Official Title: A Phase III, Open-Label, Multicenter, Three-Arm, Randomized Study to Investigate the Efficacy and Safety of Cobimetinib Plus Atezolizumab and Atezolizumab Monotherapy vs. Regorafenib in Patients With Previously Treated Unresectable Locally Advanced or Metastatic Colorectal Adenocarcinoma

NCT Number: NCT02788279

Document Date: Protocol Version 5: 28-Nov-2017

PROTOCOL

TITLE:	**A Phase III, open-label, multicenter, three-arm, randomized study to investigate the efficacy and safety of cobimetinib plus atezolizumab and atezolizumab monotherapy vs. regorafenib in patients with previously treated unresectable locally advanced or metastatic colorectal adenocarcinoma**
PROTOCOL NUMBER:	GO30182
VERSION NUMBER:	5
EUDRACT NUMBER:	2016-000202-11
IND NUMBER:	130,091
TEST PRODUCT:	Cobimetinib (RO5514041); atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	22 January 2016
DATE AMENDED:	Version 2: 30 March 2016 Version 3: 4 May 2016 Version 4: 21 October 2016 Version 5: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	28-Nov-2017 21:09:59

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Changes to Protocol GO30182, along with a rationale for each change, are summarized below:

- The protocol has been amended to reflect the update to the Statistical Analysis Plan (SAP). Overall survival (OS) will remain the primary endpoint. However, the hierarchical testing procedure will only include the OS comparisons between arms. The secondary endpoints (progression-free survival [PFS] and objective response rate [ORR]) will be deleted from the testing hierarchy and analyzed based on the methodologies stated in the revised SAP. The rationale for this amendment is to test the primary endpoint (OS) in both comparisons, (Arm A versus Arm C and Arm B versus Arm C) while maintaining type-1 error (Section 6.1, Figure 3). The time of analysis has been updated accordingly and will be conducted when there are approximately 235 deaths in the study, which is expected to occur 23 months after the first patient is randomized (Sections 3.2 and 6.1).
- References to Foundation Medicine have been removed from Section 4.5.7.1 because Foundation Medicine is no longer being used for centralized confirmation of RAS and microsatellite testing.
- References to guidelines for managing cobimetinib-specific adverse events have been updated (Sections 5.1.1.1, 5.1.1.2, and 5.1.1.3).
- The reporting of adverse events after initiation of study drug has been updated to align with the Schedule of Assessments and to align with current model document language (Section 5.3.1).
- The reporting of the term “sudden death” has been updated to also require the presumed cause of death (Section 5.3.5.8).
- Event reporting for hospitalization has been clarified (Section 5.3.5.11).
- Contact information regarding Medical Monitors has been updated (Section 5.4.1).
- Language has been added to clarify that the end of the adverse event reporting is defined as 90 days after the last dose of study drug or initiation of a new anti-cancer treatment, whichever comes first (Sections 5.4.2.2 and 5.6).
- The reference document for assessing the expectedness of adverse events for regorafenib has been updated from local prescribing information to Summary of Product Characteristics (Section 5.7).
- The process for reviewing and handling protocol deviations has been updated per internal standard operating procedures (Section 9.2).
- The web address for the Roche Global Policy on Sharing of Clinical Trials Data (Section 9.5).
- Guidelines for managing patients who experience atezolizumab-associated adverse events have been revised to include guidelines for hypophysitis and myocarditis and have been provided in an appendix so there is no longer a need to consult the Atezolizumab Investigator's Brochure for management guidelines (Appendix 9). The list of risks was updated in Section 5.1.2 and cross-references have been updated (Sections 1.4.2.2, 4.3.2.2, 5.1.2, 5.1.4.2, 5.1.4.3, 5.1.4.4, and Appendix 3).

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.

PROTOCOL AMENDMENT, VERSION 5:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.4.2.2: Ongoing Clinical Studies Immune–Mediated Adverse Events

Refer to the atezolizumab Investigator's Brochure *and Appendix 9* for details regarding immune–mediated adverse events and identified risks (adverse drug reactions) observed in patients treated with atezolizumab as well as recommended management guidelines for atezolizumab-specific immune–mediated adverse events.

SECTION 3.2: END OF STUDY AND LENGTH OF STUDY

The OS final analysis will be conducted when there are approximately *235 deaths in the study.* ~~178 deaths for the comparison of Arm A versus Arm C and approximately 127 deaths for the comparison of Arm B versus Arm C.~~ This is expected to occur approximately ~~21~~*23* months after the first patient is randomized.

SECTION 4.3.2.2: Atezolizumab

Dose modifications to atezolizumab are not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events associated with cobimetinib and atezolizumab are provided in Section 5.1.4 and Appendix 3. For information regarding management of atezolizumab-associated adverse events, please refer to ~~the atezolizumab Investigator's~~ *Appendix 9.*

SECTION 4.5.7.1: Archival and Fresh Tumor Sample for Screening

Extended RAS mutation is defined as mutations occurring in KRAS and NRAS gene codons 12 and 13 of exon 2; 59 and 61 of exon 3; and 117 and 146 of exon 4 (Allegra et al. 2016). Local RAS testing results will be accepted with a copy of the results and interpretation as part of the screening process with a requirement for central confirmation*.* ~~by Foundation Medicine NGS–based genomic profiling.~~

MSI status can be defined by several methods such as IHC detection of hMLH1 and hMSH2 gene products, NGS testing, or PCR testing by the fraction of MSI loci that exhibit differently sized repeats (Lindor et al. 2002; Salipante et al. 2014). Local MSI testing results will be accepted with a copy of the results and interpretation as part of the screening process with a requirement for central confirmation. ~~by Foundation Medicine NGS–based genomic profiling.~~

SECTION 5.1.1.1: Important Identified Risks Associated with Cobimetinib Serous Retinopathy

Guidelines for management of patients who develop Grade ≥ 2 visual disorders or retinopathy are provided in *Appendix 3*~~Section5.1.4.3.~~

Left Ventricular Dysfunction

…Most left ventricular ejection fraction reduction events in patients on cobimetinib plus vemurafenib (62%) improved or resolved with management according to the dose-modification guidelines (see *Appendix 3*~~Section5.1.4.3~~).

Photosensitivity (when Administered with Vemurafenib)

…Grade ≥ 3 photosensitivity events in the cobimetinib plus vemurafenib arm were primarily treated with topical medication in conjunction with interruption of study agents. ~~Refer to Section 5.1.4.3 for photosensitivity management guidelines.~~

Pneumonitis

…There were no reported Grade ≥ 3 events in either study arm. Serious events were reported in 2 patients (0.8%) treated with cobimetinib plus vemurafenib. *Refer to Appendix 3 for pneumonitis management guidelines.*

SECTION 5.1.1.2: Potential Risks Associated with Cobimetinib

Liver Laboratory Abnormalities and Severe Hepatotoxicity

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

SECTION 5.1.1.3: Other Risks with Cobimetinib

Rash

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

Gastrointestinal Toxicity

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 antiemetic prophylaxis is not recommended. *Refer to Appendix 3 for gastrointestinal toxicity management guidelines.*

SECTION 5.1.2: <u>Risks Associated with Atezolizumab</u>

Atezolizumab has been associated with risks such as IRRs and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, ~~and~~ meningoencephalitis*, myocarditis, and hypophysitis.* In addition, systemic immune activation is a potential risk associated with atezolizumab. Refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab *and Appendix 9*.

SECTION 5.1.4.2: Atezolizumab Dose Modifications

Additional guidelines for specific adverse events delineated by the different study arms are provided in the subsections below and the specific management guidelines are highlighted in Appendix 3 for cobimetinib plus atezolizumab. For information regarding management of atezolizumab-associated adverse events, please refer to the ~~atezolizumab Investigator's Brochure~~ *Appendix 9.*

SECTION 5.1.4.3: Management of Cobimetinib- and Atezolizumab-Specific Adverse Events (Arm A)

Toxicities associated or possibly associated with cobimetinib plus atezolizumab treatment should be managed according to standard medical practice. ~~See Section 5.1.4.4 for management of adverse events related to atezolizumab.~~

Guidelines for management of patients who experience atezolizumab-associated adverse events, including infusion-related reactions and immune-related events (e.g., endocrine, ocular, pancreatic, and neurologic events), are provided in ~~the Atezolizumab Investigator's Brochure~~*Appendix 9.*

SECTION 5.1.4.4: Management of Adverse Events in the Atezolizumab Monotherapy Arm (Arm B)

Guidelines for management of patients who experience specific adverse events associated with atezolizumab, including infusion-related reactions and immune-related events (e.g., pulmonary, hepatic, gastrointestinal, endocrine, ocular, pancreatic, dermatologic, and neurologic events), are provided in ~~the Atezolizumab Investigator's Brochure~~ *Appendix 9*.

SECTION 5.3.1: Adverse Event Reporting Period

After initiation of study drug, all *serious adverse events and Adverse Events of Special Interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first.* ~~adverse events will be reported until 90 days after the last dose of study drug. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment~~ *Instructions for reporting adverse events that occur after the adverse event reporting period are provided in* ~~(see~~ Section 5.6~~)~~.

SECTION 5.3.5.8: Deaths

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. ~~The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or~~

~~without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.~~ 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").*

SECTION 5.3.5.11: Hospitalization or Prolonged Hospitalization

~~The following hospitalization scenarios are not considered to be adverse events:~~ *An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:*

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:~~The following hospitalization scenario is not considered to be a serious adverse event, but should be reported as an adverse event instead:~~

SECTION 5.4.1: Emergency Medical Contacts

For all other non-emergency medical questions, please contact your clinical study monitor ~~or one of~~ the following Medical Monitor~~s~~:

- [redacted], M.D.: [redacted]
- ~~[redacted], Ph.D.: [redacted]~~

SECTION 5.4.2.2: Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug *or initiation of another anti-cancer drug, whichever comes first*. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

SECTION 5.6: POST-STUDY ADVERSE EVENTS

After the end of the reporting period for serious adverse events and adverse events of special interest ~~After the end of the adverse event reporting period~~ (defined as 90 days after the last dose of study drug *or initiation of a new anti-cancer treatment whichever comes first*), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF. In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior study drug treatment, the event should be reported through use of the Adverse Event eCRF.

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

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

- ~~Local prescribing information~~*Summary of Product Characteristics (SPC)* for regorafenib *(Stigvara® SPC 2017)*

SECTION 6.1: DETERMINATION OF SAMPLE SIZE

The OS final analysis will be conducted when there are approximately 235 deaths in the study. This is expected to occur approximately 23 months after the first patient is randomized. At that time, it is expected that approximately 178 deaths for the comparison of Arm A versus Arm C and approximately 127 deaths for the comparison of Arm B versus Arm C will have occurred. ~~The OS final analysis will be conducted when there are approximately 178 deaths for the comparison of Arm A versus Arm C and approximately 127 deaths for the comparison of Arm B versus Arm C. This is expected to occur approximately 22 months after the first patient is randomized. If 178th event from Arms A and C occurs after 127th event from Arms B and C, the OS final analysis will be conducted after 178th event from Arms A and C has occurred.~~

SECTION 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.*

SECTION 9.5: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

~~http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf~~*http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf*

Figure 3: Overview of Hierarchical Testing Sequence for Type I Error [a] Control (2-Sided)

Figure 3 was updated to indicate that overall survival (OS) will be tested at a 2-sided significance level $\alpha = 0.05$ only if the result of previous testing is positive (i.e., statistically significant). The testing of secondary endpoints (PFS and ORR) have been removed.

Appendix 3: Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A)

All references to the Atezolizumab Investigator's Brochure have been updated to Appendix 9.

Appendix 9: *Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab*

Appendix 9 was added.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A Phase III, open-label, multicenter, three-arm, randomized study to investigate the efficacy and safety of cobimetinib plus atezolizumab and atezolizumab monotherapy vs. regorafenib in patients with previously treated unresectable locally advanced or metastatic colorectal adenocarcinoma**
PROTOCOL NUMBER:	GO30182
VERSION NUMBER:	5
EUDRACT NUMBER:	2016-000202-11
IND NUMBER:	130,091
TEST PRODUCT:	Cobimetinib (RO5514041); atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by your local site monitor.

PROTOCOL SYNOPSIS

TITLE:	**A Phase III, open-label, multicenter, three-arm, randomized study to investigate the efficacy and safety of cobimetinib plus atezolizumab and atezolizumab monotherapy vs. regorafenib in patients with previously treated unresectable locally advanced or metastatic colorectal adenocarcinoma**
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TEST PRODUCT:	Cobimetinib (RO5514041); atezolizumab (RO5541267)
PHASE:	III
INDICATION:	Previously treated unresectable locally advanced or metastatic colorectal adenocarcinoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of cobimetinib plus atezolizumab compared to regorafenib (standard of care) in patients with previously treated, unresectable locally advanced or metastatic colorectal cancer (CRC) on the basis of overall survival (OS). Atezolizumab monotherapy will also be evaluated compared to regorafenib on the basis of OS.

Secondary Efficacy Objectives

The secondary efficacy objectives include:

- Investigator-assessed progression-free survival per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 of patients in the cobimetinib plus atezolizumab arm and the atezolizumab monotherapy arm compared to the regorafenib arm.
- Investigator-assessed objective response rate per RECIST v1.1 of patients in the cobimetinib plus atezolizumab arm and atezolizumab monotherapy arm compared to the regorafenib arm
- Duration of response of patients in the cobimetinib plus atezolizumab arm and atezolizumab monotherapy arm compared to the regorafenib arm
- Impact on functioning as measured by changes from baseline on the five-item physical functioning sub-scale of the patient–completed European Organization for Research and Treatment of Cancer Quality of Life Core 30 questionnaire (EORTC QLQ-C30)
- Impact on health–related quality of life as measured by changes from baseline on the two-item global health status/quality of life sub-scale of the EORTC QLQ-C30

Safety Objective

The safety objective for this study is to evaluate the safety profile and adverse events encountered by patients in the cobimetinib plus atezolizumab arm and atezolizumab monotherapy arm compared to the regorafenib arm.

Pharmacokinetic Objective

The PK objective for this study is to characterize the cobimetinib and atezolizumab PK profiles on the basis of the following:

- Plasma concentration of cobimetinib at timepoints specified in Appendix 2
- Serum concentration of atezolizumab in both the cobimetinib plus atezolizumab arm and the monotherapy atezolizumab arm at timepoints specified in Appendix 2

Immunogenicity Objective

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab on the basis of the following endpoint:

- Incidence of anti-therapeutic antibodies (ATAs) during the study relative to the prevalence of ATAs at baseline in both the cobimetinib plus atezolizumab arm and the atezolizumab monotherapy arm.

The exploratory immunogenicity objective for this study is to evaluate potential effects of ATAs on efficacy, safety, or pharmacokinetics.

Biomarker Objectives

The exploratory biomarker objectives for this study are as follows:

- To assess the following molecular characteristics in tumor samples during pretreatment, on treatment, and at progression:
  - Genetic profile including but not limited to somatic mutations and microsatellite (MSI) status or mutation load as identified through next-generation sequencing or other genetic analysis.
  - Immune contextures, such as programmed death-ligand 1 (PD-L1), CD8 T cells or major histocompatibility complex expression, as identified by immunohistochemistry and gene signature profiling
  - CRC molecular subtyping as defined by genetic and RNA and protein profiles
- To evaluate the relationship between circulating tumor biomarkers (including but not limited to carcinoembryonic antigen [CEA], tumor-associated mutations in cell-free DNA) and measures of efficacy

Patient-Reported Outcomes Objectives

The additional patient-reported outcome objective of the study is to assess treatment impact and disease symptoms from the sub-scales of the EORTC QLQ-C30 that assess diarrhea, constipation, lack of appetite, fatigue, and two additional items from the EORTC item bank that assess bloating and abdominal pain associated with cobimetinib plus atezolizumab compared with regorafenib in patients with metastatic CRC (mCRC).

Pharmacoeconomic Objectives

In addition, a study objective is to obtain general measures of health as measured by the EuroQoL 5 Dimensions questionnaire for health economic modeling of cobimetinib plus atezolizumab or atezolizumab monotherapy compared with regorafenib in patients with mCRC. This information is not intended to be included in the clinical study report.

Study Design

Description of Study

This is a Phase III, multicenter, open-label, three-arm, randomized study in patients with unresectable locally advanced or metastatic CRC who have received at least two prior regimens of cytotoxic chemotherapy for metastatic disease. The study compares regorafenib, a standard of care therapy in this setting, to cobimetinib plus atezolizumab and atezolizumab monotherapy.

The primary objective of the study is to evaluate the efficacy of cobimetinib plus atezolizumab compared to regorafenib in patients with unresectable locally advanced or metastatic CRC who have received at least two prior regimens of chemotherapy in the metastatic setting.
The efficacy of atezolizumab monotherapy compared to regorafenib in the same patient population will also be evaluated as a primary objective.

This study will be conducted globally and approximately 360 patients will be randomized in a 2:1:1 ratio to receive:

- Arm A: cobimetinib 60 mg orally on Days 1–21 plus atezolizumab 840 mg intravenous (IV) on Day 1 and Day 15 in a 28-day cycle (n ≈ 180), or
- Arm B: atezolizumab monotherapy 1200 mg IV on Day 1 in a 21-day cycle (n ≈ 90), or
- Arm C: regorafenib 160 mg orally on Days 1–21 in a 28-day cycle (n ≈ 90).

At least 50% patients with extended RAS-mutant tumors will be enrolled in each arm. Enrollment of patients with MSI-high status will be limited to approximately 5% to reflect the natural prevalence in mCRC.

Stratification factors are extended RAS mutation status of the tumor and time since diagnosis of first metastasis (<18 months vs. ≥ 18 months). Permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm. Randomization and stratification will be managed through an interactive voice/web response system.

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

After signing informed consent, patients will undergo screening procedures that include testing the tumor for extended RAS mutation status and MSI status (local tests accepted but confirmatory centralized testing required); laboratory tests (e.g., hematology, chemistries, liver function tests); left-ventricular function evaluation (echocardiogram or multigated acquisition scan); contrast-enhanced computed tomography scan or magnetic resonance imaging of the chest, abdomen, and pelvis; and ophthalmologic assessments.

All eligible patients will be randomized to treatment in either Arm A (cobimetinib plus atezolizumab), Arm B (atezolizumab monotherapy) or Arm C (regorafenib).

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

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

Treatment will continue until the patient has disease progression according to RECIST v1.1, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurs first. A rising CEA level alone is not considered disease progression. No crossover will be allowed. Patients are allowed to receive study treatment beyond disease progression if certain conditions are met.

After discontinuation of study treatment, patients may receive any subsequent line therapy as directed by their treating physician.

Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. In the absence of disease progression, tumor assessments should continue regardless of whether patients start a new anti-cancer therapy, unless consent is withdrawn. All patients will be followed for survival unless consent is withdrawn.

Number of Patients

Approximately 360 patients with unresectable locally advanced or metastatic CRC who have received at least two different chemotherapy regimens for metastatic disease will be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

Disease-specific inclusion criteria:

- Histologically confirmed adenocarcinoma originating from the colon or rectum (Stage IV American Joint Committee on Cancer 7th edition)
- Experienced disease progression on at least two prior systemic chemotherapy regimens for mCRC
    1. Prior systemic cytotoxic chemotherapy must include ALL of the following agents:
        a) Fluoropyrimidines
        b) Irinotecan
        c) Oxaliplatin
    2. Patients who have received prior anti-angiogenic therapy (e.g., bevacizumab) and/or anti-epidermal growth factor receptor therapy (e.g., cetuximab) are eligible.
    3. Patients must have had documented disease progression within 3 months of the last systemic therapy administration.
    4. Patients who were intolerant to prior systemic chemotherapy regimens are eligible if there is documented evidence of clinically significant intolerance despite adequate supportive measures.
    5. For patients who had disease recurrence within 6 months of completing adjuvant chemotherapy, the adjuvant regimen can be considered as one chemotherapy regimen for metastatic disease.

General inclusion criteria:

- Signed Informed Consent Form
- Age $\geq$ 18 years
- In the investigator's judgment, patient is able to comply with the requirements and assessments of the study protocol
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Anticipated life expectancy $\geq$ 3 months
- Able to comply with the requirements and assessments of the study protocol
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to first dose of study drug treatment:
    1. Hemoglobin $\geq$ 9 g/dL, platelet count $\geq$ 100,000/mm^3, ANC $\geq$ 1500/mm^3
    2. Creatinine clearance $\geq$ 30 mL/min
    3. Amylase and lipase $\leq$ 1.5 $\times$ the upper limit of normal (ULN)
    4. Serum bilirubin $\leq$ 1.5$\times$ ULN; patients with known Gilbert's disease may have a bilirubin $\leq$ 3.0x ULN
    5. AST, ALT, and alkaline phosphatase (ALP) $\leq$ 2.5 $\times$ ULN with the following exceptions:
        a) Patients with documented liver metastases: AST and/or ALT $\leq$ 5 $\times$ ULN
        b) Patients with documented liver or bone metastases: ALP $\leq$ 5 $\times$ ULN
    6. INR and PTT $\leq$ 1.5 $\times$ ULN. Patients who are on therapeutic doses of anti-coagulants are eligible if they are on a stable dose of anti-coagulant for 28 days with stable INR and PTT values.

- Women of childbearing potential must agree to appropriately use an effective form of contraception (failure rate of $<1\%$ per year) during the treatment period, within 5 months after the last dose of atezolizumab, and within 3 months after the last dose of cobimetinib and regorafenib.
    1. A woman of childbearing potential is defined as a sexually mature woman without prior oophorectomy or hysterectomy who have had menses within the last 12 months.
    2. A woman is not considered to be of childbearing potential if she has become amenorrheic for >12 months and has a follicle-stimulating hormone level ≥ 40 IU/L.
- Men must agree not to donate sperm or have intercourse with a female partner without using appropriate barrier contraception during the treatment period and for 3 months after the last dose of either cobimetinib or regorafenib.
- Available and adequate baseline tumor tissue sample (archival or newly obtained biopsy)

Exclusion Criteria

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

Cancer-related exclusion criteria:

- After the approximate 5% cap for MSI-high patients is reached, only MSI-stable patients will be eligible.
- Once the 50% cap for wild-type RAS has been reached, only extended RAS-mutant patients will be eligible.
- Major surgery or radiotherapy within 21 days prior to Cycle 1 Day 1 or anticipation of needing such procedure while receiving study treatment.
- Treatment with any anti-cancer agent within 14 days prior to Cycle 1 Day 1
- Uncontrolled tumor-related pain. Patients requiring narcotic pain medication must be on a stable regimen at study entry.
    1. Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to start of study treatment.
    2. Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to the start of study treatment.
- Uncontrolled pleural effusion, pericardial effusion or ascites requiring repeated drainage more than once every 28 days. Indwelling drainage catheters (e.g., PleurX®) are allowed.
- Active or untreated CNS metastases are excluded. Patients with treated and asymptomatic CNS metastases are eligible, if they meet all of the following:
    1. Evaluable or measurable disease outside the CNS
    2. No metastases to midbrain, pons, medulla or within 10 mm of the optic nerves and chiasm
    3. No history or evidence of intracranial hemorrhage or spinal cord hemorrhage
    4. No evidence of clinically significant vasogenic edema
    5. Not on corticosteroids for ≥ 2 weeks; anti-convulsants at a stable dose are allowed.
    6. No evidence of clinical and radiographic disease progression in the CNS for ≥ 3 weeks after radiotherapy or surgery.

Exclusion criteria related to study medication:

1. Any cancer immunotherapy including CD137 agonists, anti–programmed death-1, anti–PD-L1, or anti-CTLA4
2. Any MEK or ERK inhibitor
3. Regorafenib

- Patients with active malignancy (other than CRC) or a prior malignancy within the past 3 years are excluded. Patients with completely resected cutaneous melanoma (early stage), basal cell carcinoma, cutaneous squamous cell carcinoma, cervical carcinoma in-situ, breast carcinoma in-situ, and localized prostate cancer are eligible.

Exclusion criteria based on organ function or medical history:

Cardiovascular:

- Unstable angina, new onset angina within last 3 months, myocardial infarction within last 6 months and current congestive heart failure New York Heart Association Class II or higher.
- Left ventricular ejection fraction below institutional lower limit of normal or below 50%, whichever is lower.
- Poorly controlled hypertension, defined as a blood pressure consistently above 150/90 mmHg despite optimal medical management.

Infections:

- HIV infection
- Active tuberculosis infection
- Severe infections within 2 weeks prior to Cycle 1 Day 1
- Signs or symptoms of significant infection within 2 weeks prior to Cycle 1 Day 1
- Received oral or IV antibiotics within 2 weeks prior to Cycle 1 Day 1

  Patients receiving prophylactic antibiotics (e.g., for prevention of urinary tract infection or chronic obstructive pulmonary disease) are eligible
- Active or chronic viral hepatitis B or C infection
  1. Patients with hepatitis B virus (HBV) infection are eligible if test for hepatitis B surface antigen and HBV DNA are negative
  2. Patients with hepatitis C virus (HCV) infection are eligible if polymerase chain reaction test for HCV RNA is negative.

Ocular:

- History of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for central serous retinopathy, retinal vein occlusion, or neovascular macular degeneration
- Patients will be excluded if they currently have any of the following risk factors for retinal vein occlusion:
  1. Uncontrolled glaucoma with intra ocular pressure $\geq$ 21 mmHg
  2. Uncontrolled hypercholesterolemia $>$ 300 mg/dL or 7.75 mmol/L
  3. Uncontrolled hypertriglyceridemia $>$ 300 mg/dL or 3.42 mmol/L
  4. Fasting hyperglycemia $>$ 160 mg/dL or 8.9 mmol/L

Autoimmune conditions and immunomodulatory drugs:

- History of autoimmune disease except for the following:
  1. Patients with autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible.
  2. Patients with controlled type 1 diabetes mellitus on a stable dose of insulin regimen are eligible.
- Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis) are permitted provided that they meet the following conditions:

  Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations

  Rash must cover less than 10% of body surface area

Disease is well controlled at baseline and only requiring low−potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)

No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral steroids)

- History of idiopathic pulmonary fibrosis, organizing pneumonia, bronchiolitis obliterans, drug-induced pneumonitis, or idiopathic pneumonitis

  Patients with radiation pneumonitis within the radiation field are eligible.
- History of organ transplantation including allogeneic bone marrow transplantation

Other medical conditions or medications:

- Any hemorrhage or bleeding event CTCAE Grade 3 or higher within 28 days of Cycle 1 Day 1
- History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to Day 1
- Proteinuria $>$ 3.5 g/24 hours
- Serum albumin $<$ 2.5 g/dL
- Foods, supplements or drugs that are potent CYP3A4 enzyme inducer or inhibitors are prohibited at least 7 days prior to Cycle 1 Day 1 and during study treatment. These include St. John's wort or hyperforin (potent CYP3A4 enzyme inducer) and grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor).

General exclusion criteria:

- Inability to swallow medications
- Malabsorption condition that would alter the absorption of orally administered medications
- Pregnant, lactating, breastfeeding, or intending to become pregnant during the study
- History of severe hypersensitivity reactions to components of:
  1. Cobimetinib formulation
  2. Regorafenib formulation
  3. Atezolizumab formulation
- Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation of a live attenuated vaccine will be required during the study
- Any anti-cancer therapy, including chemotherapy, or hormonal therapy within 2 weeks prior to initiation of study treatment
- Treatment with systemic immunostimulatory agents (including but not limited to interferons, IL-2) within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to Cycle 1 Day 1
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to Cycle 1 Day 1

End of Study

The OS final analysis will be conducted when there are approximately *235 deaths in the study.* This is expected to occur approximately *23* months after the first patient is randomized.

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis (i.e., OS) or safety follow-up is received from the last patient, whichever occurs later.

Length of Study

LPLV is expected to occur 3 years after the first patient is enrolled. The study will end at any time if the Sponsor decides to end the trial.

Investigational Medicinal Products and Non-Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are cobimetinib and atezolizumab. Regorafenib is an approved treatment for mCRC and is considered a standard of care in this disease setting and administered in this study at the same dose that was used in the pivotal clinical trials and the approved and marketed dose for this indication. In this study, regorafenib is considered a non-investigational medicinal product, unless depending on local classification, regorafenib is deemed an IMP. If considered an IMP, then appropriate information on formulation, packaging, handling, and administration will be provided.

Test Products (Investigational Drugs)

Patients randomized to cobimetinib will receive 60 mg (three tablets of 20 mg each) orally once daily for Days 1–21 of a 28-day cycle. This 4-week period is considered a treatment cycle.

Atezolizumab dose and schedule will depend on the treatment arm:

- Arm A: cobimetinib plus atezolizumab 840 mg IV every 2 weeks
- Arm B: atezolizumab 1200 mg IV every 3 weeks as monotherapy

Comparator

Patients randomized to Arm C: regorafenib, will receive 160 mg (four tablets of 40 mg each) of regorafenib to be taken orally once daily on Days 1–21 of a 28-day cycle. This 4-week period is considered a treatment cycle.

Other Non-Investigational Medicinal Products

The following therapies are permitted in the study:

- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as low-molecular weight heparin or warfarin at a stable dose level)
- Palliative radiotherapy (e.g., treatment of known bone metastases) provided it does not interfere with assessment of tumor target lesions

  It is not required to withhold atezolizumab during palliative radiotherapy.
- Inactive influenza vaccinations during influenza season ONLY
- Megastrol administered as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)

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

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, as per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion–associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

Statistical Methods

Primary Analysis

The primary efficacy endpoint is OS, which is defined as the time (in months) between the date of randomization and the date of death due to any cause. Patients who have not died at the time of analysis will be censored at the date when they were last known to be alive.

Comparisons with respect to OS between two treatment arms (i.e., Arm A vs. Arm C, Arm B vs. Arm C) will be tested based on a stratified log-rank test. The stratification factors will be extended RAS mutation status of the tumor and time since diagnosis of first metastasis (<18 months and ≥ 18 months).

Each comparison will be tested at a 2-sided significance level of 0.05 within the intent-to-treat (ITT) population:

- Test to reject the null hypothesis of no difference in OS between either experimental arm (i.e., Arm A or Arm B) and the control arm (Arm C) in the ITT population. If the 2−sided p-value corresponding to the stratified log-rank test is less than 0.05, the null hypothesis will be rejected.

The hazard ratio (HR) for OS will be estimated using a stratified Cox model. Two-sided 95% CIs for the HR will be provided. The stratified analyses will incorporate extended RAS mutation status and time since diagnosis of first metastasis as stratification factors. Results from an unstratified log-rank test and the unstratified HR will also be presented. Kaplan-Meier methodology will be used to estimate median OS for each treatment arm, and the Kaplan-Meier curves will be provided. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS for each treatment arm.

The comparison between the two experimental arms (Arm A vs. Arm B) will be conducted for descriptive purposes.

Determination of Sample Size

The study will randomize approximately 360 patients, including a minimum of 180 patients with extended RAS-mutant mCRC (assuming a prevalence of at least 50%), to cobimetinib plus atezolizumab (Arm A), atezolizumab monotherapy (Arm B), and regorafenib (Arm C) with the randomization ratio of 2:1:1, respectively.

The type 1 error (α) for the analysis of the primary endpoint of OS in the comparison of cobimetinib plus atezolizumab (Arm A) against the control arm of regorafenib (Arm C) is 0.05 (2-sided). If OS in the comparison of Arm A against Arm C is statistically significant, then the OS in the comparison of Arm B against Arm C will be tested at a 2-sided α level of 0.05.

The sample size of this study is determined on the basis of the number of events required to demonstrate efficacy with regard to OS in both comparisons (Arm A vs. Arm C and Arm B vs. Arm C).

The estimate of the number of events required to demonstrate efficacy with regard to OS is based on the following assumptions:

- Two-sided significance level of 0.05
- Arm A versus Arm C: 87% power to detect an HR of 0.61, corresponding to an improvement in median OS from 6.4 months in Arm C to 10.5 months in Arm A
- Arm B versus Arm C: 80% power to detect an HR of 0.61, corresponding to an improvement in median OS from 6.4 months in Arm C to 10.5 months in Arm B
- No interim analysis for OS
- Dropout rate of 10% in 24 months
- Hierarchical testing of Arm A versus Arm C followed by Arm B versus Arm C to control the overall α level of 5%

With these assumptions, approximately 360 patients in total will be randomized into this study, with approximately 270 patients for the comparison of Arm A versus Arm C and approximately 180 patients for the comparison of Arm B versus Arm C. *The OS final analysis will be conducted when there are approximately 235 deaths in the study. This is expected to occur*

approximately 23 months after the first patient is randomized. At that time, it is expected that approximately 178 deaths for the comparison of Arm A versus Arm C and approximately 127 deaths for the comparison of Arm B versus Arm C will have occurred.

This number of events corresponds to a minimum detectable difference in HR of approximately 0.73 for the Arm A versus Arm C comparison and approximately 0.71 for the Arm B versus Arm C comparison.

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
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ATA	anti-therapeutic antibody
AUC	area under the concentration-time curve
BOR	best overall response
BRAFi	BRAF inhibitor
CEA	carcinoembryonic antigen
cfDNA	cell-free DNA
C_{max}	maximum concentration
C_{min}	minimum concentration
CR	complete response
CRC	colorectal cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
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
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life-C30 questionnaire
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQoL 5 Dimensions
E.U.	European Union
FFPE	formalin-fixed paraffin-embedded
GWAS	genome-wide association studies
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
HR	hazard ratio
HRQoL	health–related quality of life
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
IL	Interleukin
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
IxRS	interactive Web/voice response system
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
mCRC	metastatic colorectal cancer
MDSC	myeloid–derived suppressive cells
MEKi	MEK inhibitor
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MSI	microsatellite
MSS	microsatellite stable
MTD	maximum-tolerated dose
MUGA	multigated acquisition (scan)
NCI	National Cancer Institute
NGS	next-generation sequencing
NIMP	non–investigational medicinal product
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	programmed cell death
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome

Abbreviation	Definition
PVC	polyvinylchloride
q2w	every 2 weeks
q3w	every 3 weeks
QD	once daily
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
TNF	tumor necrosis factor
ULN	upper limit of normal
VEGF	vascular epidermal growth factor
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON METASTATIC COLORECTAL CANCER

1.1.1 Incidence and Treatment of Metastatic Colorectal Cancer

Globally, colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and second in females. CRC also is the fourth leading cause of cancer mortality in males and third in females (Torre et al. 2016). The estimated incidence of new cases in 2012 in developed countries was 736,900, and mortality was 333,200, with the highest incidence rates in North America, Europe, and Australia/New Zealand (Torre et al. 2016).

In the United States, about 40% of CRC patients are diagnosed with early-stage disease, with another 40% diagnosed with regional disease, and 20% diagnosed with distant metastasis. Five-year survival rates are 90%, 70%, and 13%, respectively, with most of these patients dying from metastatic disease (Alberts and Wagman 2008; American Cancer Society 2015; Kennecke et al. 2014).

Without treatment, the median survival for patients with metastatic CRC (mCRC) is less than 1 year (Liu et al. 2003). Surgical resection of metastases can improve outcomes. The 5-year survival rates of the small fraction of patients eligible for resection of metastatic lesions are around 27%–41% (Mandalà et al. 2007; Zaydfudim et al. 2015). In the vast majority of mCRC patients, systemic cytotoxic chemotherapy is the mainstay of treatment and median overall survival (OS) is only around 30 months. Anti-vascular endothelial growth factor (VEGF) therapies such as bevacizumab, ramucirumab, and ziv-aflibercept, and anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAb) such as cetuximab and panitumumab can be used in combination with chemotherapy in first-, second-, and third-line therapies, though treatment combinations vary by region (Petrelli et al. 2015). In the United States and Western Europe, anti-VEGF and anti-EGFR therapy is used 30%–50% and 17%–30% of patients during the course of treatment, respectively (Zhao et al 2012; Abrams et al. 2014).

1.1.2 Management of Metastatic Colorectal Cancer Beyond Second-Line Chemotherapy

Once patients have exhausted standard chemotherapy regimens, their survival is less than 6 months. Recently two agents, regorafenib (Stivarga®) and trifluridine and tipiracil (TAS-102; LONSURF®) have been approved in these previously treated chemotherapy-refractory mCRC patients.

Regorafenib is a multikinase inhibitor that was approved in heavily pretreated mCRC patients based on an international, multicenter, randomized, double-blind, placebo-controlled trial in 760 patients. The median OS for regorafenib plus best supportive care was 6.4 months compared to 5 months for placebo plus best supportive care (hazard ratio [HR]=0.77; p=0.0102). Common side effects were hand-foot syndrome, fatigue, rash, diarrhea, hemorrhage, hypertension, mucositis, and infection (Grothey et al. 2013).

Trifluridine/tipiracil is an orally administered combination of a thymidine–based nucleic acid analogue, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride. It has recently been approved in the United States based upon an international, multicenter, randomized, double-blind, placebo-controlled trial in 800 patients. The median OS was 7.1 months (95% CI, 6.5 to 7.8) in the trifluridine and tipiracil group and 5.3 months (95% CI, 4.6 to 6.0) in the placebo group (HR = 0.68; $p < 0.001$). Notable side effects were neutropenia, anemia, and thrombocytopenia as well gastrointestinal toxicity (Mayer et al. 2015).

Even with the recent approvals of these two agents, a high unmet need remains in this patient population for more efficacious treatment options with better safety profiles.

1.2 THE PROGRAMMED T-CELL DEATH LIGAND-1 PATHWAY

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

Programmed T-cell death ligand-1 (PD-L1) expression is prevalent in many human tumors (e.g., lung, ovarian, melanoma, 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). PD-L1 is one of two ligands (PD-L1 and PD-L2) that bind programmed cell death-1 (PD-1). The PD-1 receptor is an inhibitory receptor expressed on T cells following T-cell activation in states of chronic stimulation, such as chronic infection or cancer (Blank et al. 2005; Keir et al. 2008). Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity that lead to the functional inactivation of T cells. Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor–specific T-cell immunity.

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

Atezolizumab is a humanized IgG1 mAb that targets PD-L1 and inhibits its interaction with its receptors, PD-1 and B7-1 (also known as CD80). Both of these interactions are reported to provide inhibitory signals to T cells. Atezolizumab was engineered to impair its binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells. Section 1.4 describes the nonclinical and clinical data of atezolizumab.

1.3 THE MAPK SIGNALING PATHWAY AND REGULATION OF THE IMMUNE TUMOR MICROENVIROMENT

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 ERK is one major MAPK pathway that has been identified that plays a significant role in normal cellular regulation (Johnson and Lapadat 2002; Roberts and Der 2007). Given the central role that the MAPK pathway plays in normal cellular development, abnormal regulation of this signaling pathway could lead to tumorigenesis through contribution to uncontrolled proliferation, invasion, metastasis, and angiogenesis as well as diminished apoptosis.

The MAPK pathway has also been implicated in the regulation of the immune microenvironment of tumors. In in vitro cell lines, blocking the MAPK pathway was shown to increase antigen expression and enhance reactivity to antigen–specific T lymphocytes (Boni et al. 2010). In melanoma patients who are treated with a combined BRAF inhibitor (BRAFi) and MEK inhibitor (MEKi), increased intratumoral lymphocytes (CD4- and CD8-positve T cells) were observed compared to pre-treatment biopsy samples (Kakavand et al. 2015). Furthermore, pre-treatment biopsies where there were increased tumor-infiltrating lymphocytes demonstrated a larger increase in tumor-infiltrating lymphocytes and PD-1 expression after treatment with a BRAFi and MEKi (Cooper et al. 2015; Kakavand et al. 2015; Liu et al. 2015). The inhibition of the MAPK pathway leads to an increase in immune effector cells in the tumor, thus priming the microenvironment to enable to immune system to attack the tumor.

Inhibition of the MAPK pathway has focused on the suppression of targets within this signaling network, such as MEK1 and MEK2. There are multiple upstream activating signals, but multiple alternative pathways exist to bypass their inhibition and still activate 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 hubs for the inhibition of the MAPK pathway.

Cobimetinib is an orally dosed, potent and highly selective inhibitor of MEK. Section 1.5 describes the nonclinical and clinical data of cobimetinib.

1.4 BACKGROUND ON ATEZOLIZUMAB MONOTHERAPY

See the atezolizumab Investigator's Brochure for additional details on nonclinical and clinical studies.

1.4.1 Summary of Nonclinical Studies with Atezolizumab

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetics, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology,

pharmacokinetic (PK), and toxicology evaluations were thus undertaken with atezolizumab.

The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Based on the similar binding affinity and pharmacologic activity of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab. Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway and supported entry into clinical studies in patients.

1.4.2 Clinical Experience with Atezolizumab

1.4.2.1 Ongoing Clinical Studies

In the United States, atezolizumab is approved for the treatment of locally advanced or metastatic urothelial bladder cancer who have progressed during or following platinum-containing chemotherapy and for metastatic non–small cell lung cancer (NSCLC) who have progressed during or following platinum-containing chemotherapy and if harboring an EGFR or ALK aberration have progressed on U.S. Food and Drug Administration-approved therapy for these aberrations. Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as monotherapy 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 Phase I Study PCD4989g, a multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion once every three weeks (q3w) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.

1.4.2.2 Clinical Safety as a Single Agent

The safety data for atezolizumab have been derived mainly from the treatment of patients in Study PCD4989g. As of 10 May 2015, the clinical database contained preliminary safety data from 558 patients who have received any amount of atezolizumab at doses between 0.01 and 20 mg/kg across multiple tumor types. No dose-limiting toxicities (DLTs) have been observed at any dose level, and no maximum tolerated dose (MTD) has been established.

Adverse Events

Of the 558 treated patients,520 (93.2%) reported an adverse event regardless of attribution to atezolizumab. The majority of these adverse events were Grade 1 or 2 in maximum severity based on the National Cancer Institute Common Terminology Criteria

for Adverse Events, Version 4.0 (NCI CTCAE v4.0). The most frequently observed adverse events (occurring in ≥10% of treated patients) included fatigue, nausea, decreased appetite, pyrexia, dyspnea, diarrhea, constipation, cough, headache, back pain, vomiting, anemia, arthralgia, rash, insomnia, asthenia, abdominal pain, chills, pruritus, generalized pain, and peripheral edema.

There were 66 patients (11.88%) who experienced Grade ≥ 3 adverse events that were assessed as related to study drug by the investigators. Grade 3 and 4 adverse events considered related by the investigator included dyspnea, pneumonitis, increased ALT, increased AST, increased γ-glutamyl transferase, lymphocyte count decreased, cardiac tamponade, asthenia, autoimmune hepatitis, pneumonia, influenza, and hypoxia.

Immune–Mediated Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune–mediated adverse events have been closely monitored during the atezolizumab clinical program. These include potential dermatologic, hepatic, gastrointestinal, endocrine, neurologic, and respiratory events as well as events of hepatitis/elevated liver function tests and influenza-like illness that are considered potential adverse drug reactions associated with atezolizumab.

Refer to the atezolizumab Investigator's Brochure *and Appendix 9* for details regarding immune–mediated adverse events and identified risks (adverse drug reactions) observed in patients treated with atezolizumab as well as recommended management guidelines for atezolizumab-specific immune–mediated adverse events.

1.4.3 Clinical Activity of Atezolizumab

Anti-tumor activity, including Response Evaluation Criteria in Solid Tumors (RECIST)–based responses (i.e., RECIST v1.1 responses), have been observed in patients with different tumor types, including NSCLC, renal cell carcinoma (RCC), melanoma, bladder cancer, CRC, head and neck cancer, gastric cancer, breast cancer, and sarcoma treated with atezolizumab monotherapy in Study PCD4989g.

Analyses of PD-L1 expression on baseline tumor tissue have been performed for Study PCD4989g, with results suggesting that PD-L1 expression is likely to be associated with response to atezolizumab.

Among 345 efficacy evaluable patients treated as of 21 October 2013 (data cutoff of 21 April 2014), with a median of 30.4 weeks of follow-up, 62 patients experienced objective responses per RECIST v1.1, with an overall response rate (ORR) of 18% (95% CI: 14.1%, 22.3%). Objective responses with atezolizumab monotherapy were observed in a broad range of malignancies, including NSCLC, RCC, melanoma, bladder cancer, CRC, head and neck cancer, gastric cancer, breast cancer, and sarcoma. The atezolizumab—F. Hoffmann-La Roche Ltd 29/Protocol GO30140, Version 1 median duration of response (DOR) was 77.6 weeks (range: 6.4+ to

97.9+ weeks, for which the "+" denotes a censored value). The majority of these responses have been durable, with 72.6% of responses (45 of 62 patients) ongoing as of the clinical cutoff date.

1.4.4 Clinical Pharmacokinetics and Immunogenicity of Atezolizumab

On the basis of available preliminary PK data (0.03–20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses ≥ 1 mg/kg. For the 1- and 20-mg/kg dose groups, the mean apparent clearance and the mean volume of distribution at steady state ranged from 3.20 to 4.44 mL/day/kg and 48.1–65.7 mL/kg, respectively, which is consistent with the expected pharmacokinetics of an IgG1 antibody in humans.

The development of anti-therapeutic antibodies (ATAs) has been observed in patients in all dose cohorts and was associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses ranging from 10–20 mg/kg. Patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between detection of ATAs and adverse events or infusion reactions has been observed.

1.5 BACKGROUND ON COBIMETINIB MONOTHERAPY

Cobimetinib is a reversible, potent, and highly selective inhibitor of MEK1 and MEK2. Cobimetinib is approved in the United States, European Union, Switzerland, and in multiple other countries across the world for use with vemurafenib for the treatment of advanced BRAF-mutated melanoma.

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 ERK phosphorylation in xenograft tumor models and stimulates apoptosis. 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 CRC, malignant melanoma, breast carcinoma, and anaplastic lung carcinoma.

A characterization of the pharmacologic and PK properties of cobimetinib was performed in a series of nonclinical studies that are summarized in the cobimetinib Investigator's Brochure.

The nonclinical toxicity of cobimetinib was characterized in single– and repeat–dose general toxicity studies in rats and dogs, in vitro genotoxicity studies, embryolethality/teratogenicity studies in rat, and cardiovascular, neurobehavioral, and respiratory safety pharmacology studies. The studies are summarized in the cobimetinib Investigator's Brochure.

1.5.2 Summary of Clinical Studies with Cobimetinib Monotherapy

As of October 2015, cobimetinib had been administered alone or with other agents to more than 1000 adult cancer patients and approximately 120 healthy volunteers in 18 clinical trials; the vast majority of patients had been treated with cobimetinib plus other agents, such as vemurafenib. These include one trial of cobimetinib as a single agent, seven clinical pharmacology studies, and nine trials of cobimetinib with other agents.

Study MEK4592g was 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 since 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 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 daily [QD] 21/7) in patients harboring 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.

Dose-Limiting Toxicities

Four DLTs were observed in Stage I (21/7 dosing schedule) of Study MEK4592g. At the 40-mg dose level, a DLT of Grade 4 hepatic encephalopathy and Grade 3 elevated ammonia was reported in a patient with pre-existing liver metastases. At the 60-mg dose level, a DLT of Grade 3 rash was reported that improved with skin toxicity management and drug holiday. At the 80-mg dose level, two DLTs were reported: 1 patient with Grade 3 diarrhea despite treatment with anti-diarrheal medications and 1 patient with Grade 3 rash.

Two DLTs were observed in Stage IA (14/14 dosing schedule), both at the 125-mg dose level. One patient had Grade 3 rash and another had Grade 3 blurred vision associated with neurosensory detachment of the retina.

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 edema peripheral (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 21/7, the most frequent treatment–emergent adverse events were diarrhea (64.4%), rash (53.3%), fatigue (48.9%), nausea and edema peripheral (31.1% each), and vomiting (28.9%).

Grade≥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 and hypokalemia (6.1% each).

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. Out of the 14 CRC patients, all patients experienced progressive disease. In Stage III of Study MEK4592g, 18 patients were accrued 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.

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

1.6 COMBINED INHIBITION OF PD-L1 AND MAPK SIGNALING PATHWAYS AS POTENTIAL ANTI-CANCER THERAPY IN METASTATIC COLORECTAL CANCER

Because of the high unmet medical need in heavily pretreated advanced mCRC, where OS is only 6 months, several clinical studies have tested checkpoint inhibitors in this

setting with disappointing results (Brahmer et al. 2012; Topalian et al. 2012; Poulin-Costello et al. 2013).

Recently, immune checkpoint inhibitors have been shown to have clinical benefit in microsatellite (MSI) unstable mCRC but not in MSI stable cohorts (Le et al. 2015). This preferential effect of checkpoint inhibitors on MSI-high CRCs has been postulated to be due to an increase in neo-antigens from a greater somatic mutation load. This increase in somatic mutations amplifies upstream pathways required for an immune response, such as recruitment of immune effector or antigen presenting cells (Llosa et al. 2015; Zhang et al. 2015). Furthermore, the mismatch repair–deficient cancers have increased CD8-positive T cells and PD-L1 expression in the tumor, which may explain why they are responsive to checkpoint inhibitors (Li et al. 2015; Smedt et al. 2015).

One potential mechanism to convert otherwise resistant cancers is to recruit immune cells to the tumor sites so that the anti-PD L1 can be effective in activating the local immune system against the cancer cells. Nonclinical models suggest that MEK inhibition may have pleiotropic effects that could impact the tumor immune microenvironment, as the MAPK pathway has been implicated in the immune resistance of tumors and inhibition of this pathway can lead to increase CD8–positive T-cell infiltration (Kakavand et al. 2015; Liu et al. 2015).

Within the tumor, MEK inhibition results in increased major histocompatibility complex (MHC) class I expression and tumor antigen presentation, which acts to enhance tumor recognition by the immune system. Interestingly, MEK inhibition in tumors also increases expression of the checkpoint receptor PD-L1, which could counteract the increased presentation of tumor antigens. Lastly, the MAPK pathway is known to regulate a number of cytokines and chemokines, such as VEGF, interleukin (IL)-6 (IL-6), IL-8, and granulocyte–macrophage colony-stimulating factor, which may impact recruitment of vascular and other stromal cell types, including myeloid–derived suppressive cells (MDSCs) that can inhibit the anti-tumor activity of T cells (Bancroft et al. 2001; Sano et al. 2001; Bancroft et al. 2002; Phan et al. 2013). Activity of MEK inhibition outside of the tumor cells may further contribute to the modulation of the immune microenvironment that could enable a more permissive immune reaction against the tumor. These effects include inhibition of tumor vascular maturity and integrity, tumor infiltration, activity of MDSCs, neutrophils, increased activity of antigen-presentation cells, such as macrophage and dendritic cells, and recruitment and activation status of T-cell subsets, including CD8-positive cytolytic and CD4–positive helper cells (Giordano et al. 2015; Liu et al. 2015; Loi et al. 2015).

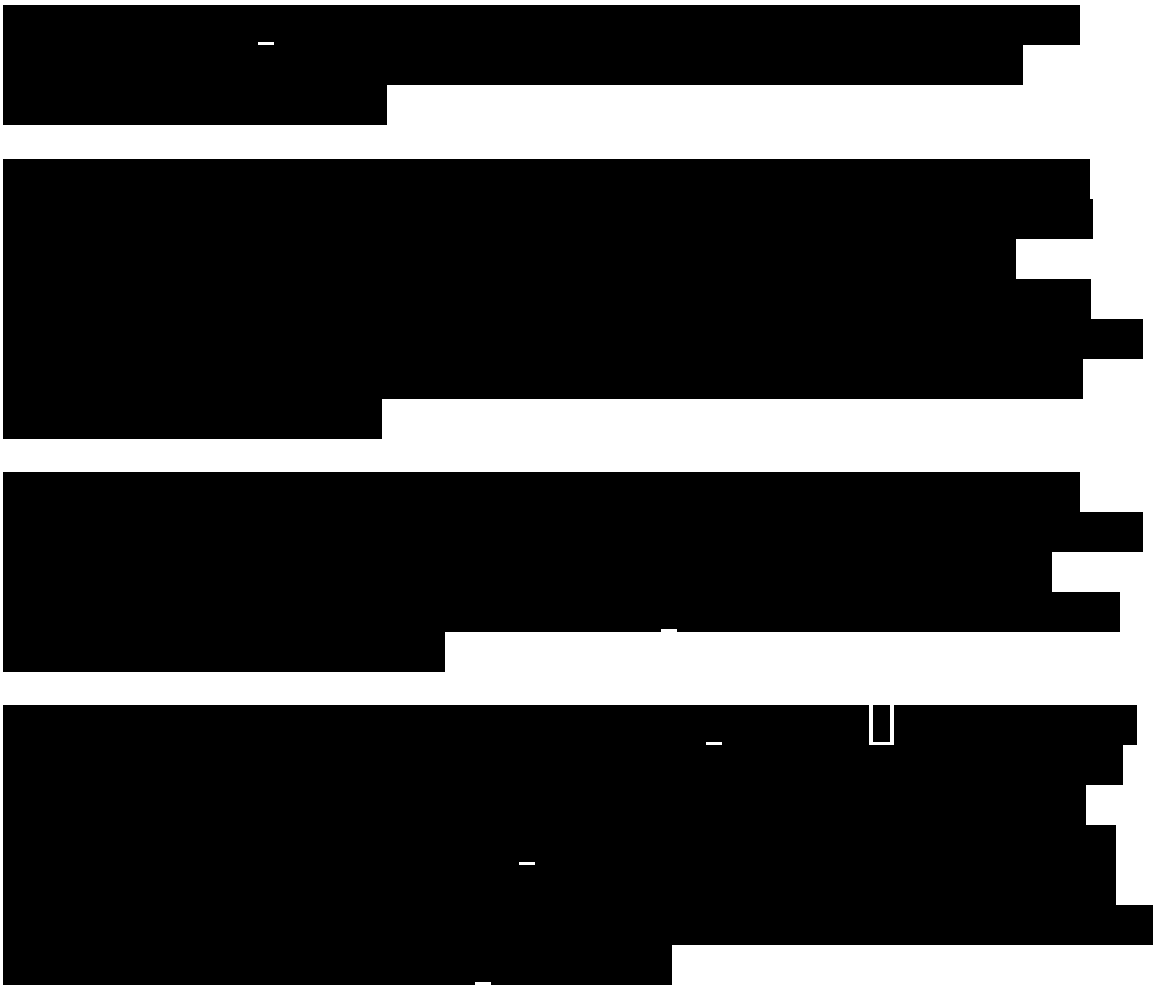
Collectively, these effects enable tumors to demonstrate stronger anti-tumor responses with the combination of a MEKi and PD-L1/PD-1 blockade in multiple mouse models, including colorectal, breast, and melanoma models (Liu et al. 2015; Loi et al. 2015). Increased anti-tumor activity is associated with increased CD8–positive T-cell infiltration

of tumors that express markers consistent with tumor–cell cytolytic activity. These data suggest that MEK inhibition can modulate the tumor immune microenvironment and enable better tumor recognition and killing by the immune system, particularly when paired with a checkpoint inhibitor against the PD-1/PD-L1 axis.

1.7 CLINICAL DATA OF COBIMETINIB PLUS ATEZOLIZUMAB IN METASTATIC COLORECTAL CANCER – STUDY GP28363

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 mCRC, NSCLC, and metastatic melanoma.



[redacted]

1.8 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The rationale for specific details of the study design are discussed in Section 3.3.

The combination of a MEKi and PD-L1 inhibitor has nonclinical and clinical data that strongly support further evaluation in previously treated mCRC patients. Both in vitro and in vivo models have shown that the MAPK pathway plays an important role in the immune tumor microenvironment, and MEK inhibition leads to increases in MHC-1 and PD-L1 expression as well as increases in CD8–positive lymphocyte recruitment into the tumor microenvironment. This enhancement of the local immune system in combination with a PD-L1 inhibitor has demonstrated increased efficacy in nonclinical and clinical models. The Phase Ib clinical trial evaluating cobimetinib plus atezolizumab in previously treated KRAS–mutated mCRC patients shows an efficacy of a 13% PR rate and a 26% SD rate, with some responses lasting more than 1 year. The regimen is well tolerated, and the safety profile is manageable and tolerable.

There is clearly a high medical need in this patient population of previously treated mCRC patients, where OS is less than 6 months and treatment options are very limited and often poorly tolerated. Cobimetinib plus atezolizumab has shown clinically efficacy in these mCRC patients and is well tolerated; thus, further study in this clinical trial is warranted.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of: 1) cobimetinib plus atezolizumab or 2) atezolizumab monotherapy, compared to regorafenib in patients with unresectable locally advanced or metastatic CRC who have been previously treated with at least two lines of chemotherapy. Specific objectives and corresponding endpoints for the study are outlined in Sections 2.1–2.7.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of cobimetinib plus atezolizumab compared to regorafenib (standard of care) in patients with previously treated, unresectable locally advanced or metastatic CRC on the basis of OS. Atezolizumab monotherapy will also be evaluated compared to regorafenib on the basis of OS.

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives include:

- Investigator-assessed progression-free survival (PFS) per RECIST v1.1 (see Appendix 5) of patients in the cobimetinib plus atezolizumab arm and the atezolizumab monotherapy arm compared to the regorafenib arm.
- Investigator-assessed objective response rate (ORR) per RECIST v1.1 (see Appendix 5) of patients in the cobimetinib plus atezolizumab arm and atezolizumab monotherapy arm compared to the regorafenib arm
- DOR of patients in the cobimetinib plus atezolizumab arm and atezolizumab monotherapy arm compared to the regorafenib arm
- Impact on functioning as measured by changes from baseline on the five-item physical functioning sub-scale of the patient–completed European Organization for Research and Treatment of Cancer Quality of Life Core 30 questionnaire (EORTC QLQ-C30)
- Impact on health–related quality of life (HRQoL) as measured by changes from baseline on the two-item global health status/quality of life sub-scale of the EORTC QLQ-C30

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety profile and adverse events encountered by patients in the cobimetinib plus atezolizumab arm and atezolizumab monotherapy arm compared to the regorafenib arm.

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the cobimetinib and atezolizumab PK profiles on the basis of the following:

- Plasma concentration of cobimetinib at timepoints specified in Appendix 2
- Serum concentration of atezolizumab in both the cobimetinib plus atezolizumab arm and the monotherapy atezolizumab arm at timepoints specified in Appendix 2

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab on the basis of the following endpoint:

- Incidence of ATAs during the study relative to the prevalence of ATAs at baseline in both the cobimetinib plus atezolizumab arm and the atezolizumab monotherapy arm.

The exploratory immunogenicity objective for this study is to evaluate potential effects of ATAs on efficacy, safety, or pharmacokinetics.

2.5 BIOMARKER OBJECTIVES

The exploratory biomarker objectives for this study are as follows:

- To assess the following molecular characteristics in tumor samples during pretreatment, on treatment, and at progression:
  - Genetic profile including but not limited to somatic mutations and MSI status or mutation load as identified through next-generation sequencing (NGS) or other genetic analysis.
  - Immune contextures, such as PD-L1, CD8 T cells or MHC expression, as identified by immunohistochemistry (IHC) and gene signature profiling
  - CRC molecular subtyping as defined by genetic and RNA and protein profiles
- To evaluate the relationship between circulating tumor biomarkers (including but not limited to carcinoembryonic antigen [CEA], tumor-associated mutations in cell-free DNA [cfDNA]) and measures of efficacy

2.6 PATIENT-REPORTED OUTCOMES OBJECTIVES

Refer to Section 2.1.2 for patient–reported secondary efficacy objectives.

The additional patient-reported outcome (PRO) objective of the study is to assess treatment impact and disease symptoms from the sub-scales of the EORTC QLQ-C30 that assess diarrhea, constipation, lack of appetite, fatigue, and two additional items from the EORTC item bank that assess bloating and abdominal pain associated with cobimetinib plus atezolizumab compared with regorafenib in patients with mCRC.

2.7 PHARMACOECONOMIC OBJECTIVES

In addition, a study objective is to obtain general measures of health as measured by the EuroQoL 5 Dimensions (EQ-5D-5L) questionnaire for health economic modeling of cobimetinib plus atezolizumab or atezolizumab monotherapy compared with regorafenib in patients with mCRC. This information is not intended to be included in the clinical study report.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, multicenter, open-label, three-arm, randomized study in patients with unresectable locally advanced or metastatic CRC who have received at least two prior regimens of cytotoxic chemotherapy for metastatic disease. The study compares regorafenib, a standard of care therapy in this setting, to cobimetinib plus atezolizumab and atezolizumab monotherapy.

The primary objective of the study is to evaluate the efficacy of cobimetinib plus atezolizumab compared to regorafenib in patients with unresectable locally advanced or metastatic CRC who have received at least two prior regimens of chemotherapy in the

metastatic setting. The efficacy of atezolizumab monotherapy compared to regorafenib in the same patient population will also be evaluated as a primary objective.

This study will be conducted globally and approximately 360 patients will be randomized in a 2:1:1 ratio to receive (Figure 1 and Figure 2):

- Arm A: cobimetinib 60 mg orally on Days 1–21 plus atezolizumab 840 mg IV on Day 1 and Day 15 in a 28-day cycle (n ≈ 180), or
- Arm B: atezolizumab monotherapy 1200 mg IV on Day 1 in a 21-day cycle (n ≈ 90), or
- Arm C: regorafenib 160 mg orally on Days 1–21 in a 28-day cycle (n ≈ 90).

At least 50% patients with extended RAS-mutant tumors (see Section 4.5.7.1 for definition) will be enrolled in each arm. Enrollment of patients with MSI-high status (see Section 4.5.7.1 for definition) will be limited to approximately 5% to reflect the natural prevalence in mCRC (Goldstein et al. 2014).

Stratification factors are extended RAS mutation status of the tumor and time since diagnosis of first metastasis (<18 months vs. ≥ 18 months). Permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm. Randomization and stratification will be managed through an interactive voice/web response system (IxRS).

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

The schedule of study assessments and procedures are detailed in Appendix 1.
After signing informed consent, patients will undergo screening procedures that include testing the tumor for extended RAS mutation status and MSI status (local tests accepted but confirmatory centralized testing required); laboratory tests (e.g., hematology, chemistries, liver function tests); left-ventricular function evaluation (echocardiogram [ECHO] or multigated acquisition scan [MUGA]); contrast-enhanced computed tomography (CT) scan or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis; and ophthalmologic assessments.

All eligible patients will be randomized to treatment in either Arm A (cobimetinib plus atezolizumab), Arm B (atezolizumab monotherapy) or Arm C (regorafenib). The dosing regimen and schedule for each treatment arm is shown in Figure 2 and Section 4.3.

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at the treatment discontinuation visit, and during the follow-up period. The NCI CTCAE v4.0 will be used to characterize the toxicity profile of the study treatments on all patients.

Patients will be assessed for adverse events according to the schedule of assessments in Appendix 1 and as necessary throughout the study.

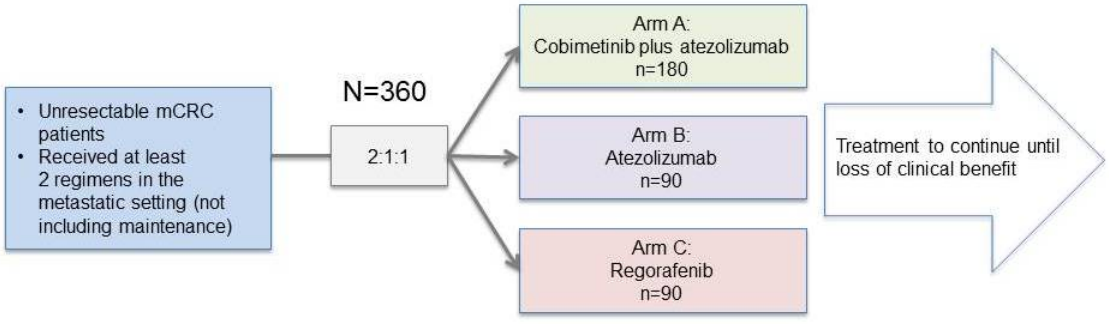
Tumor response will be evaluated according to RECIST v1.1 (see Appendix 5). Any evaluable and measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Investigators will assess tumor response at 8-week intervals, regardless of any dose delays or treatment cycle.

Treatment will continue until the patient has disease progression according to RECIST v1.1, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurs first. A rising CEA level alone is not considered disease progression. No crossover will be allowed. Patients are allowed to receive study treatment beyond disease progression if certain conditions are met (Section 4.3.2.4).

After discontinuation of study treatment, patients may receive any subsequent line therapy as directed by their treating physician.

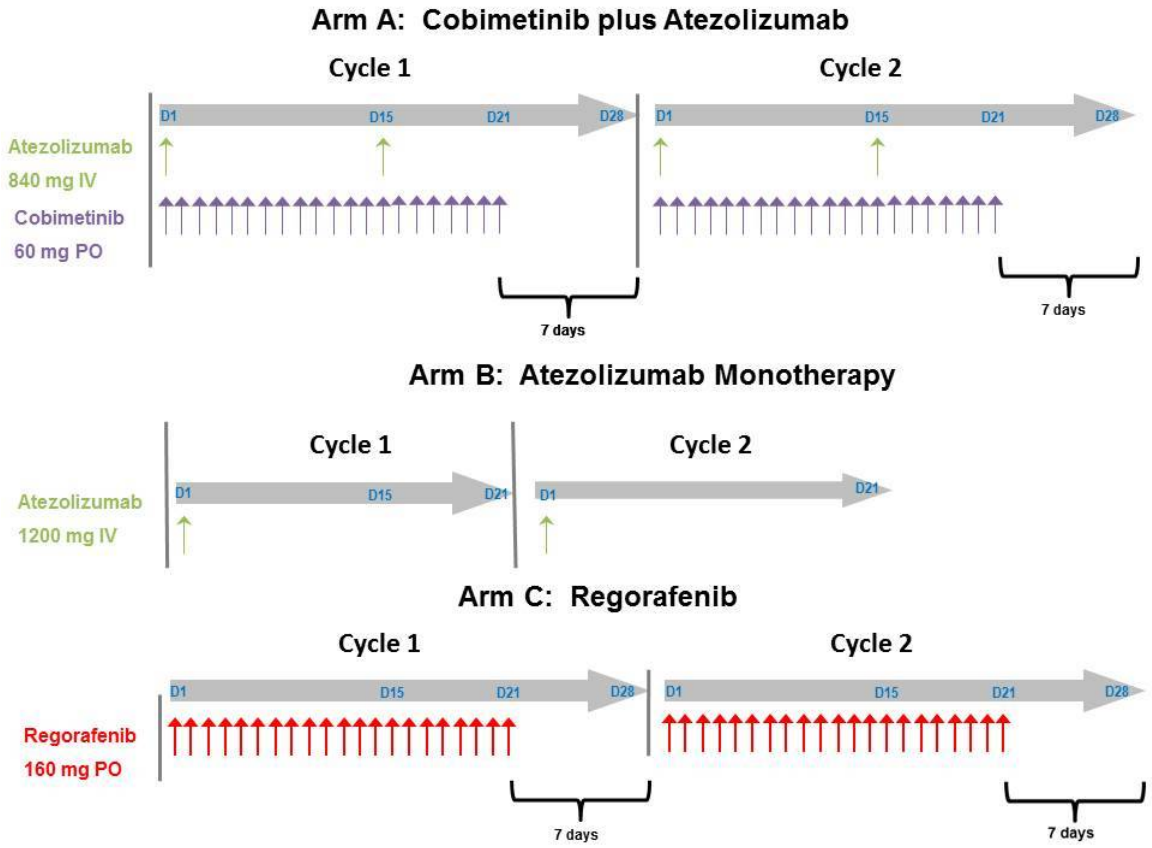
Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. In the absence of disease progression, tumor assessments should continue regardless of whether patients start a new anti-cancer therapy, unless consent is withdrawn. All patients will be followed for survival unless consent is withdrawn.

Figure 1 Study Schema



mCRC = metastatic colorectal cancer; MSI-H = microsatellite high.

Figure 2 Treatment Schedule



D = day; IV = intravenous; PO = orally (by mouth).

3.2 END OF STUDY AND LENGTH OF STUDY

The OS final analysis will be conducted when there are approximately *235 deaths in the study*. This is expected to occur approximately *23* months after the first patient is randomized.

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis (i.e., OS) or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur 3 years after the first patient is enrolled. The study will end at any time if the Sponsor decide s to end the trial.

3.3 RATIONALE FOR STUDY DESIGN

This Phase III study is designed to assess the efficacy of immunotherapy and MEK inhibition over regorafenib in unresectable mCRC patients who have received at least two prior lines of chemotherapy in this setting. Despite recent improvements in

treatment, the prognosis for these heavily pretreated patients remains dismal, with a median OS of approximately 6 months. Approved therapies are associated with significant toxicities. Therefore, there is a continuing need for more efficacious and better-tolerated treatments.

3.3.1 Rationale for Overall Survival as Primary Endpoint

Overall survival was chosen as the primary endpoint because it is the gold standard endpoint for cancer. Measurement of this endpoint is not questionable and patients with either measurable or non-measurable disease can be evaluated without the possibility of discrepancies in interpretations. This patient population has very few treatment options that would confound the assessment of OS, thus making OS a particular meaningful endpoint.

3.3.2 Rationale for Open-Label Study

The primary endpoint of the study is OS, and an open-label design would have minimal impact on OS. Given that this study is being conducted in a patient population with almost no treatment options that could affect the endpoints of the study, an open-label study design is unlikely to impart a significant bias to the study results. Furthermore, the study utilizes three study drugs with two administration routes and schedules, which introduces substantial challenges to blinding and can result in erroneous drug administration.

3.3.3 Rationale for Patient Population, Stratification Factors, and Capping

The Phase Ib trial (GP28363) evaluated the cobimetinib and atezolizumab in KRAS-mutated mCRC patients and demonstrated promising clinical activity (Section 1.7). RAS−mutated mCRC, in general, have a relatively poor immune cell infiltration and low immune inhibitory molecule expression compared to RAS wild-type colorectal tumors (Lal et al. 2015).

The proposed mechanism of action would predict that this combination would be just as effective or potentially more efficacious in patients with RAS-wild type mCRC who generally have a more favorable tumor immune microenvironment. Therefore, given the promising clinical activity and high unmet need, this Phase III study will include both RAS mutant and RAS wild-type mCRC patients.

This Phase III study will stratify patients based on their tumor extended RAS mutation status and time since diagnosis of first metastasis. These are important predictive and prognosis factors for mCRC and may potentially affect treatment outcomes.

RAS mutation status has important implications in treatment and prognosis of mCRC (Karapetis et al. 2008; De Roock et al. 2010; Sorich et al. 2015; Allegra et al. 2016). Several studies have demonstrated that RAS mutations are associated with a worse prognosis compared to RAS wild type cohorts (Sorbye et al. 2015; Sorich et al. 2015;

Vincenzi et al. 2015). This bears particular importance for regorafenib, which is the treatment in the control arm of this Phase III study. In the CORRECT study (regorafenib monotherapy for previously treated mCRC), subgroup analysis showed a treatment effect for OS in favor of regorafenib over placebo for patients with KRAS wild-type tumors whereas a numerically lower effect was reported in patients with KRAS-mutant tumors (Grothey et al. 2013). The HR (95% CI) of OS was 0.653 (0.476 to 0.895) for patients with KRAS wild-type tumors and 0.867 (0.670 to 1.123) for patients with KRAS-mutant tumors. Given that RAS mutation status has substantial prognostic significance, patients on this study will be stratified by their tumor RAS mutation status.

Time since diagnosis of first metastasis (< 18 months, ≥ 18 months) also will be used as a stratification factor. This stratification is commonly used when studying this patient population (Gothrey et al. 2014; Mayer et al 2015). The percent survival of mCRC patients is dramatically reduced from the first year from diagnosis to the second year from diagnosis of metastatic disease (Golan 2013; van der Geest 2015; Roder et al. 2015). Because time from diagnosis has great prognostic implications on survival, this trial will stratify accordingly.

In the mCRC setting, the natural frequency of tumors with MSI-high status is approximately 5% (Goldstein et al. 2014). In order to ensure generalizability of the study results, this Phase III study will limit the patients with MSI-high tumors to approximately 5%. Similarly, the frequency of extended RAS mutations in the previously treated mCRC patient population ranges from 50%−65%; thus, to reflect this prevalence, this study will enroll at least 50% mCRC patients with RAS-mutated tumors.

MSI status in CRC has important implications in both the treatment and prognosis for mCRC (Goldstein et al. 2014). In particular, recent data has shown that anti–PD-1 mAbs may be more efficacious in patients with MSI-high mCRC tumors (Le et al. 2015; Oh et al. 2015). Atezolizumab, an anti-PD-L1 mAb, inhibits the PD-L1 ligand, thereby blocking the interaction of PD-L1 with PD-1 and B7-1. Given that atezolizumab inhibits the interaction between PD-L1 and PD-1, patients with MSI-high mCRC tumors will likely experience differential efficacy compared to patients with microsatellite stable (MSS) mCRC tumors. In this study, the number of MSI-high patients will be capped at approximately 5% to represent the prevalence in this patient population. Stratification by MSI/MSS will not be necessary as the small number of MSI-high patients will likely not affect the overall results of the trial.

3.3.4 Rationale for Cobimetinib plus Atezolizumab Arm

Both nonclinical and clinical data from the Phase Ib Study GP28363 showed promising efficacy of cobimetinib plus atezolizumab in heavily pretreated KRAS−mutated mCRC patients. All the patients tested had MSI-stable tumors, unlike results from other checkpoint inhibitors (see Section 1.6). Because cobimetinib plus atezolizumab was well tolerated, and the efficacy data are promising, this combination will be further explored in this setting of high medical need.

3.3.5 Rationale for Atezolizumab Monotherapy Arm

Recent data showed that anti–PD-1 mAbs may be more efficacious in patients with MSI-high mCRC tumors (Le et al. 2015; Oh et al. 2015). In contrast to anti–PD-1 agents, atezolizumab is an anti–PD-L1 mAb, which is capable of inhibiting the interaction of PD-L1 with PD-1 and also PD-L1 with B7-1. Given that atezolizumab inhibits PD-L1 ligand from binding the PD-1 receptor and another immunomodulatory receptor (B7-1), the activity of atezolizumab may not be limited to MSI-high mCRC tumors. [redacted]. Therefore, the atezolizumab monotherapy was included in this Phase III study to further evaluate the activity of atezolizumab in mCRC.

3.3.6 Rationale for Regorafenib as Control Arm

Regorafenib and trifluridine/tipiracil are approved treatments for previously treated mCRC patients. Regorafenib was approved based on a Phase III trial that showed an improvement of OS compared to best supportive care of 1.4 months and a PFS of 0.3 months (Grothey et al. 2013). Regorafenib is approved in numerous countries worldwide, including the United States and European Union.

Trifluridine/tipiracil was recently approved in September 2015 in the United States. The approval was based on a Phase III trial demonstrating median OS improvement from 5.3 months with placebo to 7.1 months with trifluridine/tipiracil (Mayer et al. 2015).

As this is a global trial and regorafenib has been established as a standard of care treatment in patients in this setting in numerous countries, regorafenib is an appropriate treatment for the control arm.

The dosing and schedule for regorafenib that will be used in this study is the same as the dose that was used in the pivotal clinical trials (Grothey et al. 2013; Li et al. 2015) and the approved and marketed dose for this indication. Regorafenib will be administered at the recommended dose of 160 mg regorafenib (four 40 mg tablets) taken orally once daily for the first 21 days of each 28-day cycle.

3.3.7 Rationale for Dose and Schedule for Cobimetinib plus Atezolizumab and for Atezolizumab Monotherapy

In Arm A (cobimetinib plus atezolizumab), concomitant administration of atezolizumab and cobimetinib was studied in the Phase Ib Study GP28363. Cobimetinib 60 mg on a 21/7 schedule is the approved dose and schedule of cobimetinib. For administration with cobimetinib, on a 28-day cycle, a dose of 840 mg atezolizumab administered every 2 weeks has the equivalent dose exposure as the 1200 mg every 3 weeks (21–day cycle), the planned dose for the atezolizumab monotherapy arm. In Study GP28363, atezolizumab was dosed concurrently with cobimetinib at 800 mg IV q2w. The 840 mg dose is expected to be similar to the 800 mg dose of atezolizumab dose and selected in this study to simplify dose administration.

In Arm B (atezolizumab monotherapy), atezolizumab will be dosed at 1200 mg IV q3w. This is the dosing schedule that is being used in multiple Phase III studies of atezolizumab monotherapy across multiple tumor types. This dose and schedule of atezolizumab has been demonstrated to be safe and tolerable in over 1000 treated patients.

3.3.8 Rationale for Allowing Patients to Continue Treatment until Loss of Clinical Benefit

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents as increase in tumor size does not consistently reflect therapeutic failure (Wolchok et al. 2009). The phenomena of pseudo progression or infiltration of tumor by immune cells may mimic tumor progression. Therefore, as this study is evaluating an immunotherapy, the study will allow patients to continue to receive study treatment after documented RECIST v1.1–defined radiographic disease progression, provided the benefit-risk ratio for the patient remains favorable as assessed by the physician and study monitor (see Section 4.3.2.4).

3.3.9 Rationale for Patient-Related Outcomes Assessments

The patient experience of mCRC includes impacts on symptoms (disease and treatment burden), functioning, and HRQoL. Disease-specific symptoms (e.g., bloating, abdominal pain, diarrhea, constipation, loss of appetite) and other symptoms (e.g., fatigue) that negatively impact patients' functioning and quality of life are relevant in this population. Patient-completed questionnaires are included to characterize the impact of disease and treatment on patients. The collection of this type of data will provide greater insights for both the medical and patient communities to understand disease and treatment burden and resulting HRQoL when patients are exposed to cobimetinib plus atezolizumab or atezolizumab monotherapy treatments in the mCRC setting (Marventano et al. 2013).

The EQ-5D-5L will be included to derive utility to inform pharmacoeconomic models.

3.3.10 Rationale for Collection of Archival and/or Fresh Tumor Specimens, Stratification Criteria, and Biomarker Assessments

Tumor tissue samples will be collected at baseline for genetic and histopathological assessments at DNA, RNA, protein, and tissue levels to add to researchers' understanding of disease pathobiology. Gene–based CRC classification increasingly has been proposed as a way of differentiating various subtypes of CRC and may have profound effects on both treatment and prognosis. These subtypes have been shown to have different immunomodulatory affects and may influence the efficacy of this combination (Guinney et al. 2015; Kocarnik et al. 2015; Lal et al. 2015). As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored. Archival/baseline tumor analysis and classification of different CRC subtypes will be performed to further assess this possible relationship.

Tumor biopsies while on treatment and at progression are scheduled to further elucidate the possible mechanism of action or mechanisms of resistance (innate or acquired) of this regimen and may include evaluation of CD8–positive T-cell infiltrate, PD-L1 expression, and biomarkers of enhanced immune response, MAPK activation, and others involved in apoptosis or inflammation.

3.3.11 Rationale for Blood Sampling for Biomarker Assessments

An exploratory objective of this study is to evaluate biomarkers (including but not limited to cytokines, whole genome sequencing [WGS], cfDNA, and cancer-specific biomarkers, such as CEA) in blood samples. The evaluation of blood biomarkers may provide evidence for biologic activity of cobimetinib plus atezolizumab and atezolizumab monotherapy in patients with mCRC and may allow for the early prediction of clinical benefit of cobimetinib and atezolizumab use.

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

3.3.11.1 Rationale of Optional Whole Genome Sequencing

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

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

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

In addition to the link between genetic variation in drug-metabolizing enzymes and transporters and pharmacokinetics, recent studies have also identified genetic variants

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

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

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

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 360 patients with unresectable locally advanced or metastatic CRC who have received at least two different chemotherapy regimens for metastatic disease will be enrolled in this study (see Section 4.5.2 for definition of chemotherapy regimen). The patients will be stratified for extended RAS status and time since diagnosis of first metastasis (<18 months vs. ≥18 months). MSI-high status will be capped at approximately 5%, and at least 180 patients with extended RAS will be enrolled in the study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

Disease-specific inclusion criteria:

- Histologically confirmed adenocarcinoma originating from the colon or rectum (Stage IV American Joint Committee on Cancer [AJCC] 7th edition)
- Experienced disease progression on at least two prior systemic chemotherapy regimens for mCRC
    1. Prior systemic cytotoxic chemotherapy must include ALL of the following agents:
        a) Fluoropyrimidines
        b) Irinotecan
        c) Oxaliplatin

2. Patients who have received prior anti-angiogenic therapy (e.g., bevacizumab) and/or anti-EGFR therapy (e.g., cetuximab) are eligible.
3. Patients must have had documented disease progression within 3 months of the last systemic therapy administration.
4. Patients who were intolerant to prior systemic chemotherapy regimens are eligible if there is documented evidence of clinically significant intolerance despite adequate supportive measures.
5. For patients who had disease recurrence within 6 months of completing adjuvant chemotherapy, the adjuvant regimen can be considered as one chemotherapy regimen for metastatic disease.

General inclusion criteria:

- Signed Informed Consent Form
- Age $\geq$ 18 years
- In the investigator's judgment, patient is able to comply with the requirements and assessments of the study protocol
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix 6)
- Anticipated life expectancy $\geq$ 3 months
- Able to comply with the requirements and assessments of the study protocol
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to first dose of study drug treatment:
    1. Hemoglobin $\geq$ 9 g/dL, platelet count $\geq$ 100,000/mm^3, ANC $\geq$ 1500/mm^3
    2. Creatinine clearance $\geq$ 30 mL/min
    3. Amylase and lipase $\leq$ 1.5 $\times$ the upper limit of normal (ULN)
    4. Serum bilirubin $\leq$ 1.5$\times$ ULN; patients with known Gilbert's disease may have a bilirubin $\leq$ 3.0 $\times$ ULN
    5. AST, ALT, and alkaline phosphatase (ALP) $\leq$ 2.5 $\times$ ULN with the following exceptions:
        a) Patients with documented liver metastases: AST and/or ALT $\leq$ 5 $\times$ ULN
        b) Patients with documented liver or bone metastases: ALP $\leq$ 5 $\times$ ULN
    6. INR and PTT $\leq$ 1.5 $\times$ ULN. Patients who are on therapeutic doses of anti-coagulants are eligible if they are on a stable dose of anti-coagulant for 28 days with stable INR and PTT values.

- Women of childbearing potential must agree to appropriately use an effective form of contraception (failure rate of $<1\%$ per year) during the treatment period, within 5 months after the last dose of atezolizumab, and within 3 months after the last dose of cobimetinib and regorafenib.
    1. A woman of childbearing potential is defined as a sexually mature woman without prior oophorectomy or hysterectomy who have had menses within the last 12 months.
    2. A woman is not considered to be of childbearing potential if she has become amenorrheic for >12 months and has a follicle-stimulating hormone level ≥ 40 IU/L.
- Men must agree not to donate sperm or have intercourse with a female partner without using appropriate barrier contraception during the treatment period and for 3 months after the last dose of either cobimetinib or regorafenib.
- Available and adequate baseline tumor tissue sample (archival or newly obtained biopsy; see Section 4.5.7)

4.1.2 Exclusion Criteria

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

Cancer-related exclusion criteria:

- After the approximate 5% cap for MSI-high patients is reached, only MSI-stable patients will be eligible.
- Once the 50% cap for wild-type RAS has been reached, only extended RAS-mutant patients will be eligible.
- Major surgery or radiotherapy within 21 days prior to Cycle 1 Day 1 or anticipation of needing such procedure while receiving study treatment.
- Treatment with any anti-cancer agent within 14 days prior to Cycle 1 Day 1
- Uncontrolled tumor-related pain. Patients requiring narcotic pain medication must be on a stable regimen at study entry.
    1. Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to start of study treatment.
    2. Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to the start of study treatment.
- Uncontrolled pleural effusion, pericardial effusion or ascites requiring repeated drainage more than once every 28 days. Indwelling drainage catheters (e.g., PleurX®) are allowed.
- Active or untreated CNS metastases are excluded. Patients with treated and asymptomatic CNS metastases are eligible, if they meet all of the following:
    1. Evaluable or measurable disease outside the CNS

2. No metastases to midbrain, pons, medulla, or within 10 mm of the optic nerves and chiasm
3. No history or evidence of intracranial hemorrhage or spinal cord hemorrhage
4. No evidence of clinically significant vasogenic edema
5. Not on corticosteroids for $\geq$ 2 weeks; anti-convulsants at a stable dose are allowed.
6. No evidence of clinical and radiographic disease progression in the CNS for $\geq$ 3 weeks after radiotherapy or surgery.

- Exclusion criteria related to study medication:
  1. Any cancer immunotherapy including CD137 agonists, anti–PD-1, anti–PD-L1, or anti-CTLA4
  2. Any MEK or ERK inhibitor
  3. Regorafenib
- Patients with active malignancy (other than CRC) or a prior malignancy within the past 3 years are excluded. Patients with completely resected cutaneous melanoma (early stage), basal cell carcinoma, cutaneous squamous cell carcinoma, cervical carcinoma in-situ, breast carcinoma in-situ, and localized prostate cancer are eligible.

Exclusion criteria based on organ function or medical history:

Cardiovascular:

- Unstable angina, new onset angina within last 3 months, myocardial infarction within last 6 months and current congestive heart failure New York Heart Association Class II or higher.
- Left ventricular ejection fraction (LVEF) below institutional lower limit of normal or below 50%, whichever is lower.
- Poorly controlled hypertension, defined as a blood pressure consistently above 150/90 mmHg despite optimal medical management.

Infections:

- HIV infection
- Active tuberculosis infection
- Severe infections within 2 weeks prior to Cycle 1 Day 1
- Signs or symptoms of significant infection within 2 weeks prior to Cycle 1 Day 1
- Received oral or IV antibiotics within 2 weeks prior to Cycle 1 Day 1

  Patients receiving prophylactic antibiotics (e.g., for prevention of urinary tract infection or chronic obstructive pulmonary disease) are eligible

- Active or chronic viral hepatitis B or C infection
    1. Patients with hepatitis B virus (HBV) infection are eligible if test for hepatitis B surface antigen (HBsAg) and HBV DNA are negative
    2. Patients with hepatitis C virus (HCV) infection are eligible if polymerase chain reaction (PCR) test for HCV RNA is negative.

Ocular:

- History of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for central serous retinopathy, retinal vein occlusion, or neovascular macular degeneration
- Patients will be excluded if they currently have any of the following risk factors for retinal vein occlusion:
    1. Uncontrolled glaucoma with intra ocular pressure $\geq$ 21 mmHg
    2. Uncontrolled hypercholesterolemia $>$ 300 mg/dL or 7.75 mmol/L
    3. Uncontrolled hypertriglyceridemia $>$ 300 mg/dL or 3.42 mmol/L
    4. Fasting hyperglycemia $>$ 160 mg/dL or 8.9 mmol/L

Autoimmune conditions and immunomodulatory drugs:

- History of autoimmune disease except for the following:
    1. Patients with autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible.
    2. Patients with controlled type 1 diabetes mellitus on a stable dose of insulin regimen are eligible.
- Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis) are permitted provided that they meet the following conditions:

  Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations

  Rash must cover less than 10% of body surface area

  Disease is well controlled at baseline and only requiring low–potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)

  No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral steroids)
- History of idiopathic pulmonary fibrosis, organizing pneumonia, bronchiolitis obliterans, drug-induced pneumonitis, or idiopathic pneumonitis

  Patients with radiation pneumonitis within the radiation field are eligible.
- History of organ transplantation including allogeneic bone marrow transplantation

Other medical conditions or medications:

- Any hemorrhage or bleeding event CTCAE Grade 3 or higher within 28 days of Cycle 1 Day 1
- History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to Day 1
- Proteinuria > 3.5 g/24 hours
- Serum albumin < 2.5 g/dL
- Foods, supplements or drugs that are potent CYP3A4 enzyme inducer or inhibitors are prohibited at least 7 days prior to Cycle 1 Day 1 and during study treatment. These include St. John's wort or hyperforin (potent CYP3A4 enzyme inducer) and grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor).

General exclusion criteria:

- Inability to swallow medications
- Malabsorption condition that would alter the absorption of orally administered medications
- Pregnant, lactating, breastfeeding, or intending to become pregnant during the study
- History of severe hypersensitivity reactions to components of:
    1. Cobimetinib formulation
    2. Regorafenib formulation
    3. Atezolizumab formulation
- Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation of a live attenuated vaccine will be required during the study
- Any anti-cancer therapy, including chemotherapy, or hormonal therapy within 2 weeks prior to initiation of study treatment
- Treatment with systemic immunostimulatory agents (including but not limited to interferons, IL-2) within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to Cycle 1 Day 1
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [TNF] agents) within 2 weeks prior to Cycle 1 Day 1

4.2 METHOD OF TREATMENT ASSIGNMENT

After written informed consent has been obtained and eligibility established, each patient will be assigned an identification number and be randomized to 2:1:1 to one of the three treatment arms through use of an IxRS (see Figure 1 in Section 3.1).

Permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm. Randomization will be stratified by the following criteria:

- Tumor extended RAS status (RAS mutated or RAS wild-type). Extended RAS mutation is defined as mutations occurring in KRAS and NRAS gene codons 12 and 13 of exon 2; 59 and 61 of exon 3; and 117 and 146 of exon 4
- Time since diagnosis of first metastasis (<18 months vs. ≥18 months)

Once the limit of patients with MSI-high tumors has been reached (approximately 5% of patients; see Section 3.3.3), only patients whose tumors are MSI-stable or MSI-low will be enrolled and randomized.

Once the limit of patients with extended RAS wild type (50%) has been reached (see Section 3.3.3), only patients whose tumors are extended RAS mutant will be enrolled and randomized.

Patients should receive their first dose of study treatment as soon as possible and within 3 days of randomization.

4.3 STUDY TREATMENT

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

Regorafenib is an approved treatment for mCRC in this disease setting and can be considered standard of care. Regorafenib is a non–investigational medicinal product (NIMP) in this study unless local regulations require it to be an IMP.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Cobimetinib

Cobimetinib will be supplied 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. The inactive ingredients in cobimetinib are as follows: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate for the tablet core. The tablet coating consists of polyvinyl alcohol, part hydrolyzed, titanium dioxide, polyethylene glycol 3350, and talc. Cobimetinib should not be stored above 25°C (77°F). If the study drug is stored outside of the permitted temperature ranges, quarantine the affected supply and contact the monitor.

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

4.3.1.2 Atezolizumab

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

840-mg dose. For information on the formulation and handling of atezolizumab, refer to the Investigator's Brochure and Pharmacy Manual.

4.3.1.3 Regorafenib (Stivarga®)

The control arm (Arm C) is regorafenib. In countries where regorafenib is considered an NIMP by local regulations and is commercially available, the commercial formulation of regorafenib (Stivarga) will be provided by the local institution as part of standard of care treatment. It will be provided or reimbursed by the Sponsor if it is considered an IMP by local regulations (see Section 4.3.3) or not commercially available.

For information on the formulation, packaging, and handling of regorafenib, see the Stivarga (regorafenib) Prescribing Information.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Cobimetinib

Patients randomized to cobimetinib will receive 60 mg (three tablets of 20 mg each) orally once daily for Days 1–21 of a 28-day cycle as stated in Section 3.1, including Figure 2. This 4-week period is considered a treatment cycle.

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

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.4.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF (See Section 5.3).

4.3.2.2 Atezolizumab

Atezolizumab dose and schedule will depend on the treatment arm:

- Arm A: cobimetinib plus atezolizumab 840 mg IV q2w
- Arm B: atezolizumab 1200 mg IV q3w as monotherapy

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

For more detailed information on drug preparation, storage, and administration, refer to the Investigator's Brochure and Pharmacy Manual.

Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Infusions of Atezolizumab

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

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

Dose modifications to atezolizumab are not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events associated with cobimetinib and atezolizumab are provided in Section 5.1.4 and Appendix 3. For information regarding management of atezolizumab-associated adverse events, please refer to *Appendix 9*.

For anaphylaxis precautions, see Appendix 4.

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

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF (See Section 5.3).

4.3.2.3 Regorafenib

Regorafenib will be used in the commercially available formulation.

Patients randomized to regorafenib (Arm C), will receive regorafenib at the approved dose level of 160 mg (four tablets of 40 mg each) orally once daily on Days 1–21 of a 28-day cycle (see Section 3.3 and Figure 2 in Section 3.1). This 4-week period is considered a treatment cycle.

Regorafenib should be taken at the same time each day. The tablets should be swallowed whole with water after a light meal that contains < 30% fat. An example of a light (low-fat) meal would include one portion of cereal (about 30 g), one glass of skimmed milk, one slice of toast with jam, one glass of apple juice, and one cup of coffee or tea (520 calories, 2 g fat).

The study investigator may implement dose interruption or dose reduction in response to adverse events to ensure patient safety and tolerability. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.4.1. Please refer to the Stivarga (regorafenib) prescribing information for more details.

Any overdose or incorrect administration of regorafenib should be noted on the Regorafenib Administration eCRF. Adverse events associated with an overdose or incorrect administration of regorafenib should be recorded on the Adverse Event eCRF (See Section 5.3).

4.3.2.4 Dosing of Study Treatment Beyond Disease Progression

Dosing of study treatment beyond RECIST v1.1–defined disease progression is allowed for patients on all treatment arms. Patients must meet all of the following criteria to be allowed to receive study treatment beyond disease progression:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs indicating unequivocal progression of disease. Patients may continue to receive treatment beyond disease progression in the absence of clinical signs or symptoms of progression despite a rising CEA level.
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol–allowed medical interventions
- Patients must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of RECIST v1.1-defined disease progression
- Approved by the study Medical Monitor

4.3.3 Investigational Medicinal Product Accountability

The IMPs required for completion of this study (i.e., cobimetinib, atezolizumab, and regorafenib if considered an IMP by local regulations) will be supplied or reimbursed by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of cobimetinib and atezolizumab using the IxRS to confirm the

shipment condition and content. Any damaged shipments will be replaced. Where regorafenib is supplied by the Sponsor, shipment receipt will be documented using IxRS; otherwise, it will be documented per local practice.

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

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

4.3.4 Post-Trial Access to Cobimetinib and Atezolizumab

The Sponsor will offer post-trial access to the study drugs cobimetinib and atezolizumab free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below. Note that regorafenib will not be offered free of charge after study completion.

A patient will be eligible to receive cobimetinib and atezolizumab after completing the study if all of the following conditions are met:

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

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

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or 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 colorectal cancer
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for CRC
- 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 includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study drug to treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

The following therapies are permitted in the study:

- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as low-molecular weight heparin or warfarin at a stable dose level)
- Palliative radiotherapy (e.g., treatment of known bone metastases) provided it does not interfere with assessment of tumor target lesions

  It is not required to withhold atezolizumab during palliative radiotherapy.
- Inactive influenza vaccinations during influenza season ONLY
- Megastrol administered as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)

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

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, as per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion–associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and b_2-adrenergic agonists).

All medications must be recorded on the Concomitant Medications eCRF.

4.4.2 Prohibited Therapy

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

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: 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 4 weeks prior to randomization or at any time during the study or within 5 months following the last infusion of atezolizumab.
- For patients on 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, MRIs of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest 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 received in combination with atezolizumab
  - Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab
  - Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations where systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered first by the treating physician. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the treating (see Section 4.4.2)

- For patients on cobimetinib:
  - Concomitant use of strong and moderate inhibitors of CYP3A (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) should be avoided as cobimetinib is a sensitive substrate of CYP3A and exposures will be increased in presence of these agents (approximately 7-fold increase in presence of itraconazole in healthy subjects).
  - Avoid strong and moderate CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's wort) as they increase the metabolism of cobimetinib. Strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered.
- For patients on regorafenib:
  - Avoid use of strong and moderate inhibitors of CYP3A (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) as mean AUC of regorafenib was increased by 33% (Stivarga [regorafenib] Prescribing Information).
  - Avoid strong UGT1A9 inhibitor (e.g., mefenamic acid, diflunisal, and niflumic acid) during regorafenib treatment as their influence on the steady-state exposure of regorafenib and its metabolites has not been studied.
  - Avoid strong and moderate CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's wort) as they increase the metabolism of regorafenib. Strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered.

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the Internet references provided below when determining whether a certain medication is metabolized by or strongly inhibits or induces CYP3A or UGT1A9. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of assessments 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-related 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 investigator to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

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

Demographic data will include age, sex, and self-reported race/ethnicity. Baseline disease characteristics data will include AJCC disease stage at enrollment, ECOG performance status, date of diagnosis of first metastatic disease, site of primary disease, RAS status, MSI status, history of metastasectomy, location of metastasis at enrollment, number of prior chemotherapy regimens, and prior therapy (5-fluorouracil, oxaliplatin, irinotecan, trifluridine and tipiracil, anti-EGFR, anti-VEGF),

A chemotherapy regimen is defined as a set of chemotherapy agents with an initial defined dose and frequency that are given in a prescribed order, which may be concurrently. A regimen can consist of only one chemotherapy agent or multiple agents. If one of the agents is discontinued because of toxicity or other concerns, the remaining chemotherapy combination is not considered a new regimen. Maintenance therapy is also not considered a separate regimen. If a chemotherapy regimen is held and restarted at a later date, this is considered one regimen and not two separate chemotherapy regimens.

4.5.3 Physical Examinations

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

At subsequent visits (or as clinically indicated), limited, symptom–directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF (See Section 5.2).

Patients on cobimetinib plus atezolizumab will be asked specifically about vision changes as part of each physical examination in addition to interval medical history. Note: If physical examinations are performed within 7 days of Cycle 1 Day 1, they do not have to be repeated on Cycle 1 Day 1 (see Section 4.5.11).

4.5.4 Vital Signs

Vital signs are defined as: temperature (°C), heart rate, respiratory rate, and systolic and diastolic blood pressure. Height and weight will be recorded on Cycle 1 Day 1.

4.5.4.1 Vital Signs for Patients Assigned to Receive Atezolizumab with or without Cobimetinib (Arms A and B)

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

- Within 60 minutes prior to infusion
- During infusion and/or after infusion if clinically indicated

For patients in the atezolizumab arm who experienced an infusion-related reaction during the previous atezolizumab infusion, refer to Section 5.1.4.

4.5.4.2 Vital Signs for Patients Assigned to Receive Regorafenib (Arm C)

Monitor vital signs weekly for the first 6 weeks and then with every cycle, especially systolic and diastolic blood pressure as indicated by the Stivarga (regorafenib) Prescribing Information as uncontrolled hypertension has been known to occur.

4.5.5 Tumor and Response Evaluations

Baseline tumor assessments should be performed $\leq$35 days before Cycle 1 Day 1 and assessed according to RECIST v 1.1 (see Appendix 5). The same procedure used to assess disease sites at baseline should be used throughout the study (e.g., the same contrast protocol for CT scans or MRI scans). To the extent that it is feasible, the same assessor should read and evaluate the tumor assessments for the same patient throughout the study. CT or MRI scans should include chest, abdomen, and pelvic scans; CT or MRI scans of the neck should be included if clinically indicated. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

Evaluation of tumor response conforming to RECIST v1.1 must be documented every 8 weeks $\pm$ 1 week no matter where the patient is in the chemotherapy treatment cycle (this can occur mid-treatment) until documented investigator–determined progressive disease, loss of clinical benefit, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Schedule of tumor assessments are independent of any changes to the study treatment administration schedule (e.g., dose delay) and may occur mid-cycle depending on length of cycle. If a tumor assessment has to be performed early or late, subsequent assessments should be conducted according to the original schedule based on the date of first study drug administration (Cycle 1 Day 1).

Confirmation of response (PR or complete response [CR]) will be done no earlier than 28 days from study entry. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval not less than 6 weeks. Patients who discontinue study treatment for any reason other than disease progression will continue to undergo tumor response evaluations (approximately every 8 weeks) until progressive disease. A rising CEA alone without radiological evidence of progression is not considered progressive disease.

Patients who continue to experience clinical benefit in all three arms, despite evidence of radiographic progression as defined by RECIST v1.1, may continue treatment (see Section 4.3.2.4) and will continue tumor assessments as per the schedule listed above.

4.5.6 Laboratory, Biomarker, and Pharmacokinetic Samples

4.5.6.1 Local Laboratory Assessments

Screening

- Hematology (CBC, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes], and platelet count)
- Serum chemistries (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, calcium, phosphorus, total bilirubin, ALT, AST, ALP, CPK, lipase, amylase, LDH, and albumin)
- Coagulation (INR and aPTT)
- Serum pregnancy test for women of childbearing potential, including women who have had a tubal ligation.
  - A woman is not considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (defined as 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone permanent surgical sterilization (removal of bilateral ovaries and/or uterus.
- Thyroid function testing (thyroid-stimulating hormone, free T3, free T4)
- HBV serology: HBsAg, antibodies against HBsAg, anti-hepatitis B core antibody (anti-HBcAb)
- HBV DNA should be obtained prior to randomization if patient has a negative serology for HbsAg and a positive serology for anti-HBcAb.
- HCV serology: HCV antibody (anti-HCV)
- HCV RNA should be obtained prior to randomization if patient tests positive for anti-HCV
- HIV testing
  - All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical study.

On Study Treatment

- Hematology (CBC, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, and platelet count])
- Serum chemistries (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, calcium, phosphorus, total bilirubin, ALT, AST, ALP, CPK, lipase, and amylase)
- CEA

4.5.6.2 Central Laboratory Assessments

A central laboratory will coordinate the sample collection of tissue and blood samples for research-related testing at central laboratories. Instruction manuals and supply kits will be provided for all central laboratory assessments. Residual atezolizumab PK and ATA samples will be retained for further method development, validation, and characterization. Samples will be stored until they are no longer needed or until they are used up. Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- ATA assays, provided that it does not cause undue hardship to the patient (e.g., the patient is in hospice care and not able to come in for a visit)
- Serum samples also may be assayed for other anti-atezolizumab antibodies with use of validated immunoassays
- Auto-antibody testing: baseline sample to be collected on Cycle 1 Day 1 prior to the first dose of study drug. For patients who show evidence of immune-mediated toxicity, additional samples may be collected, and all samples will be analyzed centrally.
  - Anti-nuclear antibody
  - Anti–double-stranded DNA
  - Circulating anti–neutrophil cytoplasmic antibody
  - Perinuclear anti–neutrophil cytoplasmic antibody
- PK assay, provided that it does not cause undue hardship to the patient (e.g., the patient is in hospice care and not able to come in for a visit)
  - Serum samples will be assayed for atezolizumab concentrations with use of a validated immunoassay.
  - Plasma samples for cobimetinib concentrations will be measured using validated liquid chromatography combined with tandem mass spectrometry method.

- Biomarker assays in blood samples
  - Blood samples will be obtained for biomarker evaluation (including but not limited to biomarkers that are related to CRC or tumor immune biology) from all eligible patients according to the schedule in Appendix 1. Samples will be processed to obtain plasma for the determination of changes in blood-based biomarkers. Blood samples may be processed to obtain peripheral blood mononuclear cells and their derivatives (e.g., RNA and DNA) and may be evaluated for immune-related, tumor-type related, and other exploratory biomarkers (e.g., alterations in gene expression or single nucleotide polymorphisms; see Table 2). Optional blood sample for WGS may also be obtained.

Table 2 Proposed Non-Inherited Biomarkers for Exploratory Research

Sample Type	Timing	Proposed Non-Inherited Biomarkers
Plasma	Baseline and subsequent timepoints during treatment	• Cytokines • cfDNA
Tissue (e.g., tumor)	Prior to study (archival) or baseline (fresh); on treatment (optional) and at progression	• NGS • Biomarkers that may predict response, elucidate mechanism of response, or predict resistance (including but not limited to: CD8, MHC1, PD-L1, β-catenin) • RNA_{seq} for CRC subtyping

cfDNA = cell-fee DNA; CRC = colorectal cancer; MHC = major histocompatibility complex; NGS = next-generation sequencing; PD-L1 = programmed death ligand-1; RNA_{seq} = RNA sequencing.

For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

The remainder of samples obtained for study-related procedures (including blood samples and tumor tissues) will be destroyed no later than 5 years after the final Clinical Study Report has been completed or earlier depending on local regulations. Archival blocks will be returned to sites following biomarker testing.

4.5.7 Tumor Tissue Samples

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

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

4.5.7.1 Archival and Fresh Tumor Sample for Screening

Representative tumor specimens in paraffin blocks (preferred) or at least 20 serial cut, unstained slides with an associated pathology report must be submitted for determination of extended RAS status and MSI status.

Extended RAS mutation is defined as mutations occurring in KRAS and NRAS gene codons 12 and 13 of exon 2; 59 and 61 of exon 3; and 117 and 146 of exon 4 (Allegra et al. 2016). Local RAS testing results will be accepted with a copy of the results and interpretation as part of the screening process with a requirement for central confirmation.

MSI status can be defined by several methods such as IHC detection of hMLH1 and hMSH2 gene products, NGS testing, or PCR testing by the fraction of MSI loci that exhibit differently sized repeats (Lindor et al. 2002; Salipante et al. 2014). Local MSI testing results will be accepted with a copy of the results and interpretation as part of the screening process with a requirement for central confirmation.

In addition, NGS for exploratory research on non-inherited (or tumor specific) biomarkers (including, but not limited to, cancer-related genes and biomarkers associated with common molecular pathways) and exploratory biomarkers (including but not limited to markers related to immune, MAP kinase pathway, or CRC biology, such as T-cell markers or tumor mutation status) may be evaluated (see Table 2 in Section 4.5.6).

Foundation Medicine NGS–based genomic profiling will be performed. When performed by Foundation Medicine, the investigator can obtain results from the samples collected in the form of an NGS report, which is available upon request directly from Foundation Medicine. The investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions.

Archival tumor tissue should be collected as follows:

- A representative formalin–fixed, paraffin-embedded (FFPE) tumor specimen collected at first diagnosis and/or subsequent tumor recurrence(s) consistent with the patient's diagnosis is required for participation in this study (FFPE block [preferred], or a minimum of 20 unstained serial sections). This specimen must be accompanied by the associated pathology report.
  - The available tumor sample must be adequate to determine extended RAS status and MSI status.
  - The tumor sample and associated pathology report must be confirmed to be available prior to any study–specific screening procedures. Fine-needle aspiration, brushing, cell pellet from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation.

- For samples that do not meet the minimum requirements for size/slide number, contact the Medical Monitor via site contact with tissue size and tumor content/number of slides to determine eligibility.
- Alternatively, or if the archival tumor sample does not meet minimum requirements, the patient may be offered the option of undergoing a pretreatment procedure (excisional or core tumor biopsy) to obtain an adequate tumor sample, provided that his or her disease is easily accessible and tumor biopsies can be performed with minimal risk and discomfort.

If archival tissue is unavailable, a pretreatment tumor biopsy is required.

Cytological or fine-needle aspiration samples are not acceptable. Acceptable samples include:

- Core needle biopsies for deep tumor tissue; at least three cores, embedded into a single paraffin block, should be submitted for evaluation.
- Excisional or incisional tumor biopsy
- Tumor tissue resection

4.5.7.2 Optional Tumor Biopsy on Treatment

An optional biopsy while on treatment is requested on Cycle 1 Day 15 $\pm$ 5 days provided the patient's disease is easily accessible and tumor biopsies can be performed with minimal risk and discomfort.

This biopsy is for exploratory research on biomarkers associated with the MAP kinase pathway and immune-related pathways, and for DNA and RNA extraction on non-inherited biomarkers (including, but not limited to cancer-related genes).

4.5.7.3 Tumor Biopsy at Time of Progression

Patients will undergo a mandatory tumor biopsy to obtain a tumor sample at time of progression unless not clinically feasible and provided that their disease is easily accessible and tumor biopsies can be performed with minimal risk and discomfort.

This biopsy is for DNA, RNA, and protein analysis for exploratory research on non-inherited (tumor specific) biomarkers included but not limited to studying mechanisms of resistance. NGS will be performed by Foundation Medicine. When performed by Foundation Medicine, the investigator can obtain results from the samples collected in the form of an NGS report, which is available upon request directly from Foundation Medicine. The investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions.

4.5.8 Left Ventricular Ejection Fraction

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

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

- Screening
- Cycle 2 Day 1 ± 1 week
- Day 1 of every three treatment cycles thereafter starting at Cycle 5 ± 2 weeks
- Treatment discontinuation visit: The treatment discontinuation visit evaluation of LVEF does not need to be performed at the treatment discontinuation visit if an evaluation has been performed within the last 12 weeks and there are no clinically significant findings and/or changes from baseline.
- All patients who restart treatment with a reduced dose of cobimetinib because of a decrease in LVEF should have LVEF measurements taken after approximately 2 weeks, 4 weeks, 10 weeks, and 16 weeks and then resume monitoring LVEF every 3 cycles.

Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF assessment. Evaluation of LVEF must be performed by the same method (ECHO or MUGA) 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.

4.5.9 Ophthalmologic Examination

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

Ophthalmologic examination must be performed at the following timepoints:

- Screening
- Cycle 2 Day 1 ± 1 week
- Day 1 of Cycles 5, 8, and 11 (every 3 cycles) ± 2 weeks
- Day 1 of Cycles 15, 19, and 23 (every four treatment cycles) ± 2 weeks
- Day 1 of Cycles 29, 35, 41, 47, etc. (every six treatment cycles) ± 2 weeks
- Treatment discontinuation visit. If an ophthalmologic evaluation has been performed within the last 12 weeks of the treatment discontinuation visit, the ophthalmologic examination does not need to be performed during the treatment discontinuation visit.

The objective of baseline ophthalmologic examination is to evaluate for evidence of retinal pathology that may be a risk factor for central serous retinopathy or retinal vein occlusion. Ophthalmologic examination must be performed by a qualified ophthalmologist. Risk factors for retinal vein occlusion include uncontrolled serum cholesterol, hypertriglyceridemia, hyperglycemia, hypertension, and glaucoma. Patients with such conditions will be excluded from the study as detailed in the inclusion/exclusion criteria.

Baseline and serial surveillance ophthalmologic examination will include visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, spectral–domain optical coherence tomography, and Humphrey Automatic Visual Field using Swedish interactive threshold algorithm Fast-10-2 protocol.

4.5.10 Patient-Reported Outcomes

PRO data will be collected via the EORTC QLQ-C30 and two additional items from the EORTC item bank (see Section 4.5.10.1) to more fully characterize the clinical profile of cobimetinib plus atezolizumab as compared to regorafenib. In addition, to derive utility for pharmacoeconomic models, patients will complete the EQ-5D-5L.
The questionnaires will be translated as required in the local language. To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety by the patient prior to the performance of non-PRO assessments and the administration of study treatment (where applicable).

Patients will use an electronic PRO (ePRO) device to capture PRO data at in-person clinic visits. The ePRO device and/or instructions for completing the PRO questionnaires electronically will be provided by the investigator staff. The data will be transmitted via a pre-specified transmission method (e.g., web or wireless) automatically after entry to a centralized database at the ePRO vendor. The data can be accessed by the appropriate sponsor study personnel securely via the Internet.

The questionnaires will be completed on the ePRO tablet at the beginning of each cycle upon arrival at the study clinic during treatment period and at the treatment discontinuation visit. The assessments should continue until loss of clinical benefit and then follow the survival follow-up frequency at 3 and 6 months. If the survival follow-up study visits are conducted by telephone, the PRO data (the reduced EORTC QLC 30) for that visit will be collected via telephone interview and recorded by the investigative staff on the ePRO tablet.

Adverse event reports will not be derived from PRO data by the Sponsor.

4.5.10.1 European Organization for Research and Treatment of Cancer Quality of Life-C30 Questionnaire and Additional Items

The EORTC QLQ-C30 is a self-report questionnaire that assesses multiple dimensions of HRQoL among cancer patients. Responses to this 30-item questionnaire are categorized into five functional domains (i.e., physical, role, emotional, cognitive, and social) (scored on a 4-point Likert scale), one global health status domain (scored on a 7-point Likert scale), three symptom domains (i.e., fatigue, nausea/vomiting, pain), and six single items (scored on a 4-point Likert scale). Items that assess abdominal bloating and abdominal pain that are issued from the validated EORTC item bank will be added to the assessment. Each score is transformed into a 0–100-point scale. In the five functional scales and the global health status scale, a high score means a "high level of functioning or global health status." In the case of symptom scales and single items, a higher score implies a "high level of symptoms or problems."

To maintain validity and minimize patient burden, the EORTC instrument administered via telephone interview will consist of a reduced version of the EORTC QLQ items (Items 1–7, 10, 12, 13, 16, 17, 18, 29, and 30 from the C30 and the two additional items from the item bank).

4.5.10.2 EuroQoL 5 Dimensions

The EQ-5D questionnaire is a generic, preference-based health utility measure with questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are used to build a composite of the patient's health status. The EQ-5D will be utilized in this study for economic modeling. The EQ-5D questionnaire takes 5 minutes or less to complete.

To maintain validity and minimize patient burden, the EQ-5D-5L instrument administered via telephone interview will consist of the telephone interview version of the EQ-5D-5L.

4.5.11 Timing of Assessments

4.5.11.1 Screening

Screening tests and evaluations will be performed within 35 days prior to Cycle 1 Day 1. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 35 days prior to Cycle 1 Day 1 may be used; such tests do not need to be repeated for screening.

See Appendix 1 for the schedule of screening assessments and Appendix 2 for the schedule of PK and ATA assessments.

4.5.11.2 On Treatment

All treatment visits must occur within ±3 days from the scheduled date unless otherwise noted (see Appendix 1). All procedures, tests, and assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled

on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion unless otherwise noted.

4.5.11.3 Treatment Discontinuation

Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit within 30 days after the last dose of study treatment. The visit at which the investigator determines a loss of clinical benefit may be used as the treatment discontinuation visit. In the event that the decision for discontinuation is due to an adverse event and this visit also shows progressive disease, discontinuation will be marked as due to progressive disease.

See the study flowcharts provided in Appendix 1.

Patients who discontinue study treatment must be followed according to the follow-up visit schedule for progression and/or survival until death, loss to follow-up, or withdrawal of consent, which will be defined as study discontinuation.

4.5.11.4 Follow-Up

After the treatment discontinuation visit, adverse events should be followed as outlined in Section 5.6. For patients who discontinue study treatment for reasons other than disease progression, tumor assessments should continue to be performed as scheduled (i.e., every 8 weeks $\pm$ 1 week) until patient death or documented disease progression.

Survival follow-up should continue until death, withdrawal of consent, the patient is lost to follow-up, or study termination by the Sponsor, whichever occurs first. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) when permissible, to obtain information about survival status only.

See the study flowcharts provided in Appendix 1 for assessments to be performed during follow-up visits.

4.5.11.5 Unscheduled Visits

Assessments for unscheduled visits related to a patient's underlying CRC, study treatment, or adverse events should be performed as clinically indicated and entered into Unscheduled Visit eCRFs.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study

- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance

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.

4.6.2 Study Treatment Discontinuation

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

- Disease progression (see Section 4.3.2.4 for dosing beyond progression)
- Symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status
- Intolerable toxicity related to any study drug
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Use of another non–protocol anti-cancer therapy (see Section 4.4.2)
- Pregnancy

Patients must provide written consent to acknowledge deferring any standard treatment options that may exist in favor of continuing treatment at the time of initial progression.

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

4.6.3 Study and Site Discontinuation

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

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

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

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

In the United States, atezolizumab is approved for the treatment of locally advanced or metastatic urothelial bladder cancer who have progressed during or following platinum-containing chemotherapy and for metastatic non–small cell lung cancer who have progressed during or following platinum-containing chemotherapy and if harboring an EGFR or ALK aberration have progressed on U.S. Food and Drug Administration-approved therapy for these aberrations and is currently in clinical development for other indications. The safety plan is based on results from nonclinical studies, completed and ongoing clinical studies, and published data on similar molecules. Please refer to the atezolizumab Investigator's Brochure for a complete summary of safety information.

Cobimetinib (for use with vemurafenib) is approved in the United States and European Union as well as other countries for the treatment of metastatic melanoma. 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.

Regorafenib is approved in the United States, European Union, and Japan. Please refer to the Stivarga (regorafenib) Prescribing Information for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients who participate in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification, and treatment interruption or discontinuation, are provided below. There are separate guidelines for the three different arms as the toxicities and management guidelines are distinct for the three different arms. Please refer to the specific guidelines for each arm individually.

5.1 SAFETY PLAN

The risks associated with cobimetinib, atezolizumab, and regorafenib are detailed in Section 5.1.1, Section 5.1.2, and Section 5.1.3, respectively.

5.1.1 Risks Associated with Cobimetinib

Information related to risks attributed to cobimetinib is based on safety data from Phase III Study GO28141 (cobimetinib plus vemurafenib), Phase Ib Study NO25395 (cobimetinib plus vemurafenib), and 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 hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with cobimetinib. In clinical studies with cobimetinib, events of cerebral hemorrhage, gastrointestinal tract hemorrhage, reproductive tract hemorrhage, and hematuria, have been reported.

In 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 0.8% of patients receiving placebo plus vemurafenib.

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

Instructions for dose modification for hemorrhage events are included in Appendix 3.

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 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 were managed with dose modification of both cobimetinib and vemurafenib.

To address serous retinopathy with cobimetinib treatment, all patients are required to undergo a baseline ophthalmologic examination to assess for history or evidence of

retinal pathology that is considered to be a risk factor for or indicative of neurosensory retinal detachment, central serous chorioretinopathy, neovascular retinopathy, or retinopathy of prematurity. Patients will also undergo ophthalmologic examinations at specified time points throughout the study (see Appendix 1). Details regarding baseline and subsequent ophthalmologic examinations are provided in Appendix 3.

Guidelines for management of patients who develop Grade ≥ 2 visual disorders or retinopathy are provided in Appendix 3.

Left Ventricular Dysfunction

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

Left ventricular dysfunction has been characterized in the Phase III Study GO28141. The study incorporated prospective serial left ventricular ejection fraction 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 decrease). Of the patients treated with cobimetinib plus vemurafenib, 2 patients (0.8%) had symptomatic reduction in left ventricular ejection fraction and the remaining patients were asymptomatic. Most left ventricular ejection fraction reduction events in patients on cobimetinib plus vemurafenib (62%) improved or resolved with management according to the dose-modification guidelines (see *Appendix 3*).

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 Appendix 3.

Photosensitivity (when Administered with Vemurafenib)

No evidence of phototoxicity has been observed with cobimetinib as a single agent. However, photosensitivity was observed on the GO28141 trial with a higher frequency in the cobimetinib plus vemurafenib arm versus placebo plus 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 plus vemurafenib arm versus 0% in the placebo plus vemurafenib arm. Grade ≥ 3 photosensitivity events in the cobimetinib plus 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 plus vemurafenib than placebo plus vemurafenib (1.6% vs. 0.4%, all grades). There were no reported Grade ≥ 3 events in either study arm. Serious events were reported in 2 patients (0.8%) treated with cobimetinib plus vemurafenib. *Refer to Appendix 3 for pneumonitis management guidelines.*

5.1.1.2 Potential Risks Associated with Cobimetinib

Liver Laboratory Abnormalities and Severe Hepatotoxicity

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. *Refer to Appendix 3 for hepatotoxicity management guidelines.*

Impaired Female Fertility and Developmental Toxicity

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.

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 (71.7% vs. 66.7%, respectively), although Grade ≥ 3 events (approximately 16% of patients) and types of rash reported were similar between study arms. Specific events in patients treated with cobimetinib plus vemurafenib included rash (39% all grades, 5.9% Grade ≥ 3, 1.6% serious adverse events) and rash maculo-papular (14.6% all grades, 6.3% Grade ≥ 3, 1.2% serious adverse events).

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

Gastrointestinal Toxicity

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

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

Nausea and vomiting have been reported in association with cobimetinib. Most nausea and vomiting events were considered 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. 25.2%; vomiting 24.3% vs. 12.6%). However, of patients treated with cobimetinib plus vemurafenib, few experienced Grade 3 events (nausea 0.8%, vomiting 1.2%).

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

The combination of diarrhea, nausea, and vomiting has the potential to contribute to clinically significant volume depletion/dehydration from the combination of fluid losses with decreased oral intake. In the majority of cases, diarrhea has been effectively managed with antidiarrheal agents and supportive care. Routine antiemetic prophylaxis

is not recommended. *Refer to Appendix 3 for gastrointestinal toxicity management guidelines.*

Hypersensitivity

There have been few reports of hypersensitivity and/or anaphylaxis in clinical trials with patients who have been exposed to cobimetinib monotherapy or cobimetinib when used with other agents. These have appeared to be isolated reports, and in some cases, occurred in patients with 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 Atezolizumab

Atezolizumab has been associated with risks such as IRRs and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis*, myocarditis, and hypophysitis*. In addition, systemic immune activation is a potential risk associated with atezolizumab. Refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab *and Appendix 9*.

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

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

If systemic immune activation is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations.

5.1.3 Risks Associated with Regorafenib

The overall safety profile of regorafenib is based on data from more than 1200 treated patients in clinical trials including placebo-controlled Phase III data for 500 patients with metastatic colorectal cancer and 132 patients with gastrointestinal stromal tumors. The most serious adverse drug reactions in patients who receive regorafenib are severe liver injury, hemorrhage, hypertension, dermatologic toxicity, cardiac ischemia and infarction, reversible posterior leukoencephalopathy, and gastrointestinal perforation. The most frequently observed adverse drug reactions (≥ 30%) in patients who receive regorafenib are asthenia/fatigue, hand foot skin reaction, diarrhea, decreased appetite and food intake, hypertension, dysphonia and infection.

Please refer to the Stivarga (regorafenib) Prescribing Information for complete information regarding clinical safety.

5.1.4 Management of Patients Who Experience Specific Adverse Events

5.1.4.1 Cobimetinib and Regorafenib Dose Modifications

Cobimetinib and regorafenib dose modifications are provided in Table 3.

Table 3 Recommended Cobimetinib and Regorafenib Dose Modifications

Grade (CTCAE) [a]	Recommended Cobimetinib Dose	Recommended Regorafenib Dose
Grade 1 or Grade 2 (tolerable)	No dose reduction. Maintain cobimetinib at the same dose of 60 mg QD (3 tablets)	No dose reduction. Maintain regorafenib at the same dose of 160 mg QD (4 tablets)
Grade 2 (intolerable) or Grade 3 or 4 (any)		
First appearance	Interrupt treatment until Grade ≤ 1, restart treatment at40 mg QD (2 tablets)	Interrupt treatment until Grade ≤ 1, restart treatment at 120 mg QD (3 tablets)
Second appearance	Interrupt treatment until Grade ≤ 1, restart treatment at 20 mg QD (1 tablet)	Interrupt treatment until Grade ≤ 1, restart treatment at 80 mg QD (2 tablets)

Grade (CTCAE) [a]	Recommended Cobimetinib Dose	Recommended Regorafenib Dose
Third appearance	Consider permanent discontinuation	Consider permanent discontinuation

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

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

5.1.4.2 Atezolizumab Dose Modifications

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

Guidelines for management of general adverse events are outlined in Table 4.

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Arm A and Arm B

Event	Action to Be Taken
Other toxicities: Grade 1	No action required.
Other toxicities: Grade 2	No action required
Other toxicities: Grade 3 or 4	Interrupt dosing of atezolizumab (or cobimetinib if in Arm A) depending on the attribution of the toxicity, at the discretion of the investigator. During this time, treatment may continue with the other non-attributable treatment agent (i.e., either the atezolizumab in arm A or B or cobimetinib if in Arm A). If AE resolves to Grade ≤ 1 within 1 cycle, then restart dosing of the attributable drug (atezolizumab at fixed dose and cobimetinib decreased by 1 dose level). If the AE does not resolve to Grade ≤ 1 within 1 cycle, permanently discontinue the attributable drug. If one drug is discontinued dosing of the other drug may continue at the discretion of the investigator. If the Grade 4 AE recurs (a second time), the attributable drug should be discontinued. If one drug is discontinued dosing of the other drug may continue at the discretion of the investigator. For Grade ≥ 3 toxicities associated primarily with laboratory abnormalities only, study treatment may continue without interruption and/or dose reduction at the discretion of the investigator per institutional practice.

AE = adverse event.

Additional guidelines for specific adverse events delineated by the different study arms are provided in the subsections below and the specific management guidelines are highlighted in Appendix 3 for cobimetinib plus atezolizumab. For information regarding

management of atezolizumab-associated adverse events, please refer to the *Appendix 9*.

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

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

Refer to Appendix 3 for management of cobimetinib plus atezolizumab specific toxicities, including gastrointestinal toxicity, hepatotoxicity, dermatologic toxicity, pulmonary toxicity, potential eye toxicity, left ventricular ejection fraction, rhabdomyolysis and elevated CPK, hemorrhage, and systemic immune activation.

Guidelines for management of patients who experience atezolizumab-associated adverse events, including infusion-related reactions and immune-related events (e.g., endocrine, ocular, pancreatic, and neurologic events), are provided in *Appendix 9*.

5.1.4.4 Management of Adverse Events in the Atezolizumab Monotherapy Arm (Arm B)

Guidelines for management of patients who experience specific adverse events associated with atezolizumab, including infusion-related reactions and immune-related events (e.g., pulmonary, hepatic, gastrointestinal, endocrine, ocular, pancreatic, dermatologic, and neurologic events), are provided in *Appendix 9*.

5.1.4.5 Management of Regorafenib–Associated Adverse Events (Arm C)

Toxicities associated or possibly associated with regorafenib treatment should be managed according to standard medical practice. Highlighted below are the dose modifications for selected adverse events outlined in the Stivarga (regorafenib) prescribing information. Please refer to the Stivarga (regorafenib) prescribing information for further guidance.

For symptomatic Grade 2 hypertension interrupt regorafenib and reduce the dose of regorafenib by a dose level.

Recommended dose modifications for hand-foot skin reaction and palmar-plantar erythrodysesthesia syndrome are provided in Table 5, and recommended dose modifications for liver function abnormalities are provided in Table 6.

Table 5 Recommended Dose Modification and Measure for Hand–Foot Skin Reaction/Palmar-Plantar Erythrodysesthesia Syndrome

Skin Toxicity Grade	Occurrence	Recommended Dose Modification and Measures
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief
Grade 2	First occurrence	Decrease dose by 40 mg and immediately institute supportive measures. If no improvement occurs despite dose reduction, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0–1. A dose re-escalation is permitted at the discretion of the physician.
	No improvement within 7 days or second occurrence	Interrupt therapy until toxicity resolves to Grade 0–1. When restarting treatment, decrease dose by 40 mg. A dose re-escalation is permitted at the discretion of the physician
	Third occurrence	Interrupt therapy until toxicity resolves to Grade 0–1. When restarting treatment, decrease dose by 40 mg. A dose re-escalation is permitted at the discretion of the physician.
	Fourth occurrence	Discontinue treatment with regorafenib permanently.
Grade 3	First occurrence	Institute supportive measure immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0–1. When restarting treatment, decrease dose by 40 mg. A dose re-escalation is permitted at the discretion of the physician.
	Second occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0–1. When restarting treatment, decrease dose by 40 mg.
	Third occurrence	Discontinue treatment with regorafenib permanently.

Table 6 Recommended Measures and Dose Modifications in Case of Drug–Related Liver Function Test Abnormalities

Observed elevations of ALT and/or AST	Occurrence	Recommended measures and dose modification
$\leq 5 \times$ ULN (maximum Grade 2)	Any occurrence	Continue regorafenib treatment. Monitor liver function weekly until transaminases return to $< 3 \times$ ULN (Grade 1) or baseline
$> 5 \times$ ULN $< 20 \times$ ULN (Grade 3)	First occurrence	Interrupt regorafenib treatment. Monitor transaminases weekly until return to $< 3 \times$ ULN or baseline. Restart: If the potential benefit outweighs the risk of hepatotoxicity, restart regorafenib treatment, reduce dose by 40 mg, and monitor liver function weekly for at least 4 weeks.
	Re-occurrence	Discontinue treatment with regorafenib permanently.
$> 20 \times$ ULN (Grade 4)	Any occurrence	Discontinue treatment with regorafenib permanently.
$> 3 \times$ ULN (Grade 2 or higher) with concurrent bilirubin $> 2 \times$ ULN	Any occurrence	Discontinue treatment with regorafenib permanently. Monitor liver function weekly until resolution or return to baseline. Exception: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.

ULN = upper limit of normal.

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 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 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, or thyroid disease
- Systemic lupus erythematosus
- Neurologic: Guillain-Barré syndrome, myasthenia gravis, meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response system, or infusion-reaction syndromes
- Retinal vein occlusion
- Serous retinopathy, including events of retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment, and central serous chorioretinopathy
- Rhabdomyolysis or Grade $\geq$ 3 CPK elevation
- Grade $\geq$ 3 hemorrhage or any grade cerebral hemorrhage
- Grade $\geq$ 3 rash

- Grade ≥ 3 diarrhea
- Significant liver toxicity
    - 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 alkaline phosphatase)
        - 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
- Symptomatic heart failure or Grade ≥ 3 left ventricular ejection fraction reduction

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2), 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 *serious adverse events and Adverse Events of Special Interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer*

therapy, whichever occurs first. Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

Note: Based on the most recent version of NCI CTCAE v4.0 which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htmhttp://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, considering especially 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 vs. Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.5 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.5 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 5.5 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

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

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

5.3.5.8 Deaths

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

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Colorectal Cancer

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

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

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

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

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

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

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

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

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

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

The highest dose of regorafenib studied clinically was 220 mg/day. The most frequently observed adverse drug reactions at this dose were dermatological events, dysphonia, diarrhea, mucosal inflammation, dry mouth, decreased appetite, hypertension, and fatigue. Please see the Stivarga (regorafenib) Prescribing Information for more details.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

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

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

5.4.1 Emergency Medical Contacts

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.

For all other non-emergency medical questions, please contact your clinical study monitor the following Medical Monitor:

- [redacted], M.D.: [redacted]

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

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug *or initiation of another anti-cancer drug, whichever comes first*. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the 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 post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

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

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 90 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 POST-STUDY ADVERSE EVENTS

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 90 days after the last dose of study drug *or initiation of a new anti-cancer treatment whichever comes first*), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF. In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior study drug treatment, the event should be reported through use of the Adverse Event eCRF.

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

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

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

- Cobimetinib Investigator's Brochure
- Atezolizumab Investigator's Brochure
- *Summary of Product Characteristics (SPC)* for regorafenib *(Stivarga® SPC 2017)*

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a randomized, Phase III, global, multicenter, open-label study designed to evaluate the safety and efficacy of cobimetinib plus atezolizumab and atezolizumab monotherapy as compared to treatment with regorafenib in approximately 360 patients with unresectable locally advanced or metastatic colorectal adenocarcinoma.

The efficacy analyses of OS, PFS, and ORR will be performed on all randomized patients (i.e., intent to treat [ITT]) irrespective of whether the assigned treatment was actually received. DOR will be assessed in patients who have an objective response. For all efficacy analyses, patients will be grouped according to the treatment assigned at randomization.

The safety population will include all randomized patients who received any amount of study drug. Patients who are randomized into the study but do not receive any amount of study drug will not be included in the safety population. For safety analyses, patients will be grouped according to whether any amount of cobimetinib and/or atezolizumab was received, including the case when study drug (cobimetinib and/or atezolizumab) was received in error.

Statistical details for all the analyses will be documented in the Statistical Analysis Plan.

6.1 DETERMINATION OF SAMPLE SIZE

The study will randomize approximately 360 patients, including a minimum of 180 patients with extended RAS-mutant mCRC (assuming a prevalence of at least 50%), to cobimetinib plus atezolizumab (Arm A), atezolizumab monotherapy (Arm B), and regorafenib (Arm C) with the randomization ratio of 2:1:1, respectively.

The type 1 error (α) for the analysis of the primary endpoint of OS in the comparison of cobimetinib plus atezolizumab (Arm A) against the control arm of regorafenib (Arm C) is 0.05 (2-sided). If OS in the comparison of Arm A against Arm C is statistically significant, then the OS in the comparison of Arm B against Arm C will be tested at a 2-sided α level of 0.05.

The sample size of this study is determined on the basis of the number of events required to demonstrate efficacy with regard to OS in both comparisons (Arm A vs. Arm C and Arm B vs. Arm C).

The overview of the Type I error (α) control is shown in Figure 3.

Figure 3 Overview of Hierarchical Testing Sequence for Type I Error [a] Control (2-Sided)

OS = overall survival.

[a] *OS will be tested at a 2-sided significance level $\alpha = 0.05$ only if the result of previous testing is positive (i.e., statistically significant).*

The estimate of the number of events required to demonstrate efficacy with regard to OS is based on the following assumptions:

- Two-sided significance level of 0.05
- Arm A versus Arm C: 87% power to detect an HR of 0.61, corresponding to an improvement in median OS from 6.4 months in Arm C to 10.5 months in Arm A
- Arm B versus Arm C: 80% power to detect an HR of 0.61, corresponding to an improvement in median OS from 6.4 months in Arm C to 10.5 months in Arm B
- No interim analysis for OS
- Dropout rate of 10% in 24 months
- Hierarchical testing of Arm A versus Arm C followed by Arm B versus Arm C to control the overall α level of 5%

With these assumptions, approximately 360 patients in total will be randomized into this study, with approximately 270 patients for the comparison of Arm A versus Arm C and approximately 180 patients for the comparison of Arm B versus Arm C. *The OS final analysis will be conducted when there are approximately 235 deaths in the study. This is expected to occur approximately 23 months after the first patient is randomized. At that time, it is expected that approximately 178 deaths for the comparison of Arm A versus Arm C and approximately 127 deaths for the comparison of Arm B versus Arm C will have occurred.*

This number of events corresponds to a minimum detectable difference in HR of approximately 0.73 for the Arm A versus Arm C comparison and approximately 0.71 for the Arm B versus Arm C comparison.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study drug administration, and discontinuation from the study will be summarized by treatment arm. The incidence of study drug discontinuation for reasons other than disease progression will similarly be tabulated. Protocol violations, including

major violations of inclusion/exclusion criteria, will be summarized in a similar manner by treatment arm.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic characteristics, such as age, sex, race/ethnicity, and baseline disease characteristics will be summarized by treatment arms for the ITT populations. Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data. Study treatment administration will be summarized by treatment arm for all treated patients.

6.4 EFFICACY ANALYSES

Unless otherwise noted, all efficacy analyses will include all randomized patients (ITT analysis), and patients will be grouped according to the treatment assigned at randomization.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is OS, which is defined as the time (in months) between the date of randomization and the date of death due to any cause. Patients who have not died at the time of analysis will be censored at the date when they were last known to be alive.

Comparisons with respect to OS between two treatment arms (i.e., Arm A vs. Arm C, Arm B vs. Arm C) will be tested based on a stratified log-rank test. The stratification factors will be extended RAS mutation status of the tumor and time since diagnosis of first metastasis (<18 months and ≥ 18 months).

Each comparison will be tested at a 2-sided significance level of 0.05 within the ITT population:

- Test to reject the null hypothesis of no difference in OS between either experimental arm (i.e., Arm A or Arm B) and the control arm (Arm C) in the ITT population. If the 2−sided p-value corresponding to the stratified log-rank test is less than 0.05, the null hypothesis will be rejected.

The HR for OS will be estimated using a stratified Cox model. Two-sided 95% CIs for the HR will be provided. The stratified analyses will incorporate extended RAS mutation status and time since diagnosis of first metastasis as stratification factors. Results from an unstratified log-rank test and the unstratified HR will also be presented. Kaplan-Meier methodology will be used to estimate median OS for each treatment arm, and the Kaplan-Meier curves will be provided. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS for each treatment arm (Brookmeyer and Crowley 1982).

The comparison between the two experimental arms (Arm A vs. Arm B) will be conducted for descriptive purposes.

6.4.2 Secondary Efficacy Endpoints

The secondary endpoints include investigator-assessed PFS, ORR, and DOR per RECIST v1.1. The analyses of PFS, ORR, and DOR will take place at the time of the OS analysis.

PFS is defined as the time between date of randomization and the date of first documented disease progression or death, whichever occurs first. Disease progression will be determined based on investigator assessment using RECIST v1.1. Data from patients who have not experienced disease progression or death will be censored at the last tumor assessment date and known to be free of disease progression. Data from patients with no post-baseline tumor assessment will be censored at the randomization date plus 1 day. Comparisons with respect to PFS between the two treatment arms will be tested based on a 2-sided stratified log-rank test. The HR for PFS will be estimated using a stratified Cox model. Two-sided 95% CIs for the HR will be provided. Stratified analyses will incorporate the same stratification factors as for the analysis of OS.

Results from an unstratified log-rank test and the unstratified HR will also be presented. Kaplan-Meier methodology will be used to estimate median PFS for each treatment arm, and the Kaplan-Meier curves will be provided.

ORR is defined as the proportion of patients who had a confirmed objective response of CR or PR assessed by the investigator according to the RECIST v1.1. An estimate of ORR and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm.

Treatment difference in ORR will be tested using the stratified Cochrane-Mantel-Haenszel test, stratified by the same factors used in the OS analysis, and a 95% Hauck-Anderson CI will be calculated for the difference in ORR between treatment arms.

DOR is defined as the period measured from the date of the first occurrence of a CR or PR (whichever status is recorded first) until the first date that progressive disease or death is documented. Disease progression will be determined on the basis of investigator assessment with use of RECIST v1.1. DOR will be assessed in patients who have an objective response during the study as determined by the investigator with use of RECIST v1.1. Patients who have not progressed and who have not died by the date of data cutoff for analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR plus 1 day. Median DOR will be estimated using the Kaplan-Meier method, and the 95% CI will be calculated using the method of Brookmeyer and Crowley (1982). DOR analysis is

performed on the basis of a non-randomized subset of patients (i.e., patients who achieve an objective response); therefore, formal hypothesis testing will not be performed for this endpoint.

6.5 PATIENT-REPORTED OUTCOMES ANALYSES

For PROs, the EORTC QLQ-C30 questionnaire and two additional items will be scored according to the EORTC Scoring Manual.

The primary analysis population for evaluation of PRO assessments will include patients in the ITT population with a baseline PRO assessment and at least one post-baseline PRO assessment.

Data from the physical function scale and the global health status/quality of life will be analyzed as a time to deterioration, which will be compared as secondary efficacy endpoints among treatment groups with use of the log rank test (2-sided). Deterioration will be defined as 1) a decrease of 10 points on a transformed 0 to 100 score from baseline on the physical function score or the global status/quality of life scores, or 2) death, or 3) progression. The HR will be estimated using a stratified Cox proportional hazards model and its 95% CI will be provided.

For each assessment timepoint and for each treatment arm, the mean (and 95% CI) and median (and inter-quartile ranges) of the absolute scores for the EORTC QLQ-C30 and additional items and their changes from baseline (Cycle 1 Day 1), will be calculated.

Exploratory descriptive analyses will be conducted using post-treatment data.

6.6 SAFETY ANALYSES

Safety analyses will be performed on the safety population and will include all randomized patients who received at least one dose of study drug. Summaries will be presented for the safety-evaluable population by treatment arm. For safety analyses, patients will be grouped according to whether any amount of atezolizumab or cobimetinib was received, including when atezolizumab or cobimetinib was received in error. For example, if a patient assigned to Arm C received either cobimetinib or atezolizumab in error, this patient will be grouped to Arm A or Arm B, respectively. If a patient assigned to Arm A received atezolizumab but no cobimetinib at all, then this patient will be grouped to Arm B.

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

Verbatim description of adverse events will be mapped to MedDRA thesaurus terms and graded according to NCI CTCAE v4.0. All adverse events that occur during or after the first study drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grade 3, 4, and 5), adverse

events of special interest, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. The proportion of patients who experience at least one adverse event will be reported by toxicity term and treatment arm.

Deaths reported during the study treatment period and those reported during the follow-up period after treatment discontinuation will be summarized by treatment arm.

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

6.7 PHARMACOKINETIC ANALYSES

PK samples will be collected in this study as outlined in Appendix 2. Cobimetinib and atezolizumab maximum and minimum concentration data (C_{min} and C_{max}, respectively) will be tabulated and summarized (mean, standard deviation, median, range, coefficient of variation [CV%], geometric mean and geometric mean coefficient of variation [CVb%]), as appropriate.

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

6.8 IMMUNOGENICITY ANALYSES

Patients are considered to have treatment-induced ATA responses if they are ATA negative at baseline and then develop an ATA response following study drug administration. Patients are considered to have treatment-enhanced ATA responses if they are ATA 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. Patients are considered to be negative for ATAs if they are ATA negative at all timepoints. Patients are considered to be treatment unaffected if they are ATA 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.

The immunogenicity analyses will include patients with at least one predose and one postdose ATA assessment, with patients grouped according to treatment received (safety population).

The number and proportion of ATA-positive patients and ATA-negative patients during both the treatment and follow-up periods will be summarized by treatment group. Patients are considered to be ATA positive if they have treatment-induced ATA responses or treatment-enhanced ATA responses. Patients are considered to be ATA negative if they are ATA negative or unaffected by treatment.

The relationship between ATA status and safety, efficacy, and pharmacokinetics will be analyzed and reported descriptively via subgroup analyses.

ATA sampling timepoints are provided in Appendix 2.

6.9 EXPLORATORY BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with study drug response, including efficacy and/or adverse events. The blood and tumor biomarkers include but are not limited to NGS, PD-L1, and CD8, as defined by IHC, qRT-PCR, or other methods. Additional pharmacodynamic analyses will be conducted as appropriate.

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 and other non–EDC system-captured data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

An electronic device will be used to capture PRO data. The data will be transmitted to a centralized database maintained by the electronic device vendor.

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

7.4 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, 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 7.6.

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

7.5 USE OF COMPUTERIZED SYSTEMS

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

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

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

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

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

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

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

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). 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.

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC

policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This study is sponsored by F. Hoffmann-La Roche Ltd. Approximately 75 study centers will participate in this study globally and enroll a total of approximately 360 patients. The Sponsor will provide clinical operations oversight, data management support, and medical monitoring.

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

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

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

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Assessments

Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (28-Day Cycle)

	Screening[a]	Cycle 1		Cycle 2		Cycle 3 +		Treatment Discontinuation[b]	ATA Visit	Survival FU[c]
Day	-35 to 1	1	15	1	15	1	15	< 30 d after last dose	120 d after last dose	q3m
Informed consent[d]	x									
Demographics	x									
Medical and CRC history	x									
Vital signs[e,f]	x	x	x	x	x	x	x			
ECOG PS	x	x		x		x				
Weight	x	x		x		x				
Height	x									
Complete physical examination	x									
Limited physical examination		x[g]		x		x				
Hematology[h]	x	x		x		x				
Coagulation (INR and aPTT)	x									
PK sample for cobimetinib	See Appendix 2									
PK and ATA sample for atezolizumab	See Appendix 2								x	
Serum samples for auto antibody tests		x								
Optional WGS		x								
Chemistry[i]	x	x		x		x				
CEA		x		x		x		x		
ECHO/MUGA	x			x		x[j]				

Appendix 1
Schedule of Assessments (cont.)

Tumor assessments[k]	x	Scans will be done every 8 weeks								
Serology[l]	x									

Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (cont.)

	Screening[a]	Cycle 1		Cycle 2		Cycle 3 +		Treatment Discontinuation[b]	ATA Visit	Survival FU[c]
Day	-35 to 1	1	15	1	15	1	15	< 30 d after last dose	120 d after last dose	q3m
Thyroid function	x	x		x		x[m]				
Ophthalmologic exam[n]	x			x		x[n]		x		
Pregnancy test[o]	x	x		x		x				
Adverse events	x[p]	x	x	x	x	x	x	x[q]		x
Tumor biopsy[r]	x		x					x		
Concomitant medications	x	x		x		x		x		
EORTC QLQ-C30 EQ-5D-5L[s]		x		x		x		x		x[s]
Survival and anti-cancer therapy follow-up										x
Biomarker blood samples		x		x		x		x		
Atezolizumab administration[t]		x	x	x	x	x	x			
Cobimetinib administration[u]		x		x		x				

ATA = anti-therapeutic antibody; C3 = Cycle 3; C4 = Cycle 4; CEA = carcinoembryonic antigen; CRC = colorectal cancer; d = day; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life-C30 questionnaire; EQ-5D-5L = EuroQoL 5 Dimensions; FU = follow-up; MUGA = multigated acquisition scan; PK = pharmacokinetic; q3m = every 3 months; WGS = whole genome sequencing.

Appendix 1
Schedule of Assessments (cont.)

[a] Results of standard of care tests or examinations performed prior to obtaining informed consent and within 35 days prior to Day 1 may be used; such tests do not need to be repeated for screening

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit.

[c] 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.

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

[e] 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

[f] Vital signs will be measured and recorded at the following timepoints: within 60 minutes prior to infusion and during and after infusion if clinically indicated.

[g] If physical examinations are assessed within 7 days of the Cycle 1 Day 1 visit, they do not have to be repeated at Day 1.

[h] Hematology (CBC, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes], and platelet count) ± 3 days.

[i] Serum chemistry (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, calcium, phosphorus, total bilirubin, ALT, AST, ALP, CPK, lipase, amylase [albumin and LDH at screening only]) ± 3 days.

[j] All patients will undergo evaluation of left ventricular dysfunction, either by ECHO or MUGA, screening. Evaluation of LVEF by ECHO or MUGA must be performed at the following timepoints <u>only for patients taking cobimetinib</u>:

- Cycle 2, Day 1 ± 1 week
- Day 1 of every three treatment cycles thereafter starting at cycle 5 ± 2 weeks
- The treatment discontinuation visit evaluation of LVEF does not need to be performed at the treatment discontinuation visit if an evaluation has been performed within the last 12 weeks and there are no clinically significant findings and/or changes from baseline.
- All patients restarting treatment with a dose reduction of Cotellic because of a decrease in LVEF should have LVEF measurements taken after approximately 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then resume monitoring LVEF every three treatment cycles.

Appendix 1
Schedule of Assessments (cont.)

[k] Tumor assessments will continue until disease progression per RECIST v1.1, loss of clinical benefit (patients who continue treatment after disease progression according to RECIST v1.1), consent withdrawal, study termination by the Sponsor, or death, whichever occurs first.

Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first.

[l] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical study.

- HBV serology will include HBsAg, antibodies against HBsAg, total HBcAg antibody (anti-HBcAb). HBV DNA should be obtained prior to randomization if patient has a negative serology for HBsAg and a positive serology for anti-HBcAb.
- HCV serology will include HCV antibody (anti-HCV). HCV RNA should be obtained prior to randomization if patient tests positive for anti-HCV

[m] Thyroid function testing (TSH, free T3, free T4) collected at Day 1 of every cycle thereafter for patients on atezolizumab only ± 3 days.

[n] All patients will undergo ophthalmologic examination (see Section 4.5.9 for exam requirements) at screening. Ophthalmologic examination must be performed at the following timepoints only for patients taking cobimetinib:

- Cycle 2 Day 1 ± 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. The treatment discontinuation visit evaluation does not need to be performed if an evaluation has been performed within the last 12 weeks and there are no clinically significant findings and/or changes from baseline.

[o] All women of childbearing potential will have a serum pregnancy test within 14 days before Cycle 1 Day 1. Urine pregnancy tests will be performed at specific subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Refer to Section 5.4.3 for details.

[p] Only serious adverse events caused by protocol-mandated intervention should be reported.

[q] All serious adverse events and Adverse Events of Special Interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After this period the investigator should report any serious adverse events or adverse events of special interest that are believed to be related to prior study drug.

[r] Archival or fresh baseline tumor tissue collected during screening; Optional on treatment biopsy at Cycle 1 Day 15±5 days; Mandatory biopsy at progression if clinically feasible.

Appendix 1
Schedule of Assessments (cont.)

[s] PRO instruments EORTC QLQ-C30 and EQ-5D-5L will be completed in this order using an electronic device on Day 1 of each cycle during a visit and prior to any assessments. Data will be collected at end of study and at survival follow-up at 3 and 6 months only. In the event a study visit is conducted by telephone, the PRO data for that visit will be collected via telephone interview and recorded by the investigative staff on the ePRO tablet. To maintain validity and minimize patient burden, the PRO instruments administered via telephone interview will consist of a reduced version of the EORTC QLQ items (Items 1–7, 10, 12, 13, 16, 17, 18, 29, and 30 from the C30 and the two additional items from the item bank) and the telephone interview version of the EQ-5D-5L.

[t] The initial dose will be delivered over 60 (± 10) minutes. If the first infusion is well tolerated all subsequent infusions will be delivered over 30 (± 10) minutes until loss of clinical benefit. Dose can be given ± 7 days from scheduled Day 1 of each cycle.

[u] Cobimetinib 60 mg/day PO will be given in a 21/7 dosing schedule. Dose can be given ± 7 days from scheduled Day 1 of each cycle, but the scheduled 7-day break must be ≥ 5 days.

Appendix 1
Schedule of Assessments (cont.)

Arm B: Atezolizumab Monotherapy Schedule of Assessments (21-Day Cycle)

	Screening [a]	Cycle 1		Cycle 2	Cycle 3 +	Treatment Disc[b]	ATA Visit	Survival FU[c]
Day	-35 to 1	1	15	1	1	< 30 d after last dose	120 d after last dose	q3m
Informed consent[d]	x							
Demographics	x							
Medical and CRC history	x							
Vital signs[e,f]	x	x		x	x			
ECOG PS	x	x		x	x			
Weight	x	x		x	x			
Height	x							
Complete physical examination	x							
Limited physical examination[g]		x		x	x			
Hematology[h]	x	x		x	x			
Coagulation (INR and aPTT)	x							
Serum sample for autoantibody tests		x				x		
Chemistry[i]	x	x		x	x			
CEA		x		x	x	x		
WGS (optional)		x						
PK and ATA sample	See Appendix 2						x	
ECHO/MUGA	x							
Tumor assessments[j]	x	Scan assessments every 8 weeks						
Serology[k]	x							

Appendix 1
Schedule of Assessments (cont.)

Thyroid function[l]	x	x		x	x			
Ophthalmologic exam	x							
Pregnancy test[m]	x	x		x	x			

Arm B: Atezolizumab Monotherapy Schedule of Assessments (cont.)

	Screening[a]	Cycle1		Cycle 2	Cycle 3 +	Treatment Disc[b]	ATA Visit	Survival FU[c]
Day	-35 to 1	1	15	1	1	< 30 d after last dose	120 d after last dose	q3m
Adverse events	x[n]	x	x	x	x	x		x[o]
Tumor biopsy[p]	x		x			x		
Concomitant medications	x	x	x	x	x	x		
EORTC QLQ-C30 and EQ-5D-5L[q]		x		x	x	x		x[q]
Survival and anti-cancer therapy follow-up								x[r]
Biomarker blood samples		x		x	x	x		
Atezolizumab administration[s]		x		x	x			

ATA = anti-therapeutic antibody; C3 = Cycle 3; C4 = Cycle 4; CEA = carcinoembryonic antigen; CRC = colorectal cancer; d = day; disc = discontinuation; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life-C30 questionnaire; EQ-5D-5L = EuroQoL 5 Dimensions; FU = follow-up; MUGA = multigated acquisition scan; PK = pharmacokinetic; q3m = every 3 months; WGS = whole genome sequencing.

[a] Results of standard of care tests or examinations performed prior to obtaining informed consent and within 35 days prior to Day 1 may be used; such tests do not need to be repeated for screening

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit

[c] 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. .

Appendix 1
Schedule of Assessments (cont.)

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

[e] 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

[f] Vital signs will be measured and recorded at the following timepoints: within 60 minutes prior to infusion and during and after infusion if clinically indicated.

[g] If physical examinations are assessed within 7 days of the Cycle 1 Day 1 visit, they do not have to be repeated at Day 1.

[h] Hematology (CBC, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes], and platelet count) ± 3 days

[i] Serum chemistry (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, calcium, phosphorus, total bilirubin, ALT, AST, ALP, LDH, CPK, lipase, amylase, [albumin and LDH at screening only]) ± 3 days.

[j] Tumor assessments will continue until disease progression per RECIST v1.1, loss of clinical benefit (patients who continue treatment after disease progression according to RECIST v1.1), consent withdrawal, study termination by the Sponsor, or death, whichever occurs first.

Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first.

[k] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical study.

HBV serology will include HBsAg, antibodies against HBsAg, total HBcAg antibody (anti-HBcAb). HBV DNA should be obtained prior to randomization if patient has a negative serology for HBsAg and a positive serology for anti-HBcAb.

HCV serology will include HCV antibody (anti-HCV). HCV RNA should be obtained prior to randomization if patient tests positive for anti-HCV

[l] Thyroid function testing (TSH, free T3, free T4) collected at Day 1 of every cycle thereafter for patients on atezolizumab only ± 3 days.

[m] All women of childbearing potential will have a serum pregnancy test within 14 days before Cycle 1 Day 1. Urine pregnancy tests will be performed at specific subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Refer to Section 5.4.3 for details.

[n] Only serious adverse events caused by protocol-mandated intervention should be reported

[o] All serious adverse events and Adverse Events of Special Interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After this period the investigator should report any serious adverse events or adverse events of special interest that are believed to be related to prior study drug.

Appendix 1
Schedule of Assessments (cont.)

[p] Archival or fresh baseline tumor tissue collected during screening; Optional on treatment biopsy at Cycle 1 Day 15 ± 5 days; Mandatory biopsy at progression if clinically feasible.

[q] PRO instruments EORTC QLQ-C30 and EQ-5D-5L will be completed in this order using an electronic device on Day 1 of each cycle during a visit and prior to any assessments. Data will be collected at end of study treatment and at survival follow-up at 3 and 6 months only. In the event a study visit is conducted by telephone, the PRO data for that visit will be collected via telephone interview and recorded by the investigative staff on the ePRO tablet. To maintain validity and minimize patient burden, the PRO instruments administered via telephone interview will consist of a reduced version of the EORTC QLQ (Items 1–7, 10, 12, 13, 16, 17, 18, 29, and 30 from the C30 and the two additional items from the item bank) and the telephone interview version of the EQ-5D-5L.

[r] Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first.

[s] The initial dose will be delivered over 60 (± 10) minutes. If the first infusion is well tolerated all subsequent infusions will be delivered over 30 (± 10) minutes until loss of clinical benefit. Dose can be given ± 7 days from Day 1.

Appendix 1
Schedule of Assessments (cont.)

Arm C: Regorafenib Schedule of Assessments

	Screening[a]	Cycle 1				Cycle 2			Cycle 3 +	Treatment Discontinuation[b]	Survival FU[c]
Day	-35 to 1	1	8	15	22	1	8	15	1	< 30 d after last dose	q3m
Informed consent[d]	x										
Demographics	x										
Medical and CRC history	x										
Vital signs[e,f]	x	x	x	x	x	x	x	x	x		
ECOG PS	x	x				x			x		
Weight	x	x				x			x		
Height	x										
Complete physical examination	x										
Limited physical examination		x[g]				x			x		
Hematology[h]	x	x				x			x		
Coagulation (INR and aPTT)	x										
Chemistry[i]	x	x		x		x		x	x		
CEA		x				x			x	x	
WGS (Optional)		x									
ECHO/MUGA	x										
Tumor assessments	x	Scan assessments every 8 weeks[j]									
Serology[k]	x										
Thyroid function	x										

Appendix 1
Schedule of Assessments (cont.)

Ophthalmologic exam	x										
Pregnancy test[l]	x	x				x			x		
Adverse events	x[m]	x	x	x	x	x	x	x	x	x[n]	x

Arm C: Regorafenib Schedule of Assessments (cont.)

	Screening[a]	Cycle 1				Cycle 2			Cycle 3 +	Treatment Discontinuation[b]	Survival FU[c]
Day	-35 to 1	1	8	15	22	1	8	15	1	< 30 d after last dose	q3m
Tumor biopsy[o]	x			x						x	
Concomitant medications	x	x				x			x	x	
EORTC QLQ-C30, EQ-5D-5L[p]		x				x			x	x	x
Survival and anti-cancer therapy follow-up											x[q]
Biomarker blood samples		x				x			x	x	
Regorafenib administration[r]		x				x			x		

ATA = anti-therapeutic antibody; C3 = Cycle 3; C4 = Cycle 4; CEA = carcinoembryonic antigen; CRC = colorectal cancer; d = day; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life-C30 questionnaire; EQ-5D-5L = EuroQoL 5 Dimensions; FU = follow-up; MUGA = multigated acquisition scan; PK = pharmacokinetic; q3m = every 3 months; WGS = whole genome sequencing.

[a] Results of standard of care tests or examinations performed prior to obtaining informed consent and within 35 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit

[c] 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. .

Appendix 1
Schedule of Assessments (cont.)

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

[e] 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

[f] Monitor vital signs weekly for the first 6 weeks and then with every cycle, especially systolic and diastolic blood pressure.

[g] If physical examinations are assessed within 7 days of the Cycle 1 Day 1 visit, they do not have to be repeated at Day 1.

[h] Hematology (CBC, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)

[i] Serum chemistry (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, calcium, phosphorus, total bilirubin, ALT, AST, ALP, LDH, CPK, lipase, amylase, [albumin and LDH at screening only]). LFTs are tested every 2 weeks for the first 2 months of treatment and then at every cycle thereafter. All other labs are tested at the beginning of each cycle.

[j] Tumor assessments will continue until disease progression per RECIST v1.1, loss of clinical benefit (patients who continue treatment after disease progression according to RECIST v1.1), consent withdrawal, study termination by the Sponsor, or death, whichever occurs first.

Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first.

[k] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical study.

HBV serology will include HBsAg, antibodies against HBsAg, total HBcAg antibody (anti-HBcAb). HBV DNA should be obtained prior to randomization if patient has a negative serology for HBsAg and a positive serology for anti-HBcAb.

HCV serology will include HCV antibody (anti-HCV). HCV RNA should be obtained prior to randomization if patient tests positive for anti-HCV

[l] All women of childbearing potential will have a serum pregnancy test within 14 days before Cycle 1 Day 1. Urine pregnancy tests will be performed at specific subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Refer to Section 5.4.3 for details.

[m] Only serious adverse events caused by protocol-mandated intervention should be reported

[n] All serious adverse events and Adverse Events of Special Interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After this period the investigator should report any serious adverse events or adverse events of special interest that are believed to be related to prior study drug.

Appendix 1
Schedule of Assessments (cont.)

[o] Archival or fresh baseline tumor tissue collected during screening; Optional on treatment biopsy at Cycle 1 Day 15 ± 5 days; Mandatory biopsy at progression.

[p] PRO instruments EORTC QLQ-C30 and EQ-5D-5L will be completed in this order using an electronic device on Day 1 of each cycle during a visit and prior to any assessments. Data will be collected at end of study treatment and at survival follow-up at 3 and 6 months only. In the event a study visit is conducted by telephone, the PRO data for that visit will be collected via telephone interview and recorded by the investigative staff on the ePRO tablet. To maintain validity and minimize patient burden, the PRO instruments administered via telephone interview will consist of a subset of the EORTC QLQ items (Items 1-7, 10, 12, 13, 16, 17, 18, 29 and 30 from the C30 and the two additional items from the item bank) and the telephone interview version of the EQ-5D-5L.

[q] Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first.

[r] Regorafenib 160 mg/day PO will be given in a 21/7 dosing schedule. Dose can be given ± 7 days from Day 1 but the scheduled 7-day break must be ≥ 5 days.

Appendix 2
Schedule of Pharmacokinetic and Immunogenicity Samples

Visit	Timepoint	Sample Type	Drug
[a]Cycle 1 Day 15 [a]Cycle 4 Day 15	Predose and 3 to 6 hours after dose	Plasma PK	Cobimetinib
Day 1 of Cycles 1–4	Predose (prior to infusion)	Serum PK	Atezolizumab
		Serum ATA	Atezolizumab
Day 1 of Cycles 1 and 4	30 minutes (± 10) after infusion	Serum PK	Atezolizumab
Day 1 of Cycle 8 and every 8 cycles after Cycle 8	Predose (prior to infusion)	Serum PK	Atezolizumab
		Serum ATA	Atezolizumab
Treatment discontinuation [b]	At visit	Serum PK	Atezolizumab
		Serum ATA	Atezolizumab
120 days ± 30 days after treatment discontinuation [b]	At visit	Serum PK	Atezolizumab
		Serum ATA	Atezolizumab

ATA = anti-therapeutic antibody; PK = pharmacokinetic.

[a] Arm A (cobimetinib with atezolizumab) only.

[b] These samples will be collected provided that the blood draws are clinically feasible and do not cause the patient undue hardship (e.g., the patient is in hospice care and not able to come in for a visit).

Appendix 3
Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A)

Note: For information regarding management of atezolizumab-associated adverse events, including infusion-related reactions and immune-related events (e.g., endocrine, ocular, pancreatic, and neurologic events), please refer *Appendix 9*.

GASTROINTESTINAL TOXICITY

Diarrhea and colitis have been associated with the administration of cobimetinib plus atezolizumab.

Diarrhea can frequently be managed with anti-diarrheal agents but can also progress to clinically significant dehydration and/or electrolyte imbalances with effects on other organs, possibly resulting in renal, hepatic, and/or cardiac failure. Patients should be instructed to promptly contact the investigators if they develop diarrhea. Investigators should treat diarrhea and intervene promptly for patients who appear to be at increased risk of developing significant dehydration, electrolyte imbalances, and/or multi-organ failure. Patients should receive maximum supportive care per institutional guidelines.

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

Appendix 3 Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A) (cont.)

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

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

Appendix 3 Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A) (cont.)

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

Event	Management
Diarrhea, Grade 2 (intolerable) or Grade 3	Withhold atezolizumab and cobimetinib. Initiate supportive care and monitor patient closely. Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. If event resolves to Grade 1 or better within 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.
Diarrhea, Grade 4	Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor. [c] Initiate supportive care and monitor patient closely. Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. Rule out bowel perforation. Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.
Colitis, Grade 1	Continue atezolizumab and cobimetinib. Initiate supportive care and monitor patient closely. Discontinue medications that may exacerbate colitis (e.g., NSAIDS). Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy if symptoms persist for > 7 days.
Colitis, Grade 2	Withhold atezolizumab and cobimetinib. Initiate supportive care and monitor patient closely. Discontinue medications that may exacerbate colitis (e.g., NSAIDS). Refer patient to 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.

Appendix 3 Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A) (cont.)

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

Colitis, Grade 3	Withhold atezolizumab and cobimetinib. Initiate supportive care and monitor patient closely. Discontinue medications that may exacerbate colitis (e.g., NSAIDS). Refer patient to 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.

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

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

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

Appendix 3 Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A) (cont.)

HEPATOTOXICITY

Hepatoxicity has been associated with the administration of atezolizumab and 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 2.

Appendix 3 Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A) (cont.)

Table 2 Guidelines for Managing Atezolizumab and Cobimetinib–Associated Hepatotoxicity

LFT Abnormalities	Management
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin < 2 × ULN	Continue atezolizumab and cobimetinib. Continue with the standard monitoring plan (i.e., LFTs q4w before dosing).
AST/ALT > 3 × baseline values to < 5 × ULN with total bilirubin < 2 × ULN	Continue all study treatment. Monitor LFTs at least weekly. Consider referral to a hepatologist and liver biopsy. For suspected immune related events of > 5 days duration o Consider withholding atezolizumab [c] o Consider administering 1-2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper o Restart atezolizumab if event resolves to Grade 1 or better within 12 weeks [a, b] o Permanently discontinue atezolizumab and cobimetinib if event does not resolve to Grade 1 or better within 12 weeks [a, b, c]
AST/ALT > 5 × baseline values to < 10 × ULN with total bilirubin < 2 × ULN	Continue all study treatment. Monitor LFTs at least weekly. Consider referral to a hepatologist and liver biopsy. For suspected immune related events o Withhold atezolizumab o Consider administering 1-2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper o 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. o Permanently discontinue atezolizumab and cobimetinib if event does not resolve to Grade 1 or better within 12 weeks [a, b, c]

Appendix 3 Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A) (cont.)

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

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

IV = intravenous; LFT = liver function test; q4w = every 4 weeks; TNF = tumor necrosis factor; ULN = upper limit of normal.

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

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

Appendix 3 Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A) (cont.)

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.

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 3.

Appendix 3 Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A) (cont.)

Table 3 Guidelines for Managing Atezolizumab and Cobimetinib Rash

Dermatologic Toxicity/Rash (e.g., maculo-papular or purpura)	Management
Dermatologic event, Grade 1/2	Continue atezolizumab and cobimetinib. Initiate supportive care (e.g., antihistamines, topical corticosteroids). For Grade 2 rash, consider referral to dermatologist. Acneiform rash: Consider topical corticosteroids (hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) BID for at least 4 weeks.
Dermatologic event, Grade 3	Withhold atezolizumab and cobimetinib. Refer patient to dermatologist. A biopsy should be performed if appropriate, and, if possible, photographs of the rash should be obtained and submitted to the Sponsor. Consider initiating treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. If event resolves to Grade 2 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. [a,b] Permanently discontinue atezolizumab and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks.[a, b, c] If event resolves to Grade 2 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. Acneiform rash: Consider continuation of topical corticosteroids 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline or antibiotics covering skin flora) when restarting cobimetinib.

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

Dermatologic Toxicity/Rash (e.g., maculo-papular or purpura)	Management
Dermatologic event, Grade 4	Permanently discontinue all study treatment and contact Medical Monitor.

BID = twice daily; BSA = body surface area; PRN = as needed.

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

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

PULMONARY TOXICITY

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.

Pulmonary toxicity should be managed per the guidelines in Table 4.

Appendix 3 Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A) (cont.)

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

Pulmonary Toxicity	Management
General Guidance	Mild-to-moderate events of pneumonitis have been reported with atezolizumab and cobimetinib. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. For events concerning for pneumonitis, Consider comprehensive infectious evaluation including viral etiologies.
Pneumonitis, Grade 1 (asymptomatic)	Continue atezolizumab and cobimetinib. Re-evaluate on serial imaging. Consider patient referral to pulmonary specialist. For recurrent pneumonitis, treat as Grade 3 or 4 event.
Pneumonitis, Grade 2	Withhold atezolizumab and cobimetinib. Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. If bronchoscopy is consistent with immune-mediated etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. Resume atezolizumab and cobimetinib if event resolves to Grade 1 or better within 12 weeks. [a, b] Permanently discontinue atezolizumab and 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.

Appendix 3 Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A) (cont.)

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

Pulmonary Toxicity	Management
Pneumonitis, Grade 3/4	Permanently discontinue atezolizumab and cobimetinib.[c] Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. If bronchoscopy is consistent with immune-related etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. If pulmonary event does not improve within 48 hr or worsens, 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.

IV =intravenous; GGO =ground glass opacity.

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

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

POTENTIAL EYE TOXICITY

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 disease that is unresponsive to local immunosuppressive therapy.

Atezolizumab–associated ocular toxicity should be managed according to the guidelines in Table 5.

Serous retinopathy is associated with cobimetinib. In clinical trials, most events were Grade 1 (asymptomatic) or 2 (symptomatic). Most events in clinical trials resolved or improved to asymptomatic grade 1 following dose interruption or reduction. If serous retinopathy is diagnosed, cobimetinib should be withheld until visual symptoms improve to Grade ⩽1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation.

Retinal vein occlusion (RVO) has been reported in patients treated with MEK inhibitors other than cobimetinib.

Cobimetinib–associated ocular toxicity should be managed according to the guidelines in Table 6.

Table 5 Guidelines for Managing Atezolizumab–Associated Ocular Toxicity (Immune–Mediated Ocular Disease)

Description	Management
Potential immune-related ocular toxicity (e.g., uveitis, iritis, episcleritis, or retinal events)	Follow guidelines provided in the *Appendix 9*. Continue cobimetinib as clinically indicated.

Appendix 3 Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A) (cont.)

Table 6 Guidelines for Managing Cobimetinib-Associated Serous Retinopathy and Retinal Vein Occlusion

Description	Management
Serous retinopathy Severity grade assessment based on NCI CTCAE v4 "Eye Disorders – Other" scale [a-d]	Serous retinopathy, Grade 1 [a] or 2 [b] (tolerable): • Continue cobimetinib and atezolizumab without dose change. • Continue ophthalmology follow-up as clinically indicated. Serous retinopathy, Grade 2 [b] (intolerable) or 3/4 [c/d]: • Interrupt cobimetinib until Grade ≤ 1. • Continue atezolizumab as clinically indicated. • Consult ophthalmology and undergo complete ophthalmologic examination, which includes visual acuity testing, intra-ocular pressure measurements, slit lamp ophthalmoscopy, indirect ophthalmoscopy, visual field, and OCT. Consider a fluorescein angiogram and/or indocyanine green angiogram, if clinically indicated. • Cobimetinib should be dose reduced by 1 dose level when restarting. • Consider permanent discontinuation of cobimetinib if serous retinopathy recurs despite 2 dose level reductions
Retinal vein occlusion Any grade	If RVO (any grade) is diagnosed, cobimetinib dosing should be permanently discontinued and RVO treated per institutional guidelines. Continue atezolizumab.

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

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

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

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

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

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

Decreased left ventricular ejection fraction (LVEF) has been seen with cobimetinib (see Section 5.1.1.1). Refer to Table 7 for guidelines for management of LVEF. Permanent discontinuation of cobimetinib treatment should be considered if cardiac symptoms are attributed to cobimetinib and do not improve after temporary interruption.

Appendix 3 Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A) (cont.)

Table 7 Recommended Dose Modifications for Cobimetinib in Patients with Left Ventricular Ejection Fraction Decrease from Baseline

Patient	LVEF value	Recommended action with cobimetinib and atezolizumab	LVEF value following treatment break	Recommended cobimetinib daily dose
Asymptomatic	≥50% (or 40%–49% and <10% absolute decrease from BL)	Continue at current dose	N/A	N/A
	<40% (or 40%–49% and ≥10% absolute decrease from BL)	Interrupt treatment for 2 weeks Continue atezolizumab as clinically indicated	<10% absolute decrease from BL	First occurrence: 40 mg
				Second occurrence: 20 mg
				Third occurrence: permanent discontinuation
			<40% (or ≥10% absolute decrease from BL)	Permanent discontinuation
Symptomatic	N/A	Interrupt 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.

Appendix 3 Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A) (cont.)

GUIDELINES FOR MANAGEMENT OF PATIENTS WHO EXPERIENCE ELEVATED CPK AND RHABDOMYOLYSIS

Elevated CPK has been reported with cobimetinib (see Section 5.1.1.2). See Table 8 for guidelines for management of elevated CPK and rhabdomyolysis.

Appendix 3 Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A) (cont.)

Table 8 Recommended Dose Modifications for Cobimetinib and Atezolizumab in Patients with CPK Elevations and Rhabdomyolysis

Description	Management
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.
Asymptomatic CPK elevations Grade 1–3	Cobimetinib dosing and atezolizumab do not need to be modified or interrupted to manage asymptomatic Grade ≤ 3 CPK elevations
Asymptomatic CPK elevations Grade 4	Interrupt cobimetinib and atezolizumab treatment. If improved to Grade ≤ 3 within 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. If CPK elevations do not improve to Grade ≤3 within 4 weeks following dose interruption, permanently discontinue cobimetinib treatment. Resumption of atezolizumab may be considered in patients who are deriving benefit.[a,b,c]
Rhabdomyolysis or symptomatic CPK elevations	Interrupt cobimetinib and atezolizumab treatment. If improved to Grade ≤ 3 within 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. If CPK elevations do not improve to Grade ≤ 3 within 4 weeks following dose interruption, permanently discontinue cobimetinib treatment Resumption of atezolizumab may be considered in patients who are deriving benefit.[a,b,c]

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

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

Appendix 3 Management of Cobimetinib plus Atezolizumab–Associated Adverse Events (Arm A) (cont.)

GUIDELINES FOR MANAGEMENT OF PATIENTS WHO EXPERIENCE HEMORRHAGE

Hemorrhage has been reported with cobimetinib (see Section 5.1.1.2). See Table 9.

Table 9 Recommended Dose Modifications for Cobimetinib in Patients with Hemorrhage

Hemorrhage	
Grade 3 events	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.

SYSTEMIC IMMUNE ACTIVATION

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

Recommendations regarding early identification and management of systemic immune activation are provided below. In the event of suspected systemic immune activation, atezolizumab should be withheld and the Medical Monitor should be contacted immediately for additional guidance.

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

- Hypotension that is refractory to aggressive IV fluid challenge

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

  Supplemental oxygen and intubation may be required.
- Fever $>38.5°C$
- Acute renal or hepatic failure
- Bleeding from coagulopathy

- Any of the following unexplained laboratory abnormalities (change from baseline): cytopenias (in two or more lineages), significant transaminitis, and coagulopathy

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

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

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

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

- Bone marrow biopsy and aspirate (assess for evidence of hemophagocytosis)
- Soluble interleukin 2 (IL-2) receptor (sCD25)
- Natural killer cell activity
- Cytomegalovirus, Epstein-Barr virus, and herpes-simplex virus evaluation (for reactivated or active disease)

Appendix 4
Anaphylaxis Precautions

PRECAUTIONS

Equipment needed:

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

PROCEDURES

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

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

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication

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

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

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

Measurable Tumor Lesions

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

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

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

Non-Measurable Tumor Lesions

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

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

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

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Special Considerations Regarding Lesion Measurability

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

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of Lesions

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

Method of Assessment

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

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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

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

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

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

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

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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

BASELINE DOCUMENTATION OF TARGET AND NONTARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

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

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

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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

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

In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

Evaluation of Target Lesions

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

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

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

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

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

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

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

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Special Notes on the Assessment of Target Lesions

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

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

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

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

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. While some nontarget lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- **CR**: disappearance of all nontarget lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

- **Non-CR/Non-PD**: persistence of one or more nontarget lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- **PD**: unequivocal progression of existing nontarget lesions

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

Special Notes on Assessment of Progression of Nontarget Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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

New Lesions

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

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

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

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

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

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

Table 1 Timepoint Response: Patients with Target Lesions (with or without Nontarget Lesions)

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

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

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Table 2 Timepoint Response: Patients with Nontarget Lesions Only

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

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

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

Missing Assessments and Not-Evaluable Designation

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

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

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Table 3 Best Overall Response When Confirmation Is Required

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

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

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

Special Notes on Response Assessment

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

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and nontarget disease as shown in Tables Table 1, Table 2, and Table 3.

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

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

Appendix 6
Eastern Cooperative Oncology Group Performance Status

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

Appendix 7
EuroQoL 5 Dimensions Health Questionnaire

EQ-5D-5L Health Questionnaire

English version for the USA

Appendix 7
EuroQoL 5 Dimensions Health Questionnaire (cont.)

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

Appendix 7
EuroQoL 5 Dimensions Health Questionnaire (cont.)

ANXIETY / DEPRESSION

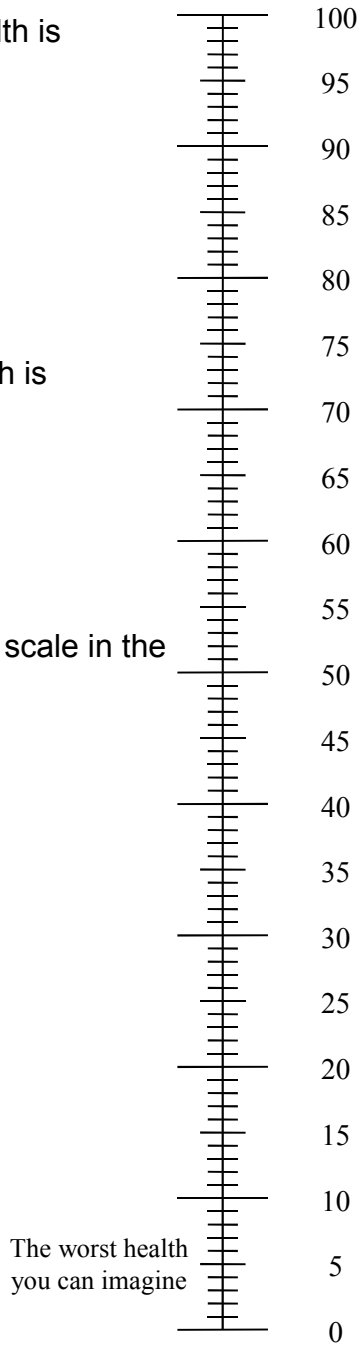
I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

Appendix 7
EuroQoL 5 Dimensions Health Questionnaire (cont.)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.

YOUR HEALTH TODAY = ☐

- Now, please write the number you marked on the scale in the box above.



Appendix 8
European Organisation for Research and Treatment of Cancer 30-Item Quality of Life Questionnaire (Version 3)

EORTC QLQ-C30 (version 3)

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

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

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

Appendix 8 European Organisation for Research and Treatment of Cancer 30-Item Quality of Life Questionnaire (Version 3) (cont.)

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 8 European Organisation for Research and Treatment of Cancer 30-Item Quality of Life Questionnaire (Version 3) (cont.)

Additional items

During the past week:	Not at All	A Little	Quite a Bit	Very Much
. Did you have abdominal pain?	1	2	3	4
Did you have a bloated feeling in your abdomen?	1	2	3	4

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

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

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for >105 days after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for >105 days to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >105 days 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 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

MANAGEMENT GUIDELINES

PULMONARY EVENTS

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

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

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

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

BAL = bronchoscopic alveolar lavage.

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

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

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

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

HEPATIC EVENTS

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

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

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

Table 2 Management Guidelines for Hepatic Events

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

LFT = liver function tests.

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

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

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

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 2 Management Guidelines for Hepatic Events (cont.)

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

LFT = liver function tests.

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

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

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

GASTROINTESTINAL EVENTS

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

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	*Management*
Diarrhea or colitis, Grade 1	• *Continue atezolizumab.* • *Initiate symptomatic treatment.* • *Endoscopy is recommended if symptoms persist for >7 days.* • *Monitor closely.*
Diarrhea or colitis, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Initiate symptomatic treatment.* • *Patient referral to GI specialist is recommended.* • *For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Diarrhea or colitis, Grade 3	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to GI specialist for evaluation and confirmatory biopsy.* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]

GI = gastrointestinal.

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

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

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

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	*Management*
Diarrhea or colitis, Grade 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Refer patient to GI specialist for evaluation and confirmation biopsy.* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

GI = gastrointestinal.

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

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

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

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections)

may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	*Management*
Asymptomatic hypothyroidism	• *Continue atezolizumab.* • *Initiate treatment with thyroid replacement hormone.* • *Monitor TSH weekly.*
Symptomatic hypothyroidism	• *Withhold atezolizumab.* • *Initiate treatment with thyroid replacement hormone.* • *Monitor TSH weekly.* • *Consider patient referral to endocrinologist.* • *Resume atezolizumab when symptoms are controlled and thyroid function is improving.*
Asymptomatic hyperthyroidism	***TSH ≥0.1 mU/L and <0.5 mU/L:*** • *Continue atezolizumab.* • *Monitor TSH every 4 weeks.* ***TSH <0.1 mU/L:*** • *Follow guidelines for symptomatic hyperthyroidism.*
Symptomatic hyperthyroidism	• *Withhold atezolizumab.* • *Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.* • *Consider patient referral to endocrinologist.* • *Resume atezolizumab when symptoms are controlled and thyroid function is improving.* • *Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-related hyperthyroidism.* [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

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

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	*Management*
Symptomatic adrenal insufficiency, Grade 2–4	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to endocrinologist.* • *Perform appropriate imaging.* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Hyperglycemia, Grade 1 or 2	• *Continue atezolizumab.* • *Initiate treatment with insulin if needed.* • *Monitor for glucose control.*
Hyperglycemia, Grade 3 or 4	• *Withhold atezolizumab.* • *Initiate treatment with insulin.* • *Monitor for glucose control.* • *Resume atezolizumab when symptoms resolve and glucose levels are stable.*

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

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

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	*Management*
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to endocrinologist.* • *Perform brain MRI (pituitary protocol).* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *Initiate hormone replacement if clinically indicated.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *For recurrent hypophysitis, treat as a Grade 4 event.*
Hypophysitis (pan-hypopituitarism), Grade 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Refer patient to endocrinologist.* • *Perform brain MRI (pituitary protocol).* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *Initiate hormone replacement if clinically indicated.*

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

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

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 5.

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 5 Management Guidelines for Ocular Events

Event	*Management*
Ocular event, Grade 1	• *Continue atezolizumab.* • *Patient referral to ophthalmologist is strongly recommended.* • *Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.* • *If symptoms persist, treat as a Grade 2 event.*
Ocular event, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Patient referral to ophthalmologist is strongly recommended.* • *Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Ocular event, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Refer patient to ophthalmologist.* • *Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

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

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

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

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-RELATED MYOCARDITIS

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 6 Management Guidelines for Immune-Related Myocarditis

Event	*Management*
Immune-related myocarditis, Grade 1	• *Refer patient to cardiologist.* • *Initiate treatment as per institutional guidelines.*
Immune-related myocarditis, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor.* • *Refer patient to cardiologist.* • *Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate.* • *Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.[a]* • *If event resolves to Grade 1 or better, resume atezolizumab. [b]* • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]*
Immune-related myocarditis, Grade 3-4	• *Permanently discontinue atezolizumab and contact Medical Monitor. [c]* • *Refer patient to cardiologist.* • *Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate.* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. [a,b]* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

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

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

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

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

INFUSION-RELATED REACTIONS

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

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

Table 7 Management Guidelines for Infusion-Related Reactions

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

IRR = infusion-related reaction.

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

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	*Management*
Amylase and/or lipase elevation, Grade 2	• *Continue atezolizumab.* • *Monitor amylase and lipase weekly.* • *For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.*
Amylase and/or lipase elevation, Grade 3 or 4	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to GI specialist.* • *Monitor amylase and lipase every other day.* • *If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.* [c]

GI = gastrointestinal.

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

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

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

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	*Management*
Immune-related pancreatitis, Grade 2 or 3	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to GI specialist.* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Immune-related pancreatitis, Grade 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Refer patient to GI specialist.* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

GI = gastrointestinal.

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

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

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

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	*Management*
Dermatologic event, Grade 1	• *Continue atezolizumab.* • *Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).*
Dermatologic event, Grade 2	• *Continue atezolizumab.* • *Consider patient referral to dermatologist.* • *Initiate treatment with topical corticosteroids.* • *Consider treatment with higher-potency topical corticosteroids if event does not improve.*
Dermatologic event, Grade 3	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to dermatologist.* • *Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Dermatologic event, Grade 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c]

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

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

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

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	*Management*
Immune-related neuropathy, Grade 1	• *Continue atezolizumab.* • *Investigate etiology.*
Immune-related neuropathy, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Investigate etiology.* • *Initiate treatment as per institutional guidelines.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Immune-related neuropathy, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Initiate treatment as per institutional guidelines.*
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [c] • *Refer patient to neurologist.* • *Initiate treatment as per institutional guidelines.* • *Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.*

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

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

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

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-RELATED MENINGOENCEPHALITIS

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for Immune-Related Meningoencephalitis

Event	*Management*
Immune-related meningoencephalitis, all grades	• *Permanently discontinue atezolizumab and contact Medical Monitor.* [a] • *Refer patient to neurologist.* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

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