by the Sponsor, or death, whichever occurs first.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as when all patients randomized have been followed until death, withdrawal of consent, lost to follow-up, or the Sponsor decides to end the trial, whichever occurs first.

The total length of the study, from first patient in until end of follow-up, as described above, is expected to be approximately 24 months.

3.3 PATIENT NUMBERS AND ASSIGNMENT TO TREATMENT GROUPS

Approximately 72 patients with R/R MM (across the three arms) will be recruited into this study, from approximately 25 centers worldwide. A Web-based randomization system will be used to collect patient screening information and randomize eligible patients.

The safety run-in phase of the study will consist of two sequentially enrolled cohorts: cobimetinib plus venetoclax safety run-in cohort (n=6), and the cobimetinib plus venetoclax plus atezolizumab safety run-in cohort (n=6); see Section 3.1.1.1. These patients will not be randomized. Once the dose levels are considered safe, the randomization phase of the study will begin. Patients will be randomized at an initial 1:2:2 ratio to one of three treatment arms (Arm A: n=12, Arm B: n=24, and Arm C: n=24). A stratified block randomization list will be used, stratified by t(11;14) translocation. A population cap will be used for recruitment to ensure that approximately 20% of patients in each arm of the randomized phase have t(11;14) translocation prior to patient randomization; that is, Arm A will randomize approximately 3 patients with t(11;14), and Arms B and C each will randomize approximately 5 patients with t(11;14).

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for the Triple-Arm Design

The combinations of cobimetinib with venetoclax and cobimetinib with venetoclax and atezolizumab are expected to have a highly synergistic anti-tumor activity. This study is designed to show the incremental additive benefit with the addition of each individual drug. Arm A will assess the activity of cobimetinib as a single agent because the single-agent activity of cobimetinib in MM has not been explored before. Ideally, the

single-agent activity of one agent should be defined to allow demonstrating the incremental benefit with the addition of each drug. Upon progression patients can be treated with the combination of cobimetinib and atezolizumab to maximize the opportunity for disease control.

From the three potential doublets that could result from combining the three study agents, the combination of cobimetinib with venetoclax together with that of cobimetinib and atezolizumab, were selected because they are the doublets with the highest expected synergism based on the mechanism of action. This expected high synergism is due to the increase of the proapoptotic protein Bim resulting from the MEK inhibition by cobimetinib, whereas venetoclax inhibits the anti-apoptotic protein Bcl-2. Thus, the combination of cobimetinib with venetoclax is the doublet that will be explored in Arm B.

The third arm (Arm C) is designed to enhance anti-tumor activity by addition of atezolizumab to the combination of cobimetinib and venetoclax.

3.4.2 Rationale for the Safety Run-In Phase

The safety run-in phase is designed to confirm safety of the doublet regimen (cobimetinib plus venetoclax) and further evaluate safety of the triplet regimen (cobimetinib plus venetoclax plus atezolizumab). Cobimetinib has been approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib. Cobimetinib monotherapy dose is well established and therefore will be directly used during the randomization phase of the study in patients randomized to Arm A.

As previously indicated, the selected starting dose of cobimetinib plus venetoclax is currently being explored in patients with R/R AML not suitable for cytotoxic therapy in study GH29914. Previous dose levels (venetoclax 400 mg and 600 mg in combination with cobimetinib 40 mg) have been considered safe in that fragile population. The safety run-in cohort for cobimetinib plus venetoclax aims to evaluate in 6 patients, as performed in dose-escalation studies with a 3+3 study design, if the starting dose can be expanded in the randomization phase of the study.

Atezolizumab will be added to cobimetinib plus venetoclax in the third safety run-in cohort.

The Phase Ib study (GP28363) has shown that cobimetinib administered at 60 mg PO 21/7 with atezolizumab 840 mg IV every 2 weeks in 28-day cycles is safe and tolerable. The starting dose of venetoclax plus cobimetinib for the triplet regimen will be the same as the dose level for the doublet regimen identified in the safety run-in cohort, once it has been shown to be safe. Furthermore, additional safety information for the combination of cobimetinib and venetoclax should be available from Study GH29914 at the time of the start of the study.

Although venetoclax has some overlapping toxicities with cobimetinib and atezolizumab, the risk mitigation measures incorporated into this protocol are expected to manage this risk, including the initial enrollment of a limited number of patients until the safety and tolerability has been evaluated. The safety run-in cohort aims to evaluate in 6 patients if the observed toxicity for the triplet regimen allows the starting dose to be expanded in the randomization phase of the study.

3.4.3 Rationale for Cobimetinib Dose and Schedule

The planned starting dose for cobimetinib is 60 mg PO daily (the current approved dose) on Days1−21 of each 28-day cycle. This dose is the standard cobimetinib dose that demonstrated acceptable safety and efficacy when administered with vemurafenib in Study GO28141 in patients with advanced BRAF-mutated malignant melanoma (Larkin et al. 2014).

The selected starting dose for cobimetinib and venetoclax in the safety run-in phase (cobimetinib 40 mg PO daily on Days 1−21; venetoclax 800 mg PO daily on Days 1−28) is the same as the dose currently being evaluated in Study GH29914 (patients with R/R AML who are not eligible for cytotoxic therapy).

For the triplet regimen, cobimetinib will be administered at a dose considered to have acceptable toxicity in the safety run-in phase.

3.4.4 Rationale for Venetoclax Dose and Schedule

As previously mentioned, the selected starting dose of venetoclax for the safety run-in phase is the same as the dose currently being evaluated in Study GH29914 (venetoclax in combination with cobimetinib 40 mg). In that study, venetoclax dose selection was based on the experience from the Phase II study M14-212 with single-agent venetoclax in patients with RR or frontline AML. In Study M14-212, doses of up to 1200 mg daily were well tolerated.

The dose of venetoclax in combination with cobimetinib will be evaluated in the safety run-in phase. Lower dose levels of venetoclax will also be evaluated in case the 800-mg dose in combination with cobimetinib at 40 mg does not demonstrate acceptable safety.

3.4.5 Rationale for Atezolizumab Dose and Schedule

Patients in Arm C (as well as patients in Arm A with disease progression), will be administered atezolizumab at a flat dose consisting of 840 mg IV on Day 1 and Day 15 (±3 days) of each 28-day cycle. This dosage is equivalent to an average body weight-based dose of 15 mg/kg Q3W. The dosage of 15 mg/kg Q3W was selected as the recommended Phase II dose for atezolizumab based on both nonclinical studies and available clinical data from a Phase I study (PCD4989g), as described below.

The target exposure for atezolizumab was projected on the basis of clinical and nonclinical parameters, including nonclinical tissue distribution data in tumor-bearing

mice, target-receptor occupancy in the tumor, and observed atezolizumab interim pharmacokinetics in humans. The target trough concentration (C_{trough}) was projected to be 6 μg/mL based on several assumptions, including the following: 1) 95% tumor receptor saturation is needed for efficacy and 2) the tumor interstitial concentration-to-plasma ratio is 0.30 based on tissue distribution data in tumor-bearing mice.

In Study PCD4989g, the first-in-human study in patients with advanced solid tumors and hematologic malignancies, 30 patients were treated with atezolizumab at doses ranging from 0.01 to 20 mg/kg Q3W during the dose-escalation stage and 247 patients were treated with atezolizumab at doses of 10, 15, or 20 mg/kg Q3W during the dose-expansion stage. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg. There was no evidence of dose-dependent toxicity in Study PCD4989g. The MTD of atezolizumab was not reached, and no DLTs were observed at any dose. Anti-drug antibodies (ADAs) to atezolizumab were associated with changes in pharmacokinetics for some patients in the lower-dose cohorts (0.3, 1, and 3 mg/kg), but patients treated at 10, 15, and 20 mg/kg maintained the expected target trough levels of drug despite the detection of ADAs. To date, no relationship has been observed between the development of measurable ADAs and safety or efficacy. After review of available PK and ADA data for a range of doses, 15 mg/kg Q3W was identified as the lowest atezolizumab dosing regimen that would maintain C_{trough} at $\geq$6 μg/mL, while further safeguarding against interpatient variability and the potential for ADAs to lead to subtherapeutic levels of atezolizumab.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following a fixed dose compared with a body weight–adjusted dose. Therefore, patients in this study will be treated Q2W at a fixed dose of 840 mg (equivalent to an average body weight–based dose of 15 mg/kg Q3W).

3.4.6 Rationale for Patient Population

This study will recruit patients with R/R MM who have received three to five prior lines of therapy (including a PI and an IMiD), who are refractory or intolerant to their last prior therapy, and who have responded to at least one line of therapy. In particular, the double refractory population has a dismal prognosis with a median OS of approximately 9 months (Kumar et al. 2012). Patients are required to have had at least a minimal response (MR) or better to one prior line of therapy.

Despite the recent approval of daratumumab for patients with MM who have received at least three prior lines of therapy, the response rate for daratumumab monotherapy is 31% and the median duration of response (DOR) is 7.6 months (Usmani et al. 2016). Therefore, a significant proportion of patients do not derive benefit from daratumumab monotherapy, and new combinations with novel mechanisms of action are highly desirable in this patient population.

3.4.7 Rationale for Blood and Bone Marrow Sampling for Biomarker Assessments

An exploratory objective of this study is to evaluate biomarkers (including but not limited to MAPK pathway, Bcl-2 pathway, and immune-related biomarkers) that will help to predict response in patients treated with cobimetinib alone (Arm A), cobimetinib plus venetoclax (Arm B), or cobimetinib plus venetoclax plus atezolizumab (Arm C). An exploratory objective of this study is to make a preliminary assessment of potential pharmacodynamic markers to provide evidence for the biologic activity of cobimetinib alone (Arm A), cobimetinib plus venetoclax (Arm B), or cobimetinib plus venetoclax plus atezolizumab (Arm C) in patients with R/R MM and may allow for the early prediction of clinical benefit or mechanism of resistance with the use of this treatment regimen.

In addition, minimal residual disease (MRD) will be assessed in this study as it is most likely one of the most important features that may contribute to the link between the depth of response and long-term outcomes (Kumar et al. 2016).

In addition, potential correlations of these biomarkers with the safety and activity of cobimetinib with venetoclax and atezolizumab will be explored.

3.4.8 Rationale for Pharmacokinetic Collection

The proposed PK sampling scheme for assessment of venetoclax, cobimetinib, and atezolizumab concentrations, together with available data from other clinical studies, will be used to investigate the impact of concomitant administration on PK parameters of each compound.

On the basis of the clearance mechanisms of each compound, it is not expected that concomitant administration of venetoclax, cobimetinib, and atezolizumab will substantially alter the pharmacokinetics of any of the administered compounds. Atezolizumab is primarily eliminated by catabolism to inactive metabolites, and therefore has a low potential for CYP-related drug interactions. Cobimetinib and venetoclax are metabolized primarily by CYP3A, based on in vitro data, which is unlikely to be affected by atezolizumab.

The pharmacokinetics of cobimetinib in combination with venetoclax (Arm B) and with venetoclax and atezolizumab (Arm C) will be compared to single-agent cobimetinib pharmacokinetics (Arm A). In addition, the pharmacokinetics of each compound will be compared with available PK data for each molecule from previous studies. Serum and plasma samples will be collected as outlined in Appendix 2.

4. MATERIALS AND METHODS

4.1 PATIENTS

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
- ECOG Performance Status of 0, 1, or 2 (see Appendix 4)
- Life expectancy of at least 12 weeks
- Documented MM as defined by the below criteria:
  - Monoclonal plasma cells in the bone marrow ≥ 10% or presence of a biopsy-proven plasmacytoma
  - Measurable disease as defined by any of the following:

    Serum M-protein level ≥ 1.0 g/dL or urine M-protein level ≥ 200 mg/24 hours; or

    Light chain MM: Serum Ig free light chain (FLC) ≥ 10 mg/dL and abnormal serum Ig kappa/lambda FLC ratio
- Received 3 to 5 prior lines of therapy for MM, including a PI and an IMiD
  - A line of therapy consists of ≥ 1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various drugs (e.g., induction therapy followed by stem cell transplantation [SCT] is considered 1 line of therapy) (Rajkumar et al. 2015)
- Achieved a response (MR or better) to at least one prior regimen
- Documented evidence of PD (as defined by the IMWG criteria) on or after their last prior therapy, or patients who were intolerant to their last prior therapy

  Note: There is no required time period between last prior therapy and evidence of PD.
- Toxicities resulting from previous therapy (including peripheral neuropathy) that must be resolved or stabilized to Grade 1
- Laboratory values as follows:
  - Hemoglobin level ≥ 7.5 g/dL (≥ 5 mmol/L) (without growth factor support)
  - Platelet count ≥ 50,000/mm^3 or ≥ 30,000 if bone marrow plasma cell > 50% (without transfusion support)
  - Absolute neutrophil count ≥ 1000/mm^3 (without growth factor support)
  - AST and ALT ≤ 2.5 × the ULN
  - Total bilirubin ≤ 1.5 × ULN

– Adequate renal function as demonstrated by a calculated creatinine clearance of ≥40 mL/min; determined via urine collection for 24-hour creatinine clearance or by the Cockcroft-Gault formula

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two contraceptive measures, and agreement to refrain from donating eggs, as defined below:

– A woman is considered to be of childbearing potential if she is post-menarcheal, 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).

– Women must remain abstinent or use two contraceptive methods with a failure rate of <1% per year during the treatment period and for at least 3 months after the final dose of cobimetinib, 1 month after the final dose of venetoclax, and 5 months after the final dose of atezolizumab. Women must refrain from donating eggs during this same period.

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

– 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.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

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

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

4.1.2 Exclusion Criteria

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

- Anti-myeloma treatment within 14 days or 5 PK half-lives of the treatment, whichever is longer, before the date of randomization
- Completion of autologous stem cell transplant within 100 days prior to the date of randomization
- Prior allogeneic stem cell transplant as well as prior solid organ transplant
- Spinal cord compression not definitively treated with surgery and/or radiation

- Prior treatment with MEK inhibitors, Bcl-2 inhibitors, or immune checkpoint inhibitor therapies including anti−CTLA-4, anti−PD-1 or anti−PD-L1
- Treatment with systemic immunostimulatory agents (including, but not limited to, CD137 agonists or interferon and interleukin 2 [IL-2]) within 28 days or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−TNF-α agents) within 14 days prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions:

– Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor approval has been obtained.

- Surgical procedure (including open biopsy, surgical resection, or any other major surgery) or significant traumatic injury within 28 days prior to enrollment, or anticipation of need for major surgical procedure during the course of the study
- Prior radiation therapy within 14 days prior to study enrollment and/or persistence of radiation-related adverse effects
- Minor surgical procedure within 7 days (including placement of a vascular access device)
- History or evidence of retinal pathology on ophthalmic examination that is considered a risk factor for neurosensory retinal detachment/central serous chorioretinopathy, retinal vein occlusion (RVO), or neovascular macular degeneration:
  - History of serous retinopathy
  - History of RVO
  - Evidence of ongoing serous retinopathy or RVO at baseline
- Left ventricular ejection fraction (LVEF) below institutional lower limit of normal
- History of clinically significant cardiovascular dysfunction including the following:

– Inadequately controlled hypertension (defined as systolic blood pressure $>$150 mmHg and/or diastolic blood pressure $>$100 mmHg that is treated or untreated)

– Prior history of hypertensive crisis or hypertensive encephalopathy

– Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months of study enrollment

– History of stroke or transient ischemic attack within 6 months prior to enrollment

– History of myocardial infarction within 6 months prior to first dose of study drug in Cycle 1

– New York Heart Association Class III or IV cardiac disease

- Unstable arrhythmias, or unstable angina
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

    History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

- Any previous venous thromboembolism Grade $>$ 3 within 12 months of study enrollment
- INR $>$ 1.5 and aPTT $>$ 1.5 $\times$ ULN within 7 days prior to study enrollment
- History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins (for patients in Arm C only)
- History of other malignancy that could affect compliance with the protocol or interpretation of results
- Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix are allowed.
- 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 7 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
- Patients with a history of autoimmune-related hypothyroidism who are on thyroid replacement hormone are eligible for the study.
- Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
- Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

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

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

    There is 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

- Uncontrolled serious medical or psychiatric illness
- History of malabsorption or other condition that would interfere with absorption of study drugs
- Active tuberculosis

- Severe infection within 28 days prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 14 days 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.

- Positive test results for hepatitis B (hepatitis B surface antigen [HBsAg] and/or total hepatitis B core antibody [HBcAb]) or hepatitis C virus (HCV) antibody

– Patients positive for HBcAb are eligible only if polymerase chain reaction (PCR) is negative for hepatitis B virus (HBV) DNA.

– Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

- Known history of HIV seropositivity
- Treatment with a live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to Cycle 1 Day 1, at any time during the study, and for at least 5 months after the last dose of study drug (for patients in Arm C only)
- Received strong CYP3A inhibitors (such as ketoconazole and clarithromycin), moderate CYP3A inhibitors (such as fluconazole, ciprofloxacin, and verapamil) strong CYP3A inducers (such as carbamazepine and phenytoin), and moderate CYP3A inducers (such as efavirenz, modafinil) within 7 days prior to the initiation of study treatment
- The following foods/supplements are prohibited at least 7 days prior to initiation of and during study treatment:

– St John's wort or hyperforin (potent CYP3A enzyme inducer)

– Grapefruit juice (potent CYP3A enzyme inhibitor)

- Pregnant or lactating, or intending to become pregnant during the study

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

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study. Patients will initially be enrolled into the safety run-in phase; these patients are not randomized. Once the dose levels are considered safe during the safety run-in phase of the study, randomization using an IxRS will begin for all three treatment arms (Arm A, Arm B, and Arm C; see Section 3.3).

4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are cobimetinib, venetoclax, and atezolizumab. Cobimetinib, venetoclax, and atezolizumab packaging will be overseen by Roche clinical trial supplies department and will bear a label with the identification required by local law as well as the protocol number. The packaging and

labeling of the study drugs will be in accordance with the Sponsor's standards and local regulations. Local packing and labeling requirements may differ in some countries.

Upon delivery of the IMPs to the site, site personnel should check for damage and verify proper identity, quality, integrity of seals and temperature conditions. Site personnel should report any deviations or product complaints to the study monitor upon discovery.

Cobimetinib, venetoclax, and atezolizumab will be stored at the clinical site under the required storage conditions as indicated on the study drug labels. Patients will be asked to store cobimetinib and venetoclax at the required storage conditions noted on the label, out of the reach of children or other co-inhabitants.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Cobimetinib

Cobimetinib will be supplied by the Sponsor as tablets. The 20-mg cobimetinib drug product is a film-coated, white, round, immediate-release tablet. Cobimetinib will be packaged in blister packs. Cobimetinib should not be stored above 25°C (77°F). If the study drug is stored outside of the permitted temperature ranges, quarantine the affected supply and contact the study monitor.

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

4.3.1.2 Venetoclax

Venetoclax (GDC-0199/ABT-0199) is manufactured by AbbVie, Inc. and will be supplied by the Sponsor as oral film-coated tablets of 100-mg strength. Venetoclax tablets will be packaged in high-density polyethylene plastic bottles to accommodate the study design. Venetoclax tablets must be stored at 15°C–25°C (59°F–77°F).

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

4.3.1.3 Atezolizumab

Atezolizumab will be supplied by the Sponsor as sterile liquid in 20-mL glass vials. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution, but may contain more than the stated volume to enable delivery of the entire 20 mL volume. 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 pharmacy manual and the Atezolizumab Investigator's Brochure.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Cobimetinib

Patients in Arm A will receive 60 mg cobimetinib (three tablets of 20 mg each) PO once daily on Days 1–21 of each 28-day cycle.

Patients in Arm B will receive cobimetinib PO on Days 1–21 of each 28-day cycle. The final dose will be confirmed after the safety run-in phase.

Patients in Arm C will start receiving cobimetinib at the established dose in the safety run-in phase. The final dose of cobimetinib will be confirmed after the safety run-in phase.

For patients in Arms B or C, cobimetinib and venetoclax should be taken at the same time, with venetoclax taken after cobimetinib. If the patient cannot take all the pills at the same time, venetoclax should be taken within 15 minutes after cobimetinib administration.

Cobimetinib should be taken at approximately the same time each day. It can be taken with or without food. If a dose of cobimetinib is missed or if vomiting occurs when the dose is taken, resume dosing with the next scheduled dose. On days that PK sampling is required, the study treatment dose should occur in the clinic to ensure accurate timing of the PK sampling.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5.

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

4.3.2.2 Venetoclax

Patients in Arm B will receive venetoclax PO daily on Days 1–28 of each 28-day cycle. The final dose will be confirmed after the safety run-in phase of the study.

Patients in Arm C will start receiving venetoclax at the established dose during the safety run-in phase.

For patients in Arms B or C, venetoclax and cobimetinib should be taken at the same time, with venetoclax taken after cobimetinib. If the patient cannot take all the pills at the same time, venetoclax should be taken within 15 minutes after cobimetinib administration.

Each dose of venetoclax will be taken PO daily with approximately 240 mL of water within approximately 30 minutes after the completion of breakfast or the patient's first meal of the day. Patients should self-administer venetoclax at approximately the same time each morning. On days that PK sampling is required, the patient’s first meal of the day and all study treatment doses should occur in the clinic to ensure accurate timing of the PK sampling. A meal containing approximately 30% of the total caloric content from fat is recommended to ensure adequate absorption of venetoclax. The following is an

example of a breakfast that contains approximately 520 Kcal that has 30% of its total caloric content from fat (approximately 17 grams of fat): 1 box cereal (30–40 g), skim milk (240 mL), 1 boiled egg, 1 slice of toast (15 g), and 1 tablespoon of margarine (14 g). The toast and margarine may be replaced with one medium croissant or two large pancakes.

If there is a substantial period of time between the patient's regular time of breakfast and his or her venetoclax dosing in the clinic on PK sampling days, the patient may have a low-fat snack in the morning. The patient must be instructed not to take the study treatment with the snack and to take their study treatments in the clinic after a meal.

Venetoclax tablets should be swallowed whole and never be chewed, cut, or crushed. If vomiting occurs, resume dosing with the next scheduled dose. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible, ensuring that the dose is taken with food within 8 hours after the missed dose. Otherwise, the dose should not be taken.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5.

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

4.3.2.3 Atezolizumab

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 6. Atezolizumab infusions will be administered per the instructions outlined in Table 3.

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Day 1 and Day 15 (±3 days) of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or symptomatic deterioration attributed to disease progression. Atezolizumab will be delivered in 250 mL 0.9% NaCl IV infusion bags.

Table 3 Administration of First and Subsequent Atezolizumab Infusions

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

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 8.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation are provided in Section 5.1.5 and Appendix 8.

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

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (cobimetinib, venetoclax, and atezolizumab) will be provided by the Sponsor where required by local health authority regulations. *The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.*

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs to confirm the shipment condition and content. Any damaged shipments will be replaced. *The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.*

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

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.

Refer to the pharmacy manual and/or the Cobimetinib, Venetoclax, and Atezolizumab Investigator's Brochures for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Post-Trial Access to Cobimetinib, Venetoclax, and Atezolizumab

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

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

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

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

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

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

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

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of 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 14 days prior to initiation of study drug to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

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

- Anti-emetics and anti-diarrheal prophylaxis
  - The use of anti-emetics and anti-diarrheal prophylaxis is strongly recommended. For patients who experience Grade 3 diarrhea, anti-diarrheal prophylaxis is mandatory (see Section 5.1.1.3). The use of drugs for anti-emetic or anti-diarrheal prophylaxis must be documented in the eCRF.
- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- G-CSF and anti-infective prophylaxis as per institutional guidelines (provided the anti-infective medication is not prohibited in this study, see Section 4.4.5).
- Inactivated influenza vaccinations during study treatment and at the initiation of screening procedures at the investigator's discretion

- Pneumococcal vaccination may be considered during the initiation of screening procedures for all patients who have not previously received the vaccine.
- Megestrol administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids (equivalent to 7.5 mg of prednisolone per day) administered for orthostatic hypotension or adrenocortical insufficiency

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

In general, investigators should manage patient care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists; see Appendix 6 for anaphylaxis precautions).

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

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

Systemic corticosteroids *or immunosuppressive medications* are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Section 5.1.5 and Appendix 8 for details).

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 4.4.5) may be used during the study at the discretion of the investigator.

4.4.3 Cautionary Therapy for Cobimetinib-Treated Patients

Hemorrhage, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with cobimetinib. Caution should be used in patients with

additional risk factors for bleeding, such as CNS tumor involvement and/or in patients that use concomitant medications that increase the risk of bleeding (including antiplatelet or anticoagulant therapy).

Cobimetinib is metabolized by CYP3A. Cobimetinib exposures were increased 6.6-fold in presence of itraconazole in healthy subjects. Cobimetinib exposures may be increased in presence of these agents, though to a lesser extent in patients with malignant diseases compared to that observed in healthy subjects.

Concomitant use of strong inhibitors of CYP3A (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) should be avoided if possible. Caution should be exercised when co-administering with moderate inhibitors of CYP3A (e.g., erythromycin, fluconazole, diltiazem, verapamil).

In clinical situations that necessarily require the concomitant administration of strong or moderate CYP3A inhibitors the cobimetinib dose should be reduced to 20 mg upon discussion with the Medical Monitor.

After discontinuation of the moderate or strong CYP3A inhibitor, wait for 7 days before increasing the cobimetinib dose back to the initial dose level.

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.4.4 Cautionary Therapy for Venetoclax-Treated Patients

Concomitant use of strong (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) and moderate (e.g., erythromycin, fluconazole, diltiazem, verapamil) inhibitors of CYP3A should be avoided if possible, unless the concurrent use of CYP3A inhibitors is considered necessary to treat or prevent a serious medical condition; consider using alternative medications.

In case the concurrent use of strong CYP3A inhibitors cannot be avoided, reduce the venetoclax dose by 75%. As well for in case of concomitant administration of moderate CYP3A inhibitors, reduce the venetoclax dose by 50%.

After discontinuation of the moderate or strong CYP3A inhibitor wait for 7 days before increasing the venetoclax dose back to the initial dose level.

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication.

In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.4.5 Prohibited Therapy

Any concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority-approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the anti-cancer agent (see Section 4.1.2), and during study treatment until disease progression is documented and patient has discontinued study treatment. This includes but is not limited to chemotherapy, hormonal therapy (except for contraceptives, hormone-replacement therapy, or megestrol acetate), immunotherapy, radiotherapy, investigational agents, or herbal therapy.

The following medications are prohibited while receiving study treatment, unless otherwise noted:

- Traditional herbal medicines, as their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity.
- Denosumab (a RANKL inhibitor) 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.
- Any live, attenuated vaccine (e.g., FluMist) within 28 days prior to Cycle 1 Day 1 or at any time during the study and for at least 5 months after the last dose of study drug (for patients in Arm C only).
- For cobimetinib:

– CYP3A inducers will result in significantly lower exposures of cobimetinib. Therefore, the medications listed below should be avoided. If use of one of these medications is necessary, the risks and benefits should be discussed with the Medical Monitor prior to concomitant administration with cobimetinib.

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

– Concomitant use of strong (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) and moderate (e.g., erythromycin, fluconazole, diltiazem, verapamil) inhibitors of CYP3A should be avoided if possible.

- For venetoclax:

– Avoid strong and moderate CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's wort) as they increase the metabolism of venetoclax. If patient requires use of strong or moderate CYP3A4

inducers during the expansion phase, once the cohort designated venetoclax dose has been reached, use with caution and contact the Medical Monitor for guidance.

- Concomitant use of strong (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) and moderate (e.g., erythromycin, fluconazole, diltiazem, verapamil) inhibitors of CYP3A should be avoided if possible.
- Avoid concomitant use of venetoclax with P-gp inhibitors (e.g., amiodarone, azithromycin, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor)

• For atezolizumab:

- Use of steroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance); in such patients, magnetic resonance imaging (MRI) or a non-contrast CT scan of the anatomical region of interest must be performed.
- Immunomodulatory agents, including but not limited to interferons or IL-2, during the entire study; these agents could potentially increase the risk for autoimmune conditions when administered with atezolizumab

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.5 STUDY ASSESSMENTS

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

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

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

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, prior surgeries, and reproductive status. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 14 days prior to Cycle 1 Day 1 drug will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity. Baseline disease characteristics data will include the international staging system, ECOG Performance Status, date of diagnosis, prior systemic therapy, and prior radiation therapy.

4.5.3 Physical Examinations

A complete physical examination should be performed at screening and should include an evaluation of the head, eyes, ears, nose, throat, neck, and lymph node regions, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

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

Height will be recorded on Cycle 1 Day 1 only. Weight will be recorded at screening and on Day 1 of each cycle.

Patients will be asked specifically about vision changes as part of each physical examination in addition to interval medical history.

4.5.4 Vital Signs

Vital signs include respiratory rate, heart rate, temperature (°C), and systolic and diastolic blood pressure while the patient is in a seated position.

For patients receiving cobimetinib as a single agent or in combination with venetoclax, vital signs will be collected as outlined in the schedule of activities (see Appendix 1).

For patients receiving atezolizumab, either with the triplet regimen (Arm C) or in those patients in which atezolizumab is added on to cobimetinib monotherapy upon PD (Arm A), vital signs will be collected at screening and thereafter as follows during each atezolizumab administration.

- **Cycle 1**

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

  – Within 60 minutes prior to infusion
  – During infusion, every 15 (±5) minutes
  – 30 (±10) minutes after infusion

- **Subsequent Cycles**

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

- Within 60 minutes prior to infusion
- During infusion, every 15 (±5) minutes
- 30 (±10) minutes after infusion

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments as specified in Appendix 1, regardless of dose delays, until disease progression per IMWG 2016 criteria (see Appendix 5). Thus, tumor assessments are to continue per schedule in patients who discontinue treatment for reasons other than disease progression, even if they start new anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if PD is suspected. All response categories require two consecutive assessments made at any time.

Screening assessments must include:

- Serum protein electrophoresis (SPEP) + serum immunofixation electrophoresis (SIFE)
- Urine protein electrophoresis (UPEP; requires 24-hour urine collection) + urine immunofixation electrophoresis (UIFE)
- Serum free light chains (sFLCs)
- β2-microglobulin
- Quantitative immunoglobulins (including IgA, IgG, IgM)
- Bone marrow aspiration and biopsy tissue sample (for local disease assessment including cytogenetics; however, parts of this sample will be sent to the central laboratory)
- Skeletal survey
  - Historical skeletal survey will be accepted if performed within 35 days of randomization and there is no clinical indication for repeating the skeletal survey in the interim between last imaging and randomization
- CT scan/positron emission tomography (PET)-CT or MRI with bidimensional measurements for the assessment of extramedullary disease in patients with a history of plasmacytomas or if clinically indicated at screening

The following samples will be collected at the beginning of each cycle, starting at Cycle 1:

- SPEP
- UPEP (requires 24-hour urine collection, only if baseline UPEP is ≥200 mg/24 hr)
- sFLCs
- Quantitative Ig levels

The following confirmatory assessments are required for all response categories (stringent complete response [sCR], CR, VGPR, PR, and MR):

- Two consecutive assessments should be obtained
- If extramedullary disease was previously present, CT scan/PET-CT or MRI with bidimensional measurements to confirm reduction in size per IMWG criteria
- No known evidence of progressive or new bone lesions (radiographic imaging is not required)
- To confirm a VGPR, the additional following assessment is required:
  - UPEP in patients being followed by serum M-protein, even if a UPEP was not performed at screening

The following assessments, in addition to all of the above, are required to confirm sCR or CR:

- SIFE and UIFE
- sFLCs
- Bone marrow aspiration and biopsy sample (repeat sample is not required for confirmation)
- If extramedullary disease was previously present, CT/PET CT scan or MRI to confirm complete resolution

Patients with a confirmed sCR, CR, VGPR, or PR will be considered to have achieved a response. In addition, patients who achieve a MR or better will be considered to have received clinical benefit (Stewart et al. 2015).

To confirm PD, the following assessments are required:

- If PD is suspected by rising M-protein, SPEP and UPEP with SIFE and UIFE should be obtained on two consecutive assessments from local laboratory readings, and ideally a bone marrow biopsy sample (does not need to be repeated for confirmation) should be obtained to determine if rising M protein is associated with an increase in malignant plasma cells. If PD is suspected on development of new bone lesions or soft tissue plasmacytomas or an increase in size of existing bone lesions or soft tissue plasmacytomas, skeletal survey/CT scan/PET-CT/MRI should be obtained and compared with baseline imaging.
- If PD is suspected on hypercalcemia attributed solely to MM, local laboratory test results of serum calcium levels should be $>$ 11.0 mg/dL and confirmed on a second assessment.

The following assessments are <u>not</u> sufficient to determine PD:

- Rising sFLC (except for light chain myeloma) or quantitative Igs
  - In this situation, SPEP and UPEP should be performed and PD determination should be made based on laboratory test results.

- Clinical relapse and relapse from CR categories
- General worsening of patient's condition

– Due to the possible delay in manifestation of clinical efficacy, investigators are requested not to discontinue patients from treatment for presumed lack of response after only one cycle of study treatment.

Bone marrow aspirate and biopsy tissue sample will be collected during the study for the assessment of percent plasma cells, morphology, and biomarker studies (see Section 4.5.6 for bone marrow collection requirements for exploratory biomarker studies); at screening, the local bone marrow assessments will also include cytogenetics by fluorescence in situ hybridization (FISH). Gene expression signatures associated with RAS/MAPK activation using genomic profiling will be conducted locally or a through a central lab and will be analyzed retrospectively. In the study, bone marrow aspiration and biopsy sample collection will be performed as described in the laboratory manual at the timepoints specified in Appendix 1 and as needed to confirm CR or PD.

Response will be assessed by the investigator with use of IMWG criteria (see Appendix 5).

4.5.5.1 Extramedullary Disease

All patients with clinically suspected extramedullary disease or known extramedullary disease at the time of screening must undergo imaging during screening (a historical imaging assessment is acceptable if performed no more than 35 days prior to randomization and there is no clinical indication for repeating the imaging survey in the interim between last imaging and randomization) to evaluate for the presence or extent of extramedullary disease. This can be performed by CT scan of the chest, abdomen, and pelvis (preferably with IV contrast if renal function is adequate), PET/CT, or whole body MRI. Patients who are found to have extramedullary disease will undergo repeat imaging (preferably the same modality as performed at screening) every 12 weeks. Imaging should also be performed upon clinical suspicion of PD or confirmation of CR. Chest X-ray or ultrasound of the abdomen, liver, or spleen may be substituted for CT, PET/CT, or MRI if, per the investigator's assessment, patients are not able to safely tolerate these imaging modalities, and the anatomic location of the extramedullary disease is compatible with these alternative imaging methods.

4.5.5.2 Skeletal Survey

A skeletal survey (including skull, all long bones, chest, and pelvis) assessed by X-ray, whole-body low-dose CT, MRI, or PET scan is required for all patients during screening (a historical study is acceptable if performed no more than 35 days prior to randomization). If necessary, a skeletal survey may be required to confirm a response (see Section 4.5.5) or may be done at any time during the study if clinically indicated. If plasmacytomas are seen on skeletal survey, bidimensional tumor measurements should be recorded.

4.5.6 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, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate (or total CO_2), glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase (ALP), ALT, AST, LDH, CPK, lipase, and amylase

– Serum chemistry includes serum cholesterol and triglycerides at baseline.

- Coagulation: PT, aPTT, INR
- Quantitative Igs
- Thyroid function testing: thyroid-stimulating hormone (TSH), free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), free thyroxine (T4)
- HIV serology

– For patients with unknown HIV status, HIV testing must be performed at screening if not in contradiction with local regulations.

- HBV serology: HBsAg, hepatitis B surface antibody, total HBcAb

– If a patient has a negative HBsAg test result and a positive total HBcAb test result at screening, an HBV DNA test must be performed to rule out active HBV infection based on HBV viral load per local guidelines.

- HCV serology: HCV antibody

– If a patient has a positive HCV antibody test result at screening, an HCV RNA test should be performed to rule out active HCV infection prior to initiation of study treatment.

- Pregnancy test

– All women of childbearing potential will have a serum pregnancy test performed at screening (within 7 days prior to initiation of study drug), and then monthly and as clinically indicated.

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

– After study treatment discontinuation, a monthly pregnancy test should be performed (in women of childbearing potential) for at least 3 months after the last dose of cobimetinib, 1 month after the last dose of venetoclax, and 5 months after the last dose of atezolizumab.

- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- Fresh bone marrow aspirate for local assessment of percent plasma cells, karyotype and myeloma FISH panel
- Serum samples for serum M-protein (SPEP ± SIFE) and sFLCs
- 24-hour urine sample for urine M-protein (UPEP ± UIFE)

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Serum samples for immunogenicity (ADA) assessment

  Serum samples will be assayed for the presence of ADAs to atezolizumab with use of validated immunoassays.

- Serum samples for PK analysis

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

- Plasma samples for PK analysis

  Plasma samples will be assayed for cobimetinib concentration with use of a validated assay.

  Plasma samples will be assayed for venetoclax concentration with use of a validated assay.

- Blood (whole blood, EDTA-plasma, and serum) samples will be obtained according to the schedule in Appendix 1 and will be evaluated from all eligible patients for immune related, tumor type related, and other exploratory research on biomarkers (including but not limited to T-cell profiling, T-cell receptor repertoire, immune cell subsets, minimal residual disease, and enumeration of T, B, and NK cells).

– Whole blood samples may be processed to obtain plasma, serum peripheral blood mononuclear cells (PBMCs) and their derivatives (e.g., RNA and DNA).

– MRD assessment will be performed using bone marrow aspirates and exploratory MRD assessment will be performed using peripheral blood.

- Serum samples for analysis of autoantibodies: anti-nuclear antibody, anti-double stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody
- Fresh bone marrow aspirate and biopsy tissue samples will be collected at screening, during the study, and at the time of confirmation of response or disease progression and will be submitted with the associated pathology report for exploratory research on biomarkers (see Appendix 1 for collection timepoints)

– For bone marrow aspirate samples, 10 mL of aspirate should be collected. Preferably, the same aspirate site used for collection of local bone marrow laboratory analyses (e.g., flow cytometry, cytogenetics, FISH) should not be used for collection of bone marrow samples for exploratory analyses. For every 10 mL of

bone marrow collected, a separate aspirate site should be selected if possible (all aspirate sites can be on the ipsilateral iliac crest). Trephine or core biopsy tissue samples should preferably be 1.5 cm in length (≥2 cm is optimal). If fresh tissue is unavailable, an archival block or 15–20 unstained slides should be sent to the Sponsor (see the laboratory manual for further details).

- Samples collected at the time of progression (mandatory), if deemed clinically feasible by the investigator, should be obtained within 30 days after progression or prior to the initiation of subsequent anti-cancer therapy, whichever is sooner.
- In patients with extramedullary disease, in the rare instance that a bone marrow biopsy is not feasible, tissue obtained from an extramedullary plasmacytoma is acceptable, but should meet the following criteria:

  If an excisional biopsy is performed, then a formalin-fixed, paraffin embedded block (preferred) or a minimum of 15 serially sectioned, unstained slides is required. If ≤10 serially sectioned slides are available, consult with the Medical Monitor. For core-needle biopsy tissue specimens, at least 3 core tissue samples should be submitted for evaluation.

  Tumor tissue should be of good quality based on total and viable tumor content.

  Acceptable samples include core-needle biopsy tissue samples for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps tissue-sample biopsies for cutaneous, subcutaneous, or mucosal lesions.

- MRD assessment will be performed using bone marrow aspirates and peripheral blood.

Exploratory biomarker research may include, but will not be limited to, the biomarkers listed in Table 4.

Blood samples will be obtained for biomarker evaluation (including but not limited to biomarkers that are related to MM or tumor immune biology) from all patients. Samples will be processed to obtain plasma for the determination of changes in blood-based biomarkers.

Table 4 Proposed Non-Inherited Biomarkers for Exploratory Research

Sample Type	Timing	Proposed Non-Inherited Biomarkers
Plasma	At multiple timepoints as indicated in Appendix 1	• Cytokine levels
Serum		• Immunofixation, including assessment of atezolizumab interference ("reflex assay")
RNA extracted from blood		• Gene expression profiling: markers of MAPK pathway, apoptosis pathway, immune cell signatures
DNA extracted from blood		• T-cell receptor clonality, MRD
PBMCs isolated from blood		• Frequency of immune cells, myeloma cells; T-cell profiling
Bone marrow aspirate	Baseline (fresh) and subsequent timepoints during and after treatment	• Frequency of immune cells, myeloma cells; T-cell profiling, MRD
DNA extracted from bone marrow aspirate/biopsy		• Oncogenic mutation panel: genomic alterations
RNA extracted from bone marrow aspirate/biopsy		• Gene expression profiling: markers of MAPK pathway, apoptosis pathway, immune cell signatures
Bone marrow biopsy	Prior to study (archival) or baseline (fresh) and Cycle 4, Day 1	• Immunohistochemistry: Bcl-2 family proteins, MHC I, T cells, tumor cells

MAPK=mitogen-activated protein kinase; MHC=major histocompatibility complex; MRD=minimal residual disease; PBMC=peripheral blood mononuclear cell.

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.10), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma/serum samples collected for PK and immunogenicity (ADA) analysis may be needed for additional PK and ADA assay development and validation and for additional immunogenicity characterization; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, serum, plasma, bone marrow aspirate, bone marrow tissue samples, and any derivatives thereof (e.g., DNA, RNA, proteins), collected for biomarker research will

be destroyed no later than 5 years after the final Clinical Study Report has been completed.

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

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

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

4.5.7 Left Ventricular Ejection Fraction

All patients will require regular evaluation of LVEF at screening and during study conduct.

Evaluation of LVEF by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan using the same method for each patient must be performed according to the timepoints specified in Appendix 1.

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

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

4.5.8 Electrocardiograms

An ECG is required at screening and on Cycle 1 Day 1. ECGs for each patient should be obtained from the same machine wherever 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.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.9 Ophthalmic Examination

All patients will require regular ophthalmic examinations at screening and during study conduct.

Ophthalmic examination must be performed according to the timepoints specified in Appendix 1.

The objective of baseline ophthalmic examination is to evaluate for evidence of retinal pathology that may be a risk factor for central serous retinopathy or RVO. Ophthalmic examination must be performed by an ophthalmologist.

Baseline and serial surveillance ophthalmic examination will include visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and optical coherence tomography (spectral- or time-domain). Spectral-domain optical coherence tomography, if not available, may be substituted with time-domain optical coherence tomography.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to the study treatment used or diseases:

- Leftover blood, serum, plasma, bone marrow aspirate, and bone marrow tissue samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing (NGS), or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.10.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens 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.

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

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

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

4.5.10.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the

date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF.

If a patient wishes to withdraw consent to the testing of his or her specimens after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from Study BO39813 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study BO39813.

4.5.10.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any adverse event that requires study treatment discontinuation per the guidelines in Section 5.1 and the Atezolizumab Investigator's Brochure
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Symptomatic deterioration attributed to disease progression
- Disease progression per IMWG criteria (see Appendix 5), as assessed by the investigator (except for patients in Arm A who may crossover to Arm B or Arm C upon discussion with the Medical Monitor).

Patients will return to the clinic for a treatment discontinuation visit within 30 (±7) days after the last dose of study treatment. The visit at which response assessment shows PD may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than PD will continue to undergo tumor response assessments as outlined in the schedule of activities (see Appendix 1).

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

The primary reason for study drug discontinuation should be documented on the appropriate eCRF.

4.6.2 Patient Discontinuation from Study

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

- Patient withdrawal of consent at any time
- Study termination or site closure
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

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

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

Cobimetinib is approved in combination with vemurafenib for the treatment of advanced BRAF V600-mutated melanoma in the United States and the European Union as well as other countries. The safety plan for patients in this study is based on clinical experience with cobimetinib in completed and ongoing studies. The anticipated important safety risks for cobimetinib are outlined below. Please refer to the Cobimetinib Investigator's Brochure for a complete summary of safety information.

Venetoclax is approved for the treatment of patients with CLL in the United States and the European Union. Please refer to the Venetoclax Investigator's Brochure for a complete summary of safety information.

Atezolizumab is approved for the treatment of patients with urothelial bladder cancer and NSCLC in the United States and is currently in clinical development for other indications. The following information is based on results from nonclinical and clinical studies and published data on similar molecules. Please refer to the Atezolizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients who participate in this study including periodic teleconferences; for the safety run-in cohorts, weekly teleconferences are planned between the Sponsor's medical personnel and the medical site staff taking care of study patients. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo close safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification, and treatment interruption or discontinuation, are provided below.

5.1 SAFETY PLAN

The risks associated with cobimetinib, venetoclax, and atezolizumab are detailed in Section 5.1.1, Section 5.1.2, and Section 5.1.3, respectively. In addition, the guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Cobimetinib

Information related to risks attributed to cobimetinib is based on safety data from the Phase III study GO28141 (cobimetinib plus vemurafenib), the Phase Ib study NO25395 (cobimetinib plus vemurafenib), and the Phase I study MEK4592g (cobimetinib monotherapy). For further information regarding clinical safety, please refer to the current Cobimetinib Investigator's Brochure.

5.1.1.1 Important Identified Risks Associated with Cobimetinib

Hemorrhage

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

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

Caution should be used in patients with additional risk factors for bleeding, such as in patients who use concomitant medications that increase the risk of bleeding (including anti-platelet or anticoagulant therapy).

Instructions for dose modifications for hemorrhage events are included in Section 5.1.5.

Serous Retinopathy

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

Serous retinopathy has been characterized in the Phase III study GO28141. The study incorporated prospective serial ophthalmic examinations for all enrolled patients. Serous retinopathy was reported more frequently in patients treated with cobimetinib plus vemurafenib than with placebo plus vemurafenib (25.5% vs. 2.8%, respectively), and approximately half the events were asymptomatic Grade 1 events. Few patients treated

with cobimetinib plus vemurafenib experienced Grade ≥ 3 ocular events (2.8%); the majority of these events were managed with dose modification of both cobimetinib and vemurafenib.

To address serous retinopathy with cobimetinib treatment, all patients are required to undergo a baseline ophthalmic examination to assess for history or evidence of retinal pathology that is considered a risk factor for or indicative of neurosensory retinal detachment, central serous chorioretinopathy, neovascular retinopathy, or retinopathy of prematurity. Patients will also undergo ophthalmic examinations at specified time points throughout the study (see Appendix 1). Details regarding baseline and subsequent ophthalmic examinations are provided in Section 4.5.9.

Guidelines for management of patients who develop Grade ≥2 visual disorders or retinopathy are provided in Section 5.1.5.7.

Left Ventricular Dysfunction

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

Left ventricular dysfunction has been characterized in the Phase III study GO28141. The study incorporated prospective serial LVEF evaluation in all patients. With active surveillance, measured reductions in left ventricular ejection fraction were observed more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (8.5% vs. 3.7%, respectively, of Grade 2 or 3 severity). Of the patients treated with cobimetinib plus vemurafenib, 2 patients (0.8%) had symptomatic reduction in LVEF, and the remaining patients were asymptomatic. Most LVEF reduction events in patients on cobimetinib plus vemurafenib (62%) improved or resolved with management according to the dose-modification guidelines (see Section 5.1.5.10).

Rhabdomyolysis and CPK Elevations

Elevations in CPK have been observed in patients who received cobimetinib monotherapy as well as when administered with other agents. The majority of CPK elevations reported were asymptomatic, non-serious, and resolved with or without study drug interruption. One event of rhabdomyolysis was reported in the Phase III Study GO28141 (cobimetinib plus vemurafenib), and rhabdomyolysis has been reported in postmarketing experience.

In Study GO28141, elevated CPK was reported as an adverse event more frequently in patients treated with cobimetinib plus vemurafenib (32.4% all grades, 11.3% Grade ≥ 3 events) than placebo plus vemurafenib (8.1% all grades, 0% Grade ≥ 3 events). CPK will be monitored at baseline and monthly during treatment or as clinically indicated. Instructions for dose modification for elevated CPK and rhabdomyolysis are included in Section 5.1.5.6.

Photosensitivity (when administered with vemurafenib)

No evidence of phototoxicity has been observed with cobimetinib as a single agent. However, photosensitivity was observed on the Study GO28141 with a higher frequency in the cobimetinib+vemurafenib arm vs. placebo+vemurafenib arm (46.3% vs. 35.4%, respectively). The majority of events were Grades 1 or 2, with Grade ≥3 events occurring in 3.6% of patients in the cobimetinib+vemurafenib arm versus 0% in the placebo+vemurafenib arm. Grade ≥ 3 photosensitivity events in the cobimetinib+vemurafenib arm were primarily treated with topical medication in conjunction with interruption of study agents.

Pneumonitis

Events of pneumonitis have been reported in cobimetinib clinical studies. Most reported events were considered non-serious and low-severity grade. In the Phase III Study GO28141, pneumonitis events were reported more frequently in patients treated with cobimetinib+vemurafenib than placebo+vemurafenib (1.6% vs. 0.4%, all grades). There were no reported Grade ≥3 events in either study arm. Serious events were reported in 2 patients (0.8%) treated with cobimetinib+vemurafenib. Guidelines for managing drug-induced pneumonitis are provided in Section 5.1.5.13.

Diarrhea

In clinical studies GO28141 and NO25395, diarrhea was the AE most commonly reported in patients who received cobimetinib+vemurafenib treatment. In the Phase III Study GO28141, 61.3% of patients in cobimetinib+vemurafenib arm experienced diarrhea. Of these, 6.9% of patients experienced Grade ≥3 diarrhea events. Three patients (1.2%) in the cobimetinib+vemurafenib arm had diarrhea reported as an SAE.

The diarrhea events were generally manageable, and few events of diarrhea occurred with concurrent dehydration, or other clinical sequelae. Overall, the diarrhea events were managed by antidiarrheal agents, and no patient in the cobimetinib+vemurafenib arm of Study GO28141 discontinued either study treatment due to diarrhea.

Guidelines for managing gastrointestinal toxicity are provided in Section 5.1.5.8.

5.1.1.2 Potential Risks Associated with Cobimetinib

Liver Laboratory Abnormalities

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 plus vemurafenib.

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

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

Impaired Female Fertility

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

While no dedicated fertility studies have been conducted with cobimetinib in animals, degenerative changes observed in reproductive tissues included increased apoptosis/necrosis of corpora lutea and seminal vesicle, epididymal and vaginal epithelial cells in rats, and epididymal epithelial cells in dogs. These changes were reversible upon discontinuation of cobimetinib administration.

Teratogenicity and Development Toxicity

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

5.1.1.3 Other Risks with Cobimetinib

Rash

In the Phase III study GO28141, combined rash events of all types and grades were reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (69% vs. 62%, respectively), although Grade ≥ 3 events (approximately 14% and 12% of patients treated with cobimetinib plus vemurafenib and placebo plus vemurafenib, respectively) and types of rash reported were similar between study arms. Specific events in patients treated with cobimetinib plus vemurafenib included rash (40% all grades, 5% Grade ≥ 3), rash maculo-papular (15% all grades, 7% Grade ≥ 3) and acneiform rash (14% all grades, 2% Grade ≥ 3).

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

Gastrointestinal Toxicity

A range of gastrointestinal adverse events, including nausea, vomiting, and diarrhea~~,~~ *(see Section 5.1.1.1 for details),* have been reported in all cobimetinib studies in adult cancer patients.

Nausea and vomiting have been reported in association with cobimetinib. Most nausea and vomiting events were considered non-serious and low-severity grade. In the Phase III study GO28141, nausea and vomiting events were reported more frequently in the active cobimetinib arm than the control arm (nausea 41.3% vs. 25.3%; vomiting

24.3% vs. 12.6%). However, of patients treated with cobimetinib plus vemurafenib, few experienced Grade 3 events (nausea <0.81%, vomiting 1.2%).

The combination of diarrhea, nausea, and vomiting has the potential to contribute to clinically significant volume depletion/dehydration from the combination of fluid losses with decreased oral intake. In the majority of cases, diarrhea has been effectively managed with antidiarrheal agents and supportive care. Routine primary antiemetic prophylaxis is not recommended. Routine primary anti-diarrheal prophylaxis is highly recommended in patients receiving cobimetinib plus venetoclax. In patients who experienced Grade 3 diarrhea secondary anti-diarrheal prophylaxis is mandatory (see Table 5).

Table 5 Gastrointestinal Prophylaxis Guidelines

Anti-Emetic Prophylaxis Guidelines
• 30–60 minutes before administration of study medication, the patient should receive a 5-HT3-receptor antagonist (e.g., ondansetron, granisetron or palonosetron) on Days 1–7. Longer-acting formulations of 5-HT3-receptor antagonists, such as granisetron transdermal system (Sancuso® patch) or extended-release (Sustol®), can also be used. • Rescue medications: – Combination of Ativan 0.5 mg, Benadryl® 12.5 mg and Haldol 2.5 mg can be given for breakthrough nausea – Dexamethasone can also be administered as a rescue medication • Caution: – Aprepitant (Emend® Oral) is a moderate CYP3A inhibitor and is a prohibited therapy on this study – Avoid agents such as metoclopramide, which may stimulate GI motility
Anti-Diarrheal Prophylaxis Guidelines
• 30 minutes before the first dose of study medication, administer loperamide prophylactically (loading dose 4 mg) followed by 2 mg/4mg QID not exceeding 16 mg in any 24-hour period. • If the patient has diarrhea, please follow the guidelines for managing gastrointestinal toxicity provided in Table 14. • For patients who do not experience diarrhea, the recommendation is to administer the treatment prophylaxis for the first 3–5 days of study treatment and if there are no signs of increased transit of bowel movements, abdominal cramps or pain, the patient may discontinue loperamide. • Caution: Use loperamide (P-gp substrate) with caution when co-administered with venetoclax (P-gp inhibitor). There is a potential for enhanced central effects when loperamide is administered with P-gp inhibitors.

GI = gastrointestinal; QID = 4 times a day.

Guidelines for managing gastrointestinal toxicity are provided in Section 5.1.5.8.

Hypersensitivity

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

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

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

5.1.2 Risks Associated with Venetoclax

Information related to venetoclax-associated risks is based mainly on review of data from Phase I–III experience (see the Venetoclax Investigator's Brochure) in CLL and Phase I–II data in AML (Studies M14-212, M14-358, and M14-387; see Table 1). Venetoclax has demonstrated that it is generally well tolerated, and toxicities appear to be mostly manageable and/or reversible. Refer to the current Venetoclax Investigator's Brochure for details on the safety data from these studies and for additional information on venetoclax warnings and precautions. Risks include infectious complications, cytopenias, effects on fertility, treatment-emergent malignancies (second primary malignancies), and food effect.

See Section 5.1.5 for the monitoring and management of specific toxicities.

Tumor Lysis Syndrome

To date, the principal adverse reaction associated with venetoclax in the single-agent Phase I dose-escalation CLL study M12-175 has been TLS (primarily but not exclusive related to the first dose). These include cases of TLS that have led to clinical sequelae including death in 2 patients. Among the non-CLL studies, 6 patients with NHL experienced Grade 3–4 adverse events of laboratory TLS. Although several events of hyperphosphatemia and two events of rising potassium have been observed in the R/R AML study (Study M14-212), no patients experienced TLS during administration of venetoclax.

Although no cases of TLS have been reported in patients with MM, patients will be actively monitored and managed to prevent potential.

Neutropenia

Neutropenia is an important identified risk for venetoclax, specifically in CLL. Clinical data from the oncology studies suggest that the neutropenia adverse events are

observed among patients who receive venetoclax as a single agent or in combination with other therapeutic agents, with slightly higher frequency observed in some combination studies. Serious adverse events of neutropenia leading to discontinuations are few across the entire venetoclax oncology program. Cytopenia management guidelines are provided in Section 5.1.5.1.

Granulocyte colony-stimulating factors can be used for supportive measures, however the guidance for their use in non-CLL indications is per routine local oncology practice.

Cytopenias

Anemia has been reported with slightly higher frequency in some oncology studies in which venetoclax is combined with other chemotherapeutic agents; however, most of the events were non-serious and confounded by disease factors and prior therapies.

Thrombocytopenia adverse events have been reported in oncology studies, with slightly higher frequency in studies in which venetoclax is combined with other agents. However, most of the events were non-serious and assessment of these events is confounded by the patients' underlying disease state, prior therapies, and preexisting thrombocytopenia, including autoimmune thrombocytopenia in several patients. The dataset in non-CLL indications is small.

Lymphopenia has been observed in nonclinical studies. Although opportunistic infections have been reported in the clinical program, data are confounded by patients' underlying disease and prior therapies. In oncology studies, anti-infective prophylaxis should be implemented as clinically indicated, including appropriate prophylaxis for viral, fungal, bacterial, or pneumocystis carinii pneumonia infections.

See Section 5.1.5.1 for the management of cytopenias.

Effects on Fertility and Reproductive Toxicity

There were no effects of venetoclax on female or male mouse fertility; however, a risk to human male fertility exists based on the testicular toxicity (germ cell depletion) observed at all dose levels in the repeat-dose dog studies. Reversibility of this finding has not been demonstrated. It is not known whether the dog testicular findings translate to humans. Male patients should be instructed to consider sperm banking before treatment with venetoclax if they are considering preservation of fertility.

In embryo-fetal development studies, venetoclax was administered to pregnant mice and rabbits during the respective periods of organogenesis. In pregnant mice, venetoclax was associated with increased post-implantation loss and decreased fetal body weight at 150 mg/kg/day (approximately 1.2 times the human AUC exposure at the 400-mg human dose). No fetal toxicity was observed in rabbits up to the highest dose tested (approximately 0.2 times the human AUC exposure at the 400-mg human dose).

Treatment-Emergent Malignancies (Second Primary Malignancies)

Events of second primary malignancies have been reported across the oncology program. No pattern has been observed. Because venetoclax is being evaluated in patients with R/R disease who had previously been treated with various cytotoxic agents, second primary malignancies are closely monitored.

Infections

Serious infection, including sepsis, is an important identified risk for venetoclax. Infections have been reported in the clinical studies of venetoclax for malignant diseases. However, these events are confounded by the common complications of the underlying malignancies, comorbidities, and concomitant immunosuppressive medications. To date, a clear relationship has not been established between serious infectious events and neutropenia. The types of infectious events observed generally have been consistent with those anticipated in the elderly population of heavily pretreated patients with hematologic malignancies and are similar across all indications. Infections are closely monitored in venetoclax program across all indications.

See Section 5.1.5.2 for the management of infection.

Food Effect

Administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold, and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared with fasting conditions. Venetoclax should be administered with a meal (see Section 4.3.2.2).

5.1.3 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, hypophysitis, meningoencephalitis, myocarditis, nephritis, myositis, and *severe cutaneous adverse reactions*. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis *(HLH)* and macrophage activation syndrome (*MAS), which are* considered to be potential risks for atezolizumab. Refer to Appendix 8 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.4 Anticipated Overlapping Adverse Events for Cobimetinib, Venetoclax, and Atezolizumab

Special consideration is given to areas of potential overlapping toxicity based on nonclinical and previous human experience data with each compound individually or with other molecules. Safety findings common to two and/or all molecules assessed as single agents individually and/or in combination with other molecules include the topics below. Patients in the three study arms should be closely monitored for evidence of

toxicity and, in the case of the Arms B and C, for overlapping and/or potentiation of these and any other acute toxicities. If any evidence of overlapping and/or potentiation of the below toxicities is observed, patients should receive maximal supportive care as clinically indicated. Any modification of study treatment should follow the guidelines in Section 5.1.5.

Hypersensitivity Reactions and/or Infusion Reactions

Hypersensitivity reactions or infusion reactions are described in the warning and precautions of the Atezolizumab Investigator's Brochure. There have been few reports of hypersensitivity and/or anaphylaxis in clinical trials with patients who have been treated with cobimetinib as single agent therapy or in combination with other agents. These have appeared to be isolated reports, and in some cases, occurred in patients with histories of drug allergies. Thus, the relationship of cobimetinib to these events is unclear. Investigators should promptly evaluate and treat patients who are suspected of experiencing a hypersensitivity reaction.

Please refer to the respective Investigator's Brochures for more details. Patients in this study should be closely monitored for any evidence of overlapping and/or potentiation of hypersensitivity and/or infusion reactions.

Dermatologic Reactions

Dermatologic reactions (i.e., rash, pruritus, maculopapular) are described in the warnings and precautions of the Atezolizumab Investigator's Brochure and are defined as adverse drug reaction in the Cobimetinib Investigator's Brochure.

Skin toxicities of rash have been reported in patients treated with cobimetinib as a single agent or with other therapies. In the pivotal study, serious events of rash, rash maculopapular and acneiform dermatitis were more frequent in the active cobimetinib arm than in the control arm. Dermatologic reactions have been reported in 42% of patients receiving single-agent atezolizumab. Reactions have been mild to moderate ($<$ 1% reported as severe).

Ocular Toxicity

Ocular toxicities have been observed with both cobimetinib and atezolizumab.

Serous retinopathy (fluid accumulation within the layers of the retina) and retinal detachment are class-effects of MEK inhibitors, including cobimetinib, and are described as both warnings and precautions as well as identified risks in the Cobimetinib Investigator's Brochure. The majority of events in cobimetinib-treated patients were reported as chorioretinopathy or retinal detachment. Uveitis has been observed in association with atezolizumab. Initial symptoms reported by patients may not distinguish between either serous retinopathy or uveitis and will require additional ophthalmic examination for a definitive diagnosis.

Baseline and serial surveillance ophthalmic examinations will be performed for patients in this study as detailed in Section 4.5.9. Please refer to Section 5.1.5.7 for further details regarding management and dose modifications related to ocular events.

Patients should be advised to use caution when driving or using machines if their vision is impaired.

Hepatic Toxicity and/or Liver Laboratory Abnormalities

Liver laboratory test abnormalities, including elevated AST, elevated ALT, elevated γ-glutamyltransferase, elevated ALP, and elevated bilirubin, are warnings and precautions for cobimetinib as described in the Cobimetinib Investigator's Brochure. The risk of immune-mediated hepatitis has been associated with the administration of atezolizumab, and it is described in the summary of important identified risks section of the Atezolizumab Investigator's Brochure.

Please refer to the respective Investigator's Brochures for more details. Patients in this study should be closely monitored for any evidence of overlapping and/or potentiation of hepatic toxicity.

Pneumonitis

Pneumonitis has been reported in 1.4% of patients receiving single-agent atezolizumab. These events have been primarily observed in patients with lung cancer. Pneumonitis is an identified risk for cobimetinib observed in patients treated with cobimetinib, as described in the Cobimetinib Investigator's Brochure.

Please refer to the Cobimetinib and Atezolizumab Investigator's Brochures for more details. Patients in this study should be closely monitored for any evidence of overlapping and/or potentiation of pneumonitis or other respiratory events.

Diarrhea, Nausea, and Vomiting

Diarrhea, nausea, and vomiting are identified risks and/or adverse drug reactions for cobimetinib, venetoclax, and atezolizumab as described in each respective Investigator's Brochure. Immune-mediated colitis has also been associated with the administration of atezolizumab. The combination of diarrhea, nausea, and vomiting has the potential to contribute to clinically significant volume depletion, dehydration, and/or electrolyte abnormalities from the combination of fluid losses with decreased oral intake.

Prompt supportive treatment should be instituted in case of gastrointestinal toxicity.

Fatigue

Fatigue is a common adverse event associated with anti-neoplastic agents, but it is also a symptom of the underlying disease, or other drug-related toxicities (e.g., anemia, electrolyte imbalance, hypothyroidism, dehydration) or a combination of all these causing factors. Fatigue has been reported in association with cobimetinib, venetoclax,

and atezolizumab. Attempts to identify and correct all potential causes of fatigue should be made in patients complaining of fatigue.

Please refer to the respective individual Cobimetinib, Venetoclax, and Atezolizumab Investigator's Brochures for more details.

Other Toxicities

In addition to the areas of potential overlapping toxicity described earlier in this section, a variety of other identified risks and/or adverse drug reactions (e.g., diarrhea, anemia) have been described in patients treated with cobimetinib, venetoclax, and/or atezolizumab. For details, please refer to the respective package inserts (if applicable) and Investigator's Brochures for this information.

Patients in this study should be closely monitored for any evidence of overlapping and/or potentiation of toxicities, including other general adverse events and/or any evidence of impaired ability to drive or use machines.

5.1.5 Management of Patients Who Experience Specific Adverse Events

Any toxicity associated with or possibly associated with study drug treatment should be managed with symptomatic treatment, dose interruptions, and/or dose reductions.
If cobimetinib and/or venetoclax are interrupted due to toxicity, the maximum allowable length of treatment interruption is 28 days before cobimetinib and/or venetoclax is considered permanently discontinued.

Criteria for treatment modifications and guidelines for the management of toxicities attributable to cobimetinib, venetoclax, and/or atezolizumab are summarized in Section 5.1.5.1–Section 5.1.5.18.

For cobimetinib and venetoclax, dose modifications may include dose reduction, dose interruption, and/or dose discontinuation. The dose levels for cobimetinib and venetoclax dose reduction are provided in Table 6 and Table 7.

Table 6 Recommended Doses of Cobimetinib in Arm A, Arm B, and Arm C

Dose Level	Cobimetinib Dose (mg) Arm A	Cobimetinib Dose (mg) Arm B and Arm C
DL-0	60	40
DL-1	40	20
DL-2	20	–

Table 7 Recommended Doses of Venetoclax in Arm B and Arm C

Dose Level	Venetoclax Dose (mg)	Reduced Dose (mg)
DL-0	800	600
DL-1	600	400
DL-2	400	200

For atezolizumab, dose modification may include holding study treatment or permanent discontinuation. There will be no dose reduction for atezolizumab in this study. Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for >12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for >12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >12 weeks if the Medical Monitor agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

Recognizing that new knowledge will be acquired and unforeseen safety issues may arise in the course of the study, the guidelines are not exhaustive and do not represent the full spectrum of care or treatment options described. The dose modification guidelines are not intended to replace clinical judgment or dictate care of individuals.

If these modifications are unclear or if a patient experiences an unexpected adverse event, please contact the Medical Monitor (see Section 5.4.1).

5.1.5.1 Cytopenias

Based on the safety profile of cobimetinib, a mild increase in the venetoclax hematologic toxicity is anticipated. In this study, blood counts will be monitored closely throughout treatment (see Appendix 1). Growth factors will be permitted for febrile neutropenia or neutropenic sepsis according to local practice, and patients will be monitored and treated promptly in case of infections. Dose interruptions or reductions will be allowed based on toxicity.

Recommended dose modifications for hematological toxicities are presented in Table 8.

Table 8 Recommended Dose Modifications for Hematological Toxicities

Grade 3 or 4 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia)	1st occurrence	• Interrupt venetoclax. • To reduce the infection risks associated with neutropenia, anti-infective prophylaxis and G-CSF for management should be considered per institutional guidelines. • Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose.
	2nd and subsequent occurrences	• Interrupt venetoclax. • Consider using anti-infective prophylaxis and G-CSF for management per institutional guidelines. • For Grade 4 (as well as for Grade 3 thrombocytopenia associated with hemorrhage) follow local institution guidelines for platelet transfusion • Follow dose reduction guidelines in Table 7 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician.

G-CSF = granulocyte colony-stimulating factor

Venetoclax may be re-initiated at a lower dose per Table 7. If a patient continues to derive clinical benefit but has persistent neutropenia, the dose of venetoclax may be further reduced per the dose reduction guidelines.

5.1.5.2 Infections

Patients with MM are at increased risk for infections. As noted in the exclusion criteria (see Section 4.1.2), patients receiving antimicrobial agents for therapeutic intent are not permitted to start treatment. Patients should be carefully screened for evidence of active or uncontrolled infections or disorders prior to enrollment. Patients receiving study medication must be closely monitored for infections and prompt therapy will be instituted, as necessary.

If indicated, anti-infective prophylaxis should be administered per institutional guidelines. Prophylactic antimicrobial therapy per institutional guidelines is permitted. Potential for drug-drug interactions should be considered. See Section 4.4.5 for details on prohibited and cautionary medications.

Patients should be advised to report fever and should be assessed for further management as per standard medical practice.

In the event of ≥Grade 3 or serious infection, treatment with venetoclax should be interrupted. Upon resolution, treatment can either be resumed at a reduced dose as outlined in Table 7 or discontinued at the discretion of the investigator.

5.1.5.3 Tumor Lysis Syndrome

TLS has not been described with the use of venetoclax in patients with MM. However, TLS cannot be excluded as a potential complication of the combination treatments. If the patient experiences TLS, study treatment should be put on hold and prompt supportive measures should be instituted as per institutional guidelines.

No prophylaxis measures for TLS are mandated in this protocol. However, it is strongly recommended to start oral hydration (approximately 1 to 2 liters as tolerated per day) starting from 72 hours prior to the first dose of venetoclax. An early chemistry laboratory analysis is requested at 4–6 hours after the administration of the first dose of venetoclax on Cycle 1 Day 1. Prophylaxis with uric acid reducing agents should be considered for patients with high uric acid levels. Clinical and laboratory evidence of TLS during treatment should be monitored and managed promptly.

For patients at higher risk (e.g., high tumor burden, plasmablastic morphology, unfavorable karyotype, or compromised renal function), more intensive measures (e.g., intravenous hydration, frequent monitoring of labs, hospitalization) should be considered at the investigator's discretion. If the patient experiences TLS, study treatment drugs should be put on hold. Continued monitoring may be necessary. If the event resolves within 24–48 hours, the patient can resume study treatment at the same dose level. For events requiring more than 48 hours to resolve, the study treatment should be resumed with a dose reduction of venetoclax to the next lower dose level.

5.1.5.4 Hepatotoxicity

Hepatotoxicity has been associated with the administration of either atezolizumab or cobimetinib. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminase, and liver function will be monitored throughout study treatment.

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

If LFTs increase, neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes for the increased LFTs. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal antibodies, and anti-smooth muscle antibody tests should be considered.

Patients with LFT abnormalities should be managed according to the guidelines in Table 9.

Table 9 Guidelines for the Management of Hepatotoxicity

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

Table 9 Guidelines for the Management of Hepatotoxicity (cont.)

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

LFT = liver function test; Q4W = every 4 weeks; TNF-α = tumor necrosis factor-alpha; ULN = upper limit of normal.

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

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

[c] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow 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.

5.1.5.5 Dermatologic Toxicity

Treatment-emergent rash has been associated with atezolizumab and cobimetinib. The majority of the cases of rash were mild in severity and self-limited, with or without pruritus. *Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab.*

A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

Dermatologic toxicity and rash should be managed according to the guidelines in Table 10.

Table 10 Guidelines for the Management of *Dermatologic Events*

Event	Action to Be Taken
General guidance	• A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.
Dermatologic event, Grade 1 or 2	• Continue study drugs. • Initiate supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve, consider treatment with higher-potency topical corticosteroids. • For Grade 2 rash, consider referral to dermatologist. Acneiform rash: • Consider topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) as clinically indicated.
Dermatologic event, Grade 3	• Withhold study drugs. • Refer patient to dermatologist. A biopsy should be performed if appropriate. • Consider initiating treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 2 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. Patients in Arm C: • If event resolves to Grade 2 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. [a, b] • Monitor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c]

Table 10 Guidelines for the Management of Dermatologic Events (cont.)

Event	Action to Be Taken
	Acneiform rash: • Consider continuation of topical corticosteroids (e.g., 2.5% alclometasone) and oral antibiotics (e.g., minocycline, doxycycline or antibiotics covering skin flora) when restarting cobimetinib.
Dermatologic event, Grade 4	• Permanently discontinue study drugs and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	*Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:* • *Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis.* • *Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy.* • *Follow the applicable treatment and management guidelines above.* • *If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.*

Note: Venetoclax dose may continue at the same level as per the investigator's judgment.

[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 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.

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

5.1.5.6 CPK Elevations and Rhabdomyolysis

Rhabdomyolysis and CPK elevation have been seen with cobimetinib (see the Cobimetinib Investigator's Brochure). Permanent discontinuation of cobimetinib treatment should be considered if rhabdomyolysis or symptomatic CPK elevations are attributed to cobimetinib and do not improve after temporary interruption. Guidelines for the management of CPK elevations and rhabdomyolysis are provided in Table 11.

Table 11 Guidelines for the Management of Grade 3 or Higher Elevations in CPK and Rhabdomyolysis

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

CPK = creatine phosphokinase; IM = intramuscular.

5.1.5.7 Visual Disorders

Serous retinopathy events have been associated with cobimetinib. Visual complaints have been associated with atezolizumab or cobimetinib, and should be evaluated by an ophthalmologist.

Uveitis or episcleritis and other immune-mediated ocular disease may be associated with atezolizumab. For further information, see the Atezolizumab Investigator's Brochure.

A severity guide for eye disorders classified as "other" per NCI CTCAE is provided in Table 12.

Table 12 National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 Eye Disorders—Other, Specify

Grade	Description
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental ADL
3	Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL
4	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye

ADL = activities of daily living.

Atezolizumab- and cobimetinib-associated ocular toxicity should be managed according to the guidelines in Table 13.

Table 13 Guidelines for Managing Ocular Toxicity

Event	Action to Be Taken
General guidance	• An ophthalmologist should evaluate visual complaints. • Uveitis or episcleritis and other immune-mediated ocular disease may be associated with atezolizumab and may be treated with topical corticosteroid eye drops. Atezolizumab should be permanently discontinued for immune-mediated ocular event that is unresponsive to local immunosuppressive therapy. • Serous retinopathy is associated with cobimetinib. In clinical trials, most events were Grade 1 (asymptomatic) or 2 (symptomatic). Most events in clinical trials resolved or improved to asymptomatic Grade 1 following dose interruption or reduction. If serous retinopathy is diagnosed, cobimetinib should be withheld until visual symptoms improve to Grade $\leq$ 1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation. • RVO has been reported in patients treated with MEK inhibitors other than cobimetinib.
Serous retinopathy Severity grade assessment based on NCI CTCAE v4.0 "Eye Disorders—Other" scale [a, b, c, d]	Serous retinopathy, Grade 1 [a] or 2 [b] (tolerable): • Continue cobimetinib and atezolizumab without dose change. • Continue ophthalmology follow-up as clinically indicated. Serous retinopathy, Grade 2 [b] (intolerable) or Grade 3 or 4 [c, d]: • Interrupt cobimetinib until Grade $\leq$ 1. • For ocular adverse events of suspected immune-mediated etiology, follow guidelines for atezolizumab provided in Appendix 8. • Consult ophthalmology and undergo complete ophthalmic examination, which includes visual acuity testing, intra-ocular pressure measurements, slit lamp ophthalmoscopy, indirect ophthalmoscopy, visual field, and OCT. Consider a fluorescein angiogram and/or indocyanine green angiogram, if clinically indicated. • Cobimetinib should be dose reduced by 1 dose level when restarting. • Consider permanent discontinuation of cobimetinib if serous retinopathy recurs despite 2 dose level reductions for patients receiving cobimetinib monotherapy or cobimetinib plus atezolizumab or one dose level reduction for patients in Arm B and Arm C.
Retinal vein occlusion (any grade)	• If RVO (any grade) is diagnosed, cobimetinib dosing should be permanently discontinued and RVO treated per institutional guidelines. • Continue atezolizumab.

Table 13 Guidelines for Managing Ocular Toxicity (cont.)

Event	Action to Be Taken
Potential immune-mediated ocular inflammatory toxicity (e.g., uveitis, iritis, episcleritis, or retinitis)	• For ocular adverse events of suspected immune-mediated etiology, follow guidelines for atezolizumab provided in Appendix 8. • Continue cobimetinib as clinically indicated.

ADL = activities of daily living; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OCT = optical coherence tomography; RVO = retinal vein occlusion.

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

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

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

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

5.1.5.8 Gastrointestinal Events

Table 14 Guidelines for Managing Gastrointestinal Toxicity

Event	Action to Be Taken
General guidance	• All events of diarrhea or colitis should be thoroughly evaluated for more common etiologies other than drug induced effects. • For events of significant duration or severity or associated with signs of systemic inflammation or acute phase reactants, check for immune-mediated colitis (see Section 5.1.5.9). • Anti-diarrheal prophylaxis (e.g., loperamide) is strongly recommended for patients treated with venetoclax in combination with cobimetinib. In patients receiving venetoclax plus cobimetinib who have experienced Grade 3 diarrhea anti-diarrheal medication is mandatory (see Table 5) • Administer anti-diarrheal agents and other maximal supportive care per institutional guidelines such as: at the first report of watery diarrhea or loose stool, initiate maximal anti-diarrheal supportive care (Lomotil® and loperamide). Suggested regimen: • Loperamide: Initiate dose with 4 mg, then 4 mg every 6 hours around the clock, alternating with Lomotil. • Lomotil (diphenoxylate and atropine): Dispense 2 tablets (diphenoxylate 5 mg, atropine 0.05 mg) every 6 hours around the clock. • Continue Lomotil and loperamide until no loose stools for 24 hours. • If Grade ≤ 2 diarrhea persists after 48 hours total treatment with Lomotil and loperamide, consider second-line agents (e.g., octreotide, budesonide, tincture of opium). Oral supplementation: • Initiate oral supplementation of potassium and/or magnesium if serum levels are < LLN. • Consider oral rehydration therapy (e.g., Pedialyte®) for Grade ≥ 1 diarrhea or vomiting. Dietary modifications: • Stop all lactose-containing products and eat small meals. • The BRAT (banana, rice, apples, toast) diet, without fiber (other vegetables and fruits), may be helpful. • Encourage adequate hydration with salt-containing liquids, such as broth or Gatorade®.
Diarrhea, Grade 1 or Grade 2 (tolerable)	• Continue cobimetinib, venetoclax, and atezolizumab. • Initiate supportive care and monitor patient closely. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis if appropriate.

Table 14 Guidelines for Managing Gastrointestinal Toxicity (cont.)

Event	Action to Be Taken
Diarrhea, Grade 2 (intolerable) or Grade 3	• Withhold cobimetinib, venetoclax, and atezolizumab. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis in patients receiving atezolizumab (e.g., NSAIDs) while investigating etiology. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate in patients receiving atezolizumab. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib and venetoclax with dose reduced by one level with continued supportive care or anti-diarrheal prophylaxis. If not, permanently discontinue cobimetinib and venetoclax. Patients in Arm C: • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. [a, b, c]
Diarrhea, Grade 4	• Permanently discontinue study drugs and contact Medical Monitor. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Rule out bowel perforation. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.

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

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

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks 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.

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

5.1.5.9 Colitis

Immune-mediated colitis has been associated with the administration of atezolizumab.

If the presence of diarrhea is of significant duration or magnitude or in case it is associated with signs of systemic inflammation or acute phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia), it is recommended to do the following:

- 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 for confirmation of the diagnosis of colitis. If possible, one or two biopsy specimens should be snap-frozen and stored.
- Perform laboratory tests to rule out alternate etiology (i.e., WBCs and stool calprotectin).

Table 15 Guidelines for the Management of Atezolizumab-Induced Colitis

Event	Action to Be Taken
Colitis, Grade 1	• Continue study drugs. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy if symptoms persist for >7 days.
Colitis, Grade 2	• Withhold study drugs. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.

Table 15 Guidelines for the Management of Atezolizumab-Induced Colitis (cont.)

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

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 *(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.

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

5.1.5.10 Cardiac Adverse Events

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

Guidelines for the management of congestive heart failure/reduction in LVEF are provided in Table 16.

Table 16 Guidelines for the Management of Congestive Heart Failure/Reduction in Left Ventricular Ejection Fraction

Patient	LVEF Value	Recommended Action with Cobimetinib and Atezolizumab [a]	LVEF Value Following Treatment Break	Recommended Cobimetinib Daily Dose
Asymptomatic	≥50% (or 40%–49% and <10% absolute decrease from BL)	• Continue atezolizumab and cobimetinib at current dose	N/A	N/A
	<40% (or 40%–49% and ≥10% absolute decrease from BL)	• Interrupt cobimetinib treatment for 2 weeks • Continue atezolizumab as clinically indicated	<10% absolute decrease from BL	• First occurrence: 40 mg [b] • Second occurrence: 20 mg [b] • Third occurrence: permanent discontinuation [b]
			<40% (or ≥ 10% absolute decrease from BL)	• Permanent discontinuation
Symptomatic	N/A	• Interrupt cobimetinib treatment for 4 weeks. • Consider withholding atezolizumab. • Discuss with Medical Monitor regarding resumption of atezolizumab. • Cardiology consultation is strongly recommended.	Asymptomatic and <10% absolute decrease from BL	• First occurrence: 40 mg • Second occurrence: 20 mg • Third occurrence: permanent discontinuation
			Asymptomatic and <40% (or ≥ 10% absolute decrease from BL)	• Permanent discontinuation
			Symptomatic regardless of LVEF	• Permanent discontinuation

BL = baseline; LVEF = left ventricular ejection fraction; N/A = not applicable.

[a] Treatment with venetoclax may continue at the discretion of the investigator.

[b] For patients in Arm B and Arm C, first occurrence: 20 mg; second occurrence: permanent discontinuation.

5.1.5.11 Hemorrhage

Treatment with venetoclax may continue at the discretion of the investigator, unless the event is related to thrombocytopenia in which case the recommendations provided for cytopenias should be followed (see Table 8).

Table 17 Guidelines for the Management of Hemorrhage

Event	Action to Be Taken
Grade 3 hemorrhage	• Interrupt cobimetinib treatment. There are no data on the effectiveness of cobimetinib dose modification for hemorrhage events. Clinical judgment should be applied when considering restarting cobimetinib treatment. • Continue atezolizumab treatment.
Grade 4 hemorrhage or any grade cerebral hemorrhage	• Interrupt cobimetinib treatment. Permanently discontinue cobimetinib for hemorrhage events attributed to cobimetinib. • Continue atezolizumab treatment.

5.1.5.12 Pancreatitis

Cobimetinib and venetoclax may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment. For management guidelines related to atezolizumab and pancreatitis, refer to Appendix 8.

5.1.5.13 Pulmonary Events, Including Pneumonitis

Table 18 Guidelines for Managing Pulmonary Events, Including Pneumonitis

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

Table 18 Guidelines for Managing Pulmonary Events, Including Pneumonitis (cont.)

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 *(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.

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

5.1.5.14 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. Guidelines for the management of neurologic disorders are provided in Appendix 8.

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

Patients may develop IRRs *or cytokine-release syndrome (CRS)* during the administration of atezolizumab.

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

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for the medical management of IRRs *and CRS* are provided in Appendix 8.

5.1.5.16 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, mental status changes, or constipation, should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies, as well as for hyponatremia or hyperkalemia. An endocrinologist should be consulted if an endocrinopathy is suspected. TSH and free T3, and T4 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 MRI of the brain (with detailed pituitary sections) may* help to differentiate primary pituitary insufficiency *from primary* adrenal insufficiency.

Guidelines for the management of hypothyroidism and hyperthyroidism, adrenal insufficiency, hyperglycemia, and hypophysitis are provided in Appendix 8.

5.1.5.17 Immune-Mediated Adverse Events

Down-modulating PD-L1/PD-1 signaling may permit the emergence of auto-reactive T cells and clinical autoimmunity. Adverse events associated with drug exposure and consistent with an autoimmune etiology are termed immune-mediated adverse events.

Patients should be informed of, and carefully monitored for, evidence of clinically immune-mediated adverse event (e.g., rash, colitis, uveitis, hepatitis, thyroid disease). Efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes prior to labeling an adverse event an immune-mediated adverse event. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity.

Although many low-grade immune-mediated adverse events respond well to symptomatic therapy, high-grade immune-mediated adverse events require corticosteroid therapy and, in rare corticosteroid-refractory cases, the use of other immune-suppressive therapies, such as infliximab or mycophenolate mofetil.

5.1.5.18 Immune-Mediated Myocarditis

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Guidelines for the management of immune-mediated myocarditis are provided in Appendix 8.

5.1.5.19 Immune-Mediated Meningoencephalitis

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Guidelines for the management of immune-mediated meningoencephalitis are provided in Appendix 8.

5.1.5.20 Immune-Mediated Nephritis

Immune-mediated nephritis is an identified risk associated with the administration of atezolizumab. Guidelines for the management of immune-mediated nephritis are provided in Appendix 8.

5.1.5.21 Other Unspecified Adverse Events

General dose modification recommendations for cobimetinib are provided in Table 19. Guidelines for the management of non-laboratory related adverse events are provided in Table 20, and guidelines for the management of unspecified Grade 3 and higher laboratory related adverse events are provided in Table 21.

Table 19 Dose Modifications Recommendations for Cobimetinib

Grade [a]	Recommended Cobimetinib Dosage
Grade 1 or Grade 2 (tolerable)	No dose reduction
Grade 2 (intolerable) or Grade 3 or 4	
1st Appearance [b]	Interrupt treatment until Grade ≤ 1, restart treatment at 40 mg once daily
2nd Appearance [b]	Interrupt treatment until Grade ≤ 1, restart treatment at 20 mg once daily
3rd Appearance [b]	Consider permanent discontinuation

NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

[a] The intensity of clinical adverse events graded by the NCI CTCAE v4.0.

[b] For patients in Arm B and Arm C, first appearance: 20 mg; second appearance: permanent discontinuation.

Cobimetinib dose modification should be based on the prescriber's assessment of individual patient safety or tolerability. If doses are omitted for toxicity; missed doses should not be replaced. Once the dose has been reduced, it should not be increased at a later time.

Table 20 Guidelines for the Management of Unspecified Related Adverse Events Grade 3 or Higher Other Than Laboratory Abnormalities

Atezolizumab dose cannot be reduced. Atezolizumab-related toxicity can be managed only by dose interruption or discontinuation.

Event	Action to Be Taken
Other unspecified related events (other than laboratory abnormalities), Grade 3	• Interrupt dosing of attributable study drug at the discretion of the investigator. During this time, treatment may continue with non-attributable study drugs. • If attributable study drug has been held and the event resolves to Grade ≤ 1 within 28 days, then restart dosing of attributable study drug. • If attributable study drug has been held and the event does not resolve to Grade ≤ 1 within 28 days, then discontinue attributable study drug. If attributable study drug is discontinued, treatment may continue with other study drugs at the discretion of the investigator.
Other unspecified related events (other than laboratory abnormalities), Grade 4 first occurrence	• During this time, treatment may continue with non-attributable study drugs. • If the Grade 4 event is attributed to one study drug: – Interrupt dosing of the attributable study drug at the discretion of the investigator. During this time, treatment may continue with non-attributable study drugs. – If the attributable study drug has been held and the event resolves to Grade ≤ 1 within 28 days, then restart dosing of the attributable study drug. – If the attributable study drug has been held and the event does not resolve to Grade ≤ 1 within 28 days, then discontinue the attributable study drug. If the attributable study drug is discontinued, treatment may continue with other study drugs at the discretion of the investigator.
Other unspecified related events (other than laboratory abnormalities), Grade 4 second occurrence	• If the Grade 4 event is attributed to cobimetinib or atezolizumab: – If the Grade 4 event recurs despite reduction of the attributable study drug by one dose level or interruption, discontinue the attributable study drug at the discretion of the investigator. During this time, treatment may continue with non-attributable study drugs.

Table 21 Guidelines for Grade 3 and Higher Unspecified Laboratory Abnormality Adverse Events

Event	Action to Be Taken
Other unspecified events that are laboratory abnormalities, Grade ≥ 3	• For Grade ≥ 3 toxicities associated primarily with laboratory abnormalities only and for which guidance has not already been specified elsewhere in this protocol (e.g., elevation of lipase or amylase, or decreases in phosphorus without clinical or other evidence of pancreatitis or other hepatic dysfunction), all study drugs may continue without interruption and/or dose reduction at the discretion of the investigator.

5.1.5.22 Immune-Mediated Myositis

Immune-mediated myositis is an identified risk associated with the administration of atezolizumab. Guidelines for the management of immune-mediated myositis are provided in Appendix 8.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

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

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

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

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see

Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

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

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

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, or hypophysitis
- Systemic lupus erythematosus
- Neurologic: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, *HLH, and MAS*
- Ocular events
  - RVO (Grade ≥ 1)
  - Serous retinopathy, including any events of retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment, and central serous chorioretinopathy
  - Ocular inflammatory toxicities (e.g., uveitis, retinitis*, optic neuritis*)
- Significant muscular toxicities
  - Rhabdomyolysis or Grade ≥ 3 CPK elevation
  - Myopathies including myositis
- Grade ≥ 3 hemorrhage or any grade cerebral hemorrhage
- Grade ≥ 3 rash
- Grade ≥ 2 cardiac events, including:
  - Symptomatic heart failure or Grade ≥ 2 left ventricular ejection fraction reduction
  - Myocarditis, pericarditis, or atrial fibrillation
- Vasculitis
- Grade ≥ 3 diarrhea
- Significant liver toxicity
  - Hepatitis, including AST and/or ALT $> 10 \times$ ULN

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

  Treatment emergent ALT or AST $>3\times$ ULN in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice, without initial findings of cholestasis (elevated serum ALP)

  No other reason can be found to explain the combination of increased ALT/AST and total bilirubin, such as: liver metastasis; viral hepatitis A, B, or C; alcoholic and autoimmune hepatitis; other liver diseases; or exposure to other drugs known to cause liver injury

- Any TLS
- Grade 4 thrombocytopenia
- Grade ≥ 3 infection
- Hepatitis B reactivation
- Myositis

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 Section 5.4–Section 5.6.

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

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 90 days after the last dose of study drug. For patients receiving atezolizumab (in both the safety run-in phase and the randomization phase), this period should be extended up to 135 days after the last dose of atezolizumab.

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

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation 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 22 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 22 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an

adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

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

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 IRRs (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. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes 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., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

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

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

5.3.5.8 Deaths

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 MM should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Multiple Myeloma

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 IMWG 2016 criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

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

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

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

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

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

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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted], M.D.

Telephone No.: [redacted]

Email: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 135 days after the last dose of study treatment for patients who receive atezolizumab and 90 days after the last dose of study treatment for patients who do not receive atezolizumab. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur 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 *through the Informed Consent Form* to immediately inform the investigator if they become pregnant during the study or within 3 months after the last dose of cobimetinib, 1 month after the last dose of venetoclax, and 5 months after the last dose of atezolizumab. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

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

5.4.3.3 Abortions

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

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

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 135 days after the last dose of atezolizumab and 90 days for patients who do not receive atezolizumab), 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 paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- Cobimetinib Investigator's Brochure
- Venetoclax Investigator’s Brochure
- Atezolizumab Investigator’s Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Data from the safety run-in phase and the randomization phase will be analyzed separately, that is, data will not be combined across the two phases for Arms B and C when listing or summarizing data. For each phase, analyses to assess safety will be conducted using the safety-evaluable population, defined as all patients who receive any amount of study drug and analyzed according to the treatment arm they received. Analyses to assess efficacy will also be conducted in the same manner using the safety population. Patients who fail to receive no component of their planned study medication

will be excluded from the safety population, and will be included in any intent-to-treat analyses.

There is no formal hypothesis testing planned therefore analyses will be solely descriptive. The safety, tolerability, clinical activity, and pharmacokinetics of the three treatment arms will be described and summarized as warranted by sample size. That is, listings may be used in lieu of summary tables in the event of a small sample size.

Continuous variables will be summarized using mean, standard deviation, median, and range; categorical variables will be summarized using counts and percentages.

Additional details regarding specific analyses and data handling will be documented in a separate statistical analysis plan.

6.1 DETERMINATION OF SAMPLE SIZE

Design considerations were not made with regard to power or to control the type I error, but to obtain preliminary efficacy, safety, tolerability, and PK information of cobimetinib as a single agent (Arm A), cobimetinib plus venetoclax (Arm B), and cobimetinib plus venetoclax plus atezolizumab (Arm C) in patients with R/R MM.

Approximately 72 patients are anticipated to be recruited in this study: approximately 12 patients in the safety run-in cohorts, 12 patients in Arm A, 24 patients in Arm B, and 24 patients in Arm C.

If patients must be replaced or additional cohorts are enrolled during the safety run-in, the total sample size for this study may increase and the study team may enroll 6 additional patients (in each safety run-in cohort, if necessary) at a reduced dose level (see Section 3.1). Depending on the outcome of the review of the clinical data from the additional 6 patients, the study team will determine if the expansion stage can initiate with this lower combination dose.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for patient discontinuations from the study treatment and from the study will be listed and summarized. Enrollment, study treatment administration, and major protocol deviations will be evaluated for their potential effects on the interpretation of study results.

For safety-evaluable patients, study drug administration data will be tabulated or listed by cohort, and any dose modifications will be flagged. Descriptive statistics will be used to summarize the total dose of cobimetinib, venetoclax, and atezolizumab received.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics such as age, sex race/ethnicity, weight, type of malignancy, and baseline ECOG Performance Status will be summarized using descriptive statistics for continuous variables and proportions for categorical variables, as appropriate.

6.4 EFFICACY ANALYSES

For all primary, secondary, and exploratory efficacy analyses listed within this section, data will be analyzed and summarized separately for the safety run-in phase and the randomization phase; data will not be combined across phases.

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective of this study is to evaluate the anti-myeloma activity of cobimetinib administered as a single agent (Arm A), cobimetinib in combination with venetoclax (Arm B), and cobimetinib in combination with venetoclax and atezolizumab (Arm C) based on the overall response rate (ORR) as determined by the investigator using the IMWG response criteria (Kumar et al. 2016). ORR is defined as sCR, CR, VGPR, or PR and will be analyzed in the efficacy population and in biomarker-selected sub-populations (e.g., MAPK activation, t[11;14]). For Arm A, ORR will also be analyzed separately in the cobimetinib single-agent arm and for those patients who are treated with cobimetinib plus atezolizumab upon disease progression.

Descriptive statistics will be used to evaluate the incidence, nature and severity of adverse events, graded according to the NCI CTCAE v4.0.

6.4.2 Secondary Efficacy Endpoints

Further analyses of anti-myeloma activity will be based on definitions of responses according to IMWG (see Appendix 5) as defined below:

- Clinical benefit rate defined as MR or better (PR, VGPR, CR, sCR)
- PFS defined as the time from randomization to the first occurrence of disease progression or relapse as determined by the investigator using the IMWG criteria or death from any cause during the study, whichever occurs first.
- DOR applies to patients achieving at least a PR, and is measured from the first observation of PR to the time of disease progression; deaths not due to progression will be censored.
- Overall survival (OS) defined as the time from randomization until death from any cause.

6.4.3 Exploratory Efficacy Endpoints

An exploratory efficacy endpoint will assess the time to next treatment, defined as the time between the start date of the current treatment line and the start date of the next treatment line, death, or last follow-up.

6.5 SAFETY ANALYSES

The safety analyses will include all patients who received at least one dose of any study drug, and will be analyzed and summarized separately for the safety run-in phase and the randomization phase; data will not be combined across phases.

Adverse events, deaths, change in laboratory test results, change in vital signs, and exposure to components of study treatment will be assessed to determine the safety of treatment regimen.

Verbatim descriptions of adverse events will be mapped to appropriate thesaurus terms. All adverse events occurring on or after treatment Day 1 will be summarized by the mapped term, appropriate thesaurus levels, and NCI CTCAE, v4.0 toxicity grade. In addition, adverse events leading to treatment withdrawal or death, and serious adverse events will be listed with more detailed information, such as the day of onset of an adverse event, duration of adverse event, toxicity grade, etc.

Relevant laboratory and vital signs (heart rate, blood pressure, and temperature) and ECG data will be displayed by time post-dose, with NCI CTCAE Grade 3 and 4 values identified where appropriate. Additionally, changes in laboratory data will be summarized by grade using the NCI CTCAE toxicity grade. Selected vital signs and selected laboratory data will be summarized by visit.

The extent of study drug exposure (dose and duration) will be examined to determine the degree of treatment tolerability. In addition to treatment duration and total dose received, any dose modification of study drugs will also be summarized. Concomitant medications received during the treatment period will be summarized.

6.6 PHARMACOKINETIC ANALYSES

The PK analyses population will consist of patients from Arm A, Arm B, and Arm C who have received at least one dose of study medication and for whom at least one evaluable PK sample is collected. PK data will be analyzed and summarized separately for the safety run-in phase and the randomization phase; data will not be combined across phases. Cobimetinib and venetoclax area under the plasma concentration vs. time curve, maximum concentration, and time to maximum concentration (AUC, C_{max}, and T_{max}) will be reported for individual patients. Atezolizumab C_{max} and C_{min} will be reported for individual patients. Summary PK data will be provided, as data permit.

Existing population PK models for cobimetinib, venetoclax, and atezolizumab will be used to investigate the relationship between drug exposure and efficacy or safety outcomes using population approaches for each medication.

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

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population for atezolizumab will consist of all patients from Arm C with any ADA assessment, with patients grouped by stage and cohort.

The numbers and proportions of ADA-positive patients and ADA-negative patients during both the treatment and follow-up periods will be summarized by safety run-in and randomization phase, and by cohort and study arm. Patients are considered to be ADA positive if they are ADA negative or missing data at baseline but develop an ADA response following study drug administration (treatment–induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., $\geq$0.60 titer units) than the titer of the baseline sample (treatment–enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

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

6.8 EXPLORATORY BIOMARKER ANALYSES

The biomarker readout and the relation to clinical activity will be summarized as warranted by the sample size.

The efficacy of Arm A, Arm B, and Arm C will be correlated to biomarkers such as MAPK hyperactivation (including RAS mutation), t(11;14) translocations, and pretreatment immune contexture. Data will be analyzed and summarized separately for the safety run-in phase and the randomization phase; data will not be combined across phases.

In the three study arms different biomarkers will be evaluated, including those associated with disease biology, the mechanism of action of cobimetinib, the resistance to study drugs, pharmacodynamics, and prognosis. Furthermore, the available biomarkers will be assessed for the improvement of diagnostic assays.

MRD will be evaluated and correlated with patient response and survival (Kumar et al. 2016).

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of

discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable 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) and applicable local, regional, and national laws.

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.

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (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 study is sponsored by F. Hoffmann-La Roche Ltd. This study will enroll a total of approximately 72 patients. The Sponsor will provide clinical operations oversight, data management support, and medical monitoring.

Randomization will occur through an interactive voice or Web-based response system (IxRS). Efficacy assessments and other specified laboratory tests throughout the study will be conducted in accredited local laboratories; local laboratory ranges will be collected. Central facilities will be used for the assessment of biomarker and PK objectives. Plasma and serum will be sent to a central laboratory for analysis and sample storage. Routine sample analysis will be performed by an accredited external vendor; local laboratory ranges will be collected.

Following the completion of the safety run-in phase, further accrual to the randomization phase will be temporarily halted while the study team reviews the totality of clinical data to determine safety and tolerability of all regimens. Only after the regimens have demonstrated acceptable safety, the randomization phase can be initiated. As it is estimated that it will take several months to complete enrollment of the safety run-in phase, the safety review should contain data from patients who have been receiving the regimen for a minimum of one cycle of treatment.

Stopping rules for patient safety are provided in Section 3.1.1.

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, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical *Study Information* at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

10. REFERENCES

Andrulis M, Lehners N, Capper D, et al. Targeting the BRAF V600E mutation in multiple myeloma. Cancer Discov 2013;3:862–9.

Atallah E, Cortes J, O'Brien S, et al. Establishment of baseline toxicity expectations with standard frontline chemotherapy in acute myelogenous leukemia. Blood 2007;110:3547–51.

Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome. Blood 2007;109:3489–95.

Avvisati G. AML: treatment-related toxicity or not? Blood 2007;110:10:3491.

Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 2012;51:119–35.

Becker N. Epidemiology of multiple myeloma. Recent Results Cancer Res 2011;183:25–35.

Besse B, Johnson M, Janne PA, et al. 16LBA: Phase II, single-arm trial (BIRCH) of atezolizumab as first-line or subsequent therapy for locally advanced or metastatic PD L1 selected non-small cell lung cancer (NSCLC). Eur J Cancer 2015;51(Suppl- 3):S717–8.

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54:307–14.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to exhaustion: an update on implications for chronic infection and tumour evasion. Cancer Immunol Immunother 2007;56:739–45.

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

Certo M, Del Gaizo Moore V, Nishino M, et al. Mitochondria primed by death signals determine cellular addiction to antiapoptotic BCL-2 family members. Cancer Cell 2006;9:351–65.

Cooper ZA, Reuben A, Austin-Breneman J, et al. Does it MEK a difference? Understanding immune effects of targeted therapy. Clin Cancer Res 2015;21;3102–4.

Cragg MS, Jansen ES, Cook M, et al. Treatment of B-RAF mutant human tumor cells with a MEK inhibitor requires Bim and is enhanced by a BH3 mimetic. J Clin Invest 2008;119:3651–9.

Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs 2016;8:593–603. doi: 10.1080/19420862.2015.1136043. Epub: 26 February 2016.

Durie BG, Harousseau J-L, Miguel JS, Blade J, et al. International uniform response criteria for multiple myeloma. Leukemia 2006; 20: 1467–73.

Durie BG, San Miguel J, Blade J et al. Clarification of the definition of complete respose in multiple myeloma. Leukemia 2015;29:2416–7.

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

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

Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 2012;367:1694–703.

Friday BB, Adjei AA. Advances in targeting the Ras/Raf/MEK/Erk mitogen-activated protein kinase cascade with MEK inhibitors for cancer therapy. Clin Cancer Res 2008;14:342–6.

Hamanishi J, Mandai M, Iwasake M, et al. Programmed cell death 1 ligant 1 and tumor infiltrating CD8+ T lymphocytes are prognostic factors for human ovarian cancer. Proc Natl Acad Sci USA 2007;104:3360–5.

Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.

Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti–PD L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563–7.

Heuck C, Chavan SS, Stein CK, et al. Comprehensive genomic profiling of multiple myeloma in the course of clinical care identifies targetable and prognostically significant genomic alterations. Blood 2015;126:369.

Heuck CJ, Jethava Y, Khan R, et al. Inhibiting MEK in MAPK pathway-activated myeloma. Leukemia 2016;30;976–80.

Hino R, Kabashima K, Kato Y, et al. Tumor cell expression of programmed cell death-1 ligand 1 is a prognostic factor for malignant melanoma. Cancer 2010;116:1757–66.

Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. J Cutan Pathol 2010;37:48–53.

Holkova B, Zingone A, Kieciak M et al. A Phase II trial of AZD6244 (Selumetinib, ARRY-142886), an oral MEK1/2 inhibitor, in relapsed/refractory multiple myeloma. Clin Cancer Res 2016;22:1067–75.

Hossain DM, Panda AK, Chakrabarty S, et al. MEK inhibition prevents tumour-shed transforming growth factor b-induced T-regulatory cell augmentation in tumour milieu. Immunology 2015;144:561–73.

Iwai Y, Ishida M, Tanaka Y, et al. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002;99:12293–7.

Johnson GL, Lapadat R. Mitogen activated protein kinase pathways mediated by ERK, JNK and p38 protein kinases. Science 2002;298:1911–12.

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

Kantoff PW, Higano CS, Shore ND, et al. IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.

Korfi K, Smith M, Swan J, et al. BIM mediates synergistic killing of B-cell acute lymphoblastic leukemia cells by BCL-2 and MEK inhibitors. Cell Death and Disease 2016;7:e2177.

Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia 2014 May;28:1122–8.

Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia 2012;26:149–57.

Kumar SK, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016;17:e328–46.

Kumar SK, Vij R, Kaufman JL,et al. Safety and efficacy of venetoclax (ABT-199/GDC-0199) monotherapy for relapsed/refractory multiple myeloma: Phase 1 preliminary results. Blood 2015;126:4219.

Kumar SK, Vij R, Kaufman JL, et al. Phase I venetoclax monotherapy for relapsed/refractory multiple myeloma [abstract]. J Clin Oncol 2016;34(suppl): abstr 8032.

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

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625–38.

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

Liu J , Hamrouni A, Wolowiec D, et al: Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN-{gamma} and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. Blood 2007;110:296–304.

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

Mey UJM, Renner C, von MoosR. Vemurafenib in combination with cobimetinib in relapsed and refractor y extramedullary multiple myeloma harboring the BRAF V600E mutation. Hematol Oncol 2016; doi: 10.1002/hon.2353. [Epub ahead of print].

Nooka AK, Kastritis E, Dimopoulos MA, et al. Treatment options for relapsed and refractory multiple myeloma. Blood 2015;125:3085–99.

Ozaki T, Honjo J. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol 2007;19:813–24.

Postel-Vinay S. Redefining dose-limiting toxicity. Clin Adv Hematol Oncol 2015;13:87–9.

Punnoose EA, Leverson JD, Peale F, et al. Expression profile of BCL-2, BCL-XL, and MCL-1 predicts pharmacological response to the BCL-2 selective antagonist venetoclax in multiple myeloma models. Mol Cancer Ther 2016;15:1132–44.

Rajkumar SV, Richardson P, San Miguel JF. Guidelines for determination of the number of prior lines of therapy in multiple myeloma. Blood 2015;126:921–2.

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

Rosenblatt J, Glotzbecker B, Mills H, et al. PD-1 blockade by CT-011, anti-PD-1 antibody, enhances ex vivo T-cell responses to autologous dendritic cell/myeloma fusion vaccine. J Immunother 2011;34:409–18.

Rosenberg J, Petrylak D, Abidoye O, et al. 21LB: Atezolizumab in patients with locally advanced or metastatic urothelial carcinoma (mUC): Results from a pivotal multicenter phase II study (IMvigor 210). Eur J Cancer 2015;51(Suppl 3):S720.

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

Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med 2013;19:202–8.

Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015;372:142–52.

Strome SE, Dong H, Tamura H, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res 2003;63:6501–5.

Tamura H, Ishibashi M, Yamashita T, et al. Marrow stromal cells induce B7-H1 expression on myeloma cells, generating aggressive characteristics in multiple myeloma. Leukemia 2013;27:464–72.

Taylor RC, Cullen SP, Martin SJ. Apoptosis: controlled demolition at the cellular level. Nat Rev Mol Cell Biol 2008;9:231–41.

Thompson RH, Kuntz SM, Leibovich BC, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer Res 2006;66:3381–5.

Usmani SZ, Weiss BM, Plesner T, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. Blood 2016;128:37–44.

VanBrocklin MW, Verhaegen M, Soengas MS, et al. Mitogen-activated protein kinase inhibition induces translocation of Bmf to promote apoptosis in melanoma. Cancer Res 2009;69:1985–94.

Vansteenkiste J, Fehrenbacher L, Spira AI, et al. 14LBA: Atezolizumab monotherapy vs docetaxel in 2L/3L non-small cell lung cancer: Primary analysis for efficacy, safety and predictive biomarkers from a randomized phase II study (POPLAR). Eur J Cancer 2015;51(Suppl 3):S716–7.

Yousef S, Marvin J, Steinbach M, et al. Immunomodulatory molecule PD-L1 is expressed on malignant plasma cells and myeloma-propagating pre-plasma cells in the bone marrow of multiple myeloma patients. Blood Cancer J 2015;5:e285.

Appendix 1
Schedule of Activities

	Screening [a]	Study Regimen Treatment Period [b]									Treatment Discontinuation [c]	Follow-up Visits [d]	Complete Response
		Cycle 1			Cycle 2			Cycle 3+					
Days	−28 to −1	1	15	22	1	15	22	1	15	22			
Informed consent [e]	x												
Demographic data	x												
Medical history	x												
Vital signs [f, g]	x	x	x		x	x		x	x		x		
Height (on Cycle 1, Day 1 only) and weight	x	x			x			x			x		
ECOG Performance Status	x	x			x			x			x		
Physical examination [h]	x	x	x		x	x		x	x		x		
ECHO or MUGA scan [i]	x				x			x			x		
12-lead ECG	x	x											
SPEP, UPEP, SIFE, UIFE [j]	x	x			x			x			x		
sFLCs [k]	x	x			x			x			x		
Skeletal survey/assessment of lytic disease	x [a]	As clinically indicated (X-ray, whole-body low-dose CT, MRI, or PET scan)											
Plasmacytoma assessment [l]	x							x					
Serum β-2 microglobulin	x												
Quantitative immunoglobulins (including IgA, IgG, IgM)	x	x			x			x			x		
Hematology [m]	x	x	x		x	x		x	x		x		
Coagulation (PT, aPTT, INR)	x	x											

Appendix 1 Schedule of Activities (cont.)

	Screening [a]	Study Regimen Treatment Period [b]									Treatment Discontinuation [c]	Follow-up Visits [d]	Complete Response
		Cycle 1			Cycle 2			Cycle 3+					
Days	−28 to −1	1	15	22	1	15	22	1	15	22			
Chemistry [n]	x	x	x		x	x		x	x		x		
Viral serology (HIV, HBsAg, hepatitis B surface antibody, total HBcAb, HCV antibody) [o]	x												
Thyroid function test [p]	x	x						x					
Urinalysis [q]	x	x			x			x			x		
Pregnancy test [r]	x	Monthly and as clinically indicated											
Ophthalmic exams [s]	x				x			x			x		
Cobimetinib dispensing		x			x			x					
Atezolizumab administration [t]		x	x		x	x		x	x				
Venetoclax dispensing		x			x			x					
Concomitant medications	Continuous from time of signed ICF until 90 days after last study treatment dose												
Adverse events [u]	Continuous from time of signed ICF until 90 days after last study treatment dose												
ADA sample	See Appendix 2												
PK sample	See Appendix 2												
Biomarker bone marrow biopsy [v]	x							x [v]					
Biomarker bone marrow aspirate sample [w]	x					x		x					x
Serum samples for analysis of autoantibodies	x	Perform if an atezolizumab-treated patient experiences a suspected immune-mediated adverse event											
Biomarker blood sample [x]		x	x		x	x		x			x		x

Appendix 1 Schedule of Activities (cont.)

	Screening [a]	Study Regimen Treatment Period [b]									Treatment Discontinuation [c]	Follow-up Visits [d]	Complete Response
		Cycle 1			Cycle 2			Cycle 3+					
Days	−28 to −1	1	15	22	1	15	22	1	15	22			
Biomarker serum sample [y]		x			x			x			x		x
Biomarker plasma sample [z]		x	x		x	x		x			x		x
Survival assessment												x [d]	

ADA = anti-drug antibody; ALP = alkaline phosphatase; CR = complete response; CT = computed tomography; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; ICF = Informed Consent Form; LVEF = left ventricular ejection fraction; MRD = minimal residual disease; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition (scan); PD = progressive disease; PET = positron emission tomography; PK = pharmacokinetic; sFLC = serum free light chain; SIFE = serum immunofixation electrophoresis; SPEP = serum protein electrophoresis; T4 = thyroxine; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; UIFE = urine immunofixation electrophoresis; UPEP = urine protein electrophoresis.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening, except for extramedullary disease and skeletal survey in which a 35-day window is allowed.

[b] A time window of ±2 days is allowed for all study assessments unless otherwise specified. Pneumococcal vaccination may be considered during the initiation of screening procedures for all patients who have not previously received the vaccine. At the investigator's discretion, inactive influenza vaccination may also be considered (live attenuated vaccines are not permitted) during the initiation of screening procedures and during study treatment.

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

[d] Required follow-up information will be collected via telephone calls and/or clinic visits every 3 months until death, withdrawal of consent, the patient is lost to follow-up, or study termination by the Sponsor, whichever occurs first.

[e] Informed consent must be documented before and study-specific screening procedure is performed and may be obtained up to 28 days before initiation of study treatment.

[f] Includes respiratory rate, heart rate, temperature, and systolic and diastolic blood pressure while the patient is in a seated position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] For patients receiving atezolizumab, either with the triplet regimen (Arm C) or in those patients in which atezolizumab is added on cobimetinib monotherapy upon PD (Arm A), vital signs will be collected at screening and thereafter as follows during each atezolizumab administration. For the first infusion (Cycle 1), vital signs will be measured and recorded within 60 minutes prior to the infusion, every 15 (± 5) minutes during the infusion, and 30 (± 10) minutes after the infusion. For subsequent cycles, vital signs will be measured and recorded within 60 minutes prior to the infusion, every 15 (± 5) minutes during the infusion, and 30 (± 10) minutes after the infusion.

[h] A complete physical examination should be performed at screening and should include an evaluation of the head, eyes, ears, nose, throat, neck, and lymph node regions, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[i] All patients will undergo evaluation of left ventricular dysfunction, either by ECHO or MUGA screening. Evaluation of LVEF by ECHO or MUGA scan (using the same method for each patient) must be performed at the following time points:

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

[j] Assessments performed at screening, Day 1 of each treatment cycle (SPEP and UPEP), to confirm sCR or CR (SIFE and UIFE), and at treatment discontinuation. SIFE and UIFE to be performed only if electrophoresis shows no measurable protein.

[k] sFLCs performed at screening, Day 1 of each treatment cycle, and treatment discontinuation; also when sCR or CR is suspected or maintained.

[l] If clinically indicated at screening by radiologic imaging (CT scan or MRI) and thereafter every 12 weeks.

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

[n] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate (or total CO_2), glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, LDH, CPK, lipase, and amylase. Serum chemistry includes serum cholesterol and triglycerides at baseline. On Cycle 1 Day 1, the chemistry panel should be repeated at 4–6 hours after the first treatment with venetoclax.

[o] If a patient has a negative HBsAg test result and a positive total HBcAb test result at screening, an HBV DNA test must be performed to rule out active HBV infection based on HBV viral load per local guidelines. If a patient has a positive HCV antibody test result at screening, an HCV RNA test should be performed to rule out active HCV infection prior to initiation of study treatment. For patients with unknown HIV status, HIV testing must be performed at screening if not in contradiction with local regulations.

[p] Thyroid function testing (TSH, free T3, or total T3 where T3 is not performed, free T4) collected on Day 1 of Cycle 1, and Day 1 of every fourth cycle thereafter.

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

[r] All women of childbearing potential will have a serum pregnancy test performed at screening (within 7 days prior to initiation of study drug), and then monthly and as clinically indicated. After study treatment discontinuation, a monthly pregnancy test should be performed (in women of childbearing potential) for at least 3 months after the last dose of cobimetinib, 1 month after the last dose of venetoclax, and 5 months after the last dose of atezolizumab.

[s] Ophthalmic examination includes visual acuity testing, intraocular pressure measurements by tonometry, slitlamp ophthalmoscopy, indirect ophthalmoscopy, and optical coherence tomography (spectral- or time-domain).

All patients must undergo ophthalmic examination at screening and at the following timepoints:

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

[t] Atezolizumab IV will be administered at a fixed dose of 840 mg IV on Days 1 and Day 15 (±3 days) in of each 28-day cycle (note: Cycle 1 of the safety run-in phase does not include the 3-day window).

[u] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 90 days after the last dose of study drug. After the end of the adverse event reporting period if the investigator becomes aware of a serious adverse event that is believed to be related to prior study drug treatment, the event should be reported through use of the Adverse Event eCRF. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcoe can be reported.

[v] Biomarker bone marrow biopsy to be collected at screening (mandatory) and Day 1 of Cycle 4 (optional).

[w] Bone marrow aspirate to be collected at screening, on Day 15 of Cycle 2, Day 1 of Cycle 4, and at CR, CR +3 months, and CR +6 months.

[x] Whole blood to be collected on Days 1 and 15 of Cycle 1, Days 1 and 15 of Cycle 2, Day 1 of Cycle 4, Day 1 of Cycle 7, at treatment discontinuation, and at CR, CR +3 months, and CR +6 months.

[y] Serum sample to be collected on Day 1 of Cycle 1, Day 1 of Cycle 2, Day 1 of Cycle 4, Day 1 of Cycle 7, at treatment discontinuation, and at CR, CR +3 months, and CR +6 months (SIFE interference assay for atezolizumab).

[z] Plasma sample to be collected on Days 1 and 15 of Cycle 1, Days 1 and 15 of Cycle 2, Day 1 of Cycle 4, Day 1 of Cycle 7, at treatment discontinuation, and at CR, CR+3 months, and CR+6 months.

Appendix 2
Schedule of Pharmacokinetic and Immunogenicity Samples

ARM A (COBIMETINIB)

Study Visit	Timepoint	Sample Type
Cycle 1 Day 1	2–4 hour post-dose	Cobimetinib PK (plasma)
Cycle 1 Day 15	Pre-dose (within 1 hour prior to dose)	Cobimetinib PK (plasma)
	2–4 hour post-dose	Cobimetinib PK (plasma)

PK = pharmacokinetic.

Note: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ±3 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays. Ensure dose times are accurately recorded on PK sampling day and the day prior to PK sampling. Ensure all sampling times are accurately recorded.

ARM B (COBIMETINIB + VENETOCLAX)

Study Visit	Timepoint	Sample Type
Cycle 1 Day 1	2–4 hour postdose	Cobimetinib PK (plasma)
	6 hour postdose (± 20 min)	Venetoclax PK (plasma)
Cycle 1 Day 15	Predose (within 1 hour prior to dose)	Venetoclax PK (plasma) Cobimetinib PK (plasma)
	2 hour postdose	Venetoclax PK (plasma) Cobimetinib PK (plasma)
	4 hour postdose	Venetoclax PK (plasma) Cobimetinib PK (plasma)
	6 hour postdose (± 20 min)	Venetoclax PK (plasma) Cobimetinib PK (plasma)
	8 hour postdose (–1 hr/+20 min), if patient is in the clinic	Venetoclax PK (plasma)
Cycle 2 Day 1	Predose (within 1 hour prior to dose)	Venetoclax PK (plasma)
Cycle 3 Day 1	Predose (within 1 hour prior to dose)	Venetoclax PK (plasma)

PK = pharmacokinetic.

Note: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ±3 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays. Ensure dose times are accurately recorded on PK sampling day and the day prior to PK sampling. Ensure all sampling times are accurately recorded.

Appendix 2
Schedule of Pharmacokinetic and Immunogenicity Samples (cont.)
ARM C (COBIMETINIB + VENETOCLAX + ATEZOLIZUMAB)

Study Visit	Timepoint	Sample Type
Cycle 1 Day 1	Prior to the first infusion	Atezolizumab PK and ADA (serum)
	30 (±10) minutes following the end of atezolizumab infusion	Atezolizumab PK (serum)
	2–4 hour post-cobimetinib dose	Cobimetinib PK (plasma)
	6 hour postdose (± 20 min)	Venetoclax PK (plasma)
Cycle 1 Day 15	Pre-dose (within 1 hour prior to dose)	Venetoclax PK (plasma) Cobimetinib PK (plasma)
	2 hour post-cobimetinib dose	Venetoclax PK (plasma) Cobimetinib PK (plasma)
	4 hour post-cobimetinib dose	Venetoclax PK (plasma) Cobimetinib PK (plasma)
	6 hour postdose (± 20 min)	Venetoclax PK (plasma) Cobimetinib PK (plasma)
	8 hour postdose (–1 hr/+20 min), if patient is in the clinic	Venetoclax PK (plasma)
Cycle 2 Day 1	Prior to the first infusion	Atezolizumab PK and ADA (serum)
	Pre-dose (within 1 hour prior to dose)	Venetoclax PK (plasma)
Cycle 3 Day 1	Prior to the first infusion	Atezolizumab PK and ADA (serum)
	Pre-dose (within 1 hour prior to dose)	Venetoclax PK (plasma)
Treatment discontinuation visit [a]	At visit	Atezolizumab PK and ADA (serum)

ADA = anti-drug antibody; PK = pharmacokinetic.

Note: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ±3 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays. Ensure dose times are accurately recorded on PK sampling day and the day prior to PK sampling. Ensure all sampling times are accurately recorded.

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

Appendix 3
Guidelines for the Determination of Prior Lines of Therapy

LINE OF THERAPY

A line of therapy is defined as ≥1 complete cycle of a single agent, combination regimen of several drugs, or a planned sequential therapy of various drugs (e.g., induction therapy followed by autologous stem cell transplantation is considered 1 line of therapy).

NEW LINE OF THERAPY

A treatment is considered a new line of therapy if any one of the following three conditions is met:

Definition of a New Line of Therapy	Comments
Discontinuation of one treatment regimen and start of another	• A regimen is considered to have been discontinued if all drugs in that given regimen have been stopped. • The reasons for discontinuation, addition, substitution or SCT do not influence how lines are counted.
Unplanned addition or substitution of 1 or more drugs in a regimen	• Unplanned addition of a new drug or switching to a different drug (or combination of drugs) due to any reason is considered a new line of therapy.
In patients undergoing >1 SCT, each SCT is considered a new line of therapy	• Except in the cases of a planned tandem SCT performed <6 months from the first SCT, each additional SCT is considered a new line of therapy.

SCT = stem cell transplant.

INTERRUPTIONS AND DOSE MODIFICATIONS

If a regimen is interrupted or discontinued for any reason and the same drug or combination is restarted without any intervening regimen, then it should be counted as a single line.

If a regimen is interrupted or discontinued for any reason and then restarted at a later timepoint, but one or more other regimens were administered in between, or the regimen is modified through the addition of one or more agents, then it should be counted as two lines.

Appendix 4
Eastern Cooperative Oncology Group
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 5
International Myeloma Working Group Uniform Response Criteria (2016)

(Adapted from Durie et al. 2015 and Kumar et al. 2016)

COMPLETE RESPONSE AND OTHER RESPONSE CATEGORIES

Response Subcategory	Response Criteria
All response categories require two consecutive assessments made any time before starting any new therapy.	
sCR	CR as defined below, plus: Normal FLC ratio and absence of clonal cells in BM by immunohistochemistry (kappa/lamda ratio ≤ 4:1 or ≥ 1:2 for kappa and lambda patients, respectively after counting ≥ 100 plasma cells) [a]
CR	No evidence of initial monoclonal protein isotype(s) on immunofixation of the serum and urine, [b] disappearance of any soft tissue plasmacytomas, and ≤5% plasma cells in BM
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis; or ≥90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 hr
PR	≥50% reduction of serum M-protein and reduction in 24 hr urinary M-protein by ≥90% or to <200 mg/24 hr. • If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If serum and urine M-protein are unmeasurable and serum FLC assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline BM plasma cell percentage was ≥ 30%. • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size (SPD) [c] of soft tissue plasmacytomas is also required.
MR	≥25% but ≤49% reductions of serum M protein and reduction in 24-hour urine M-protein by 50%–89% • In addition to the above criteria, if present at baseline, 25%–49% reduction in the size (SPD) [c] of soft tissue plasmacytomas is also required.
SD	Not meeting criteria for MR, CR, VGPR, PR, or PD

Appendix 5 International Myeloma Working Group Uniform Response Criteria (2016) (cont.)

DISEASE PROGRESSION AND RELAPSE

Relapse Subcategory	Relapse Criteria
PD [d, e]	Any increase of ≥25% from lowest response value in any one of the following: • Serum M-protein (absolute increase must be ≥0.5 g/dL) • Serum M-protein increase ≥1g/dL, if the lowest M component was ≥ 5g/dL • Urine M-protein (absolute increase must be ≥200 mg/24 hr) • In patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • In patients without measurable serum and urine M-protein levels and without measurable disease by FLC: BM plasma cell percentage irrespective of baseline status (absolute % must be ≥10%) [b] • Appearance of new lesion(s), ≥ 50% increase from nadir in SPD of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis • ≥ 50% increase in circulating plasma cells (minimum 200 cells per microliter) if this is the only measure of disease
Clinical relapse	Requires one or more of the following: • Direct indications of increasing disease and/or end organ dysfunction (CRAB features) [f] related to the underlying clonal plasma cell proliferative disorder. It is not used in calculation of time to progression or PFS but is listed here as something that can be reported optionally or for use in clinical practice. • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression) • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion. • Hypercalcemia >11 mg/dL (2.65 mmol/L) • Decrease in hemoglobin of ≥2 g/dL (1.25 mmol/L) not related to therapy or other non-myeloma related conditions • Rise in serum creatinine by 2 mg/dL or more (177 µmol/L or more) from the start of therapy and attributable to myeloma • Hyperviscosity related to serum paraprotein

Appendix 5 International Myeloma Working Group Uniform Response Criteria (2016) (cont.)

Relapse Subcategory	Relapse Criteria
Relapse from CR (to be used only if the endpoint studied is PFS) [c]	Any one or more of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥5% plasma cells in the BM • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

BM = bone marrow; CR = complete response; CT = computed tomography; FLC = free light chain; M-protein = monoclonal protein; MR = minimal response; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; SD = stable disease; SPD = sum of the products of diameters; VGPR = very good partial response.

[a] Special attention should be given to the emergence of a different M-protein following treatment, especially in the setting of patients having achieved a conventional CR, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of IgGk in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

[b] In some cases it is possible that the original M-protein light-chain isotype is still detected on immunofixation but the accompanying heavy-chain component has disappeared; this would not be considered a CR even though the heavy-chain component is not detectable, since it is possible that the clone evolved to one that secreted only light chains. Thus, if a patient has IgA lambda myeloma, then to qualify as CR there should be no IgA detectable on serum or urine immunofixation; if free lambda is detected without IgA, then it must be accompanied by a different heavy-chain isotype (IgG, IgM, etc.). Modified from Durie et al. 2006. This requires two consecutive assessments to be carried out at any time before the institution of any new therapy (Durie et al. 2015).

[c] Plasmacytoma measurements should be taken from the CT portion of the PET/CT or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, the skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

[d] Positive immunofixation alone in a patient previously classified as achieving a CR will not be considered progression. Criteria for relapse from a CR should be used only when calculating disease-free survival.

[e] In the case where a value is felt to be a spurious result per investigator discretion (e.g., a possible laboratory error), that value will not be considered when determining the lowest value.

[f] CRAB features = calcium elevation, renal failure, anemia, lytic bone lesions.

Appendix 6
Anaphylaxis Precautions

PRECAUTIONS

Equipment needed:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, IV, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, tape

PROCEDURES

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

1. Stop the study treatment infusion.
2. Call for medical assistance.
3. Maintain adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
5. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by physician in charge.
6. Continue to observe the patient and document observations.

Appendix 7
Preexisting Autoimmune Diseases *and Immune Deficiencies*

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where 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). *Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life–threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent.* Contact the Medical Monitor regarding any uncertainty over 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's syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

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

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

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

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

MANAGEMENT GUIDELINES

PULMONARY EVENTS

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

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Section 5.1.5.13.

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Section 5.1.5.4.

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

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

GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Sections 5.1.5.8 and 5.1.5.9.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

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

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 1.

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.

Table 1 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism.[c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

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

Table 1 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • *Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines.* • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

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

Table 1 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

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

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Section 5.1.5.7. Management guidelines for ocular events of suspected immune-mediated etiology are provided in Table 2.

Table 2 Management Guidelines for Ocular Events of Suspected Immune-Mediated Etiology

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

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

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

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

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 3.

Table 3 Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated myocarditis, Grade 3-4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

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

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

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

INFUSION-RELATED REACTIONS *AND CYTOKINE RELEASE SYNDROME*

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) *or cytokine-release*

syndrome (CRS) with atezolizumab may receive premedication with antihistamines*,* antipyretics*, and/or* analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs *and CRS* are provided in Table 4.

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed *as per local or* institutional guidelines.

Table 4 Management Guidelines for Infusion-Related Reactions *and Cytokine Release Syndrome*

Event	Management
Grade 1 [a] *Fever [b] with or without constitutional symptoms*	• *Immediately interrupt* infusion. • *Upon symptom resolution, wait for 30 minutes and then restart infusion at* half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • *If symptoms recur, discontinue infusion of this dose.* • *Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration.* • *In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2.* • *For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.*
Grade 2 [a] *Fever [b] with hypotension not requiring vasopressors* ***and/or*** *Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by*	• *Immediately interrupt* infusion. • *Upon symptom resolution, wait for 30 minutes and then restart* infusion at half the rate being given at the time of event onset. • *If symptoms recur, discontinue infusion of this dose.* • *Administer symptomatic treatment. [c]* • *For hypotension, administer IV fluid bolus as needed.* • *Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.* • *Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix.* • *Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).* • *Consider anti-cytokine therapy.* • *Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor. [e]* • *If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered.* For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs *and/or CRS.* • *If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.*

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

Event	Management
Grade 3 [a] *Fever [b] with hypotension requiring a vasopressor (with or without vasopressin)* ***and/or*** *Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask*	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • *Administer symptomatic treatment.* [c] • *For hypotension, administer IV fluid bolus and vasopressor as needed.* • *Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.* • *Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix.* • *Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).* • *Consider anti-cytokine therapy.* • *Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.*
Grade 4 [a] *Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin)* ***and/or*** *Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)*	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [e] • *Administer symptomatic treatment.* [c] • *Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice.* • *Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix.* • *Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).* • *Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor.* • *Hospitalize patient until complete resolution of symptoms.*

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

Event	Management

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

[a] *Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4*.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤6 L/min, and high flow is defined as oxygen delivered at >6 L/min.

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. *For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after consulting the Medical Monitor and considering the benefit–risk ratio.*

[f] *Refer to Riegler et al. (2019).*

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 5.

Table 5 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	***Amylase and/or lipase >1.5–2.0×ULN:*** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent. ***Asymptomatic with amylase and/or lipase >2.0–5.0 ×ULN:*** • *Treat as a Grade 3 event*
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI=gastrointestinal; *ULN=upper limit of normal*.

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

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

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

Table 5 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

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

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

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

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-*limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported with*

atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Section 5.1.5.5.

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 6.

Table 6 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

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

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

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

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 7.

Table 7 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Refer patient to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

RENAL EVENTS

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if

clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 8.

Table 8 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

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

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

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

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 9.

Table 9 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

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

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

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

Table 9 Management Guidelines for Immune-Mediated Myositis (cont.)

Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

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

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

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

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS*), which are considered to be potential risks for atezolizumab.*

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq 181 \times 10^9$/L (181,000/μL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 10.

Table 10 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, *and/or anti-cytokine therapy*. • *If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019).* • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

REFERENCES

Adashek ML, Feldman M. Cytokine release syndrome resulting from anti–programmed death-1 antibody: raising awareness among community oncologist. J Oncol Practice 2019;15:502–4.

La Rosée P. Treatment of hemophagocytic lymphohistiocytosis in adults. Hematology Am Soc Hematol Educ Protram 2015;1:190–6.

La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465–77.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625–38.

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355–62.

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481–9.

Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323–35.

Rotz SJ, Leino D, Szabo S, et al. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. Pediatr Blood Cancer 2017;64:e26642.

Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908–14.