Official Title: A Phase II, Open-Label, Multicenter, Multi-Cohort Study to Investigate the Efficacy and Safety of Cobimetinib Plus Atezolizumab in Patients With Solid Tumors

NCT Number: NCT03264066

Document Date: Protocol Version 4: 18-September-2018

PROTOCOL

TITLE:	**A PHASE II, OPEN-LABEL, MULTICENTER, MULTI-COHORT STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF COBIMETINIB PLUS ATEZOLIZUMAB IN PATIENTS WITH SOLID TUMORS**
PROTOCOL NUMBER:	WO39760
VERSION NUMBER:	4
EUDRACT NUMBER:	2017-000794-37
IND NUMBER:	118,753
TEST PRODUCTS:	Cobimetinib (RO5514041), Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 23 February 2017
DATES AMENDED:	Version 2: 20 October 2017 Version 3: 29 March 2018 Version 4: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	18-Sep-2018 22:13:13

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol WO39760 is being amended to update the lists of risks for atezolizumab and guidelines for managing patients who experience atezolizumab-associated adverse events to include nephritis (Section 5.1.2 and Appendix 8).

The following additional changes have been made:

- Text has been added to clarify that histologic samples are required for patients with squamous cell carcinoma of the head and neck (SCCHN) and renal cell carcinoma (RCC), and either cytological or histologic samples are acceptable for patients with urothelial carcinoma (UC) (Sections 3.1.1.3.1 and 4.1.1.2).
- The inclusion criterion for serum creatinine have been modified to allow patients with serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min by Cockcroft-Gault equation or 24-hour urine collection (Section 4.1.1.1).
- The coagulation test inclusion criterion has been amended to provide criteria for patients receiving therapeutic anticoagulation and those not receiving therapeutic anticoagulation (Section 4.1.1.1).
- The inclusion criterion that addresses female contraception has been modified to specify when women must refrain from donating eggs (Section 4.1.1.2).
- Added language to clarify use of samples after withdrawal of patient consent (Section 4.5.6.3).
- Cobimetinib dose modification has been amended to allow for dose re-escalations on a case-by-case basis after discussion with the Medical Monitor or [redacted] designee (Table 4 in Section 5.1.3).
- The Medical Monitor has changed (Section 5.4.1).
- Language has been updated to indicate that therapeutic or elective abortions are not considered adverse events unless performed because of an underlying maternal or embryofetal toxicity. In such cases, the underlying toxicity should be reported as a serious adverse event. Language has also been added to clarify that all abortions are to be reported on the paper Clinical Trial Pregnancy Reporting Form (Section 5.4.3.3).
- Language has been added for consistency with Roche's current data retention policy and to accommodate more stringent local requirements (if applicable) (Section 7.5).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, OPEN-LABEL, MULTICENTER, MULTI-COHORT STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF COBIMETINIB PLUS ATEZOLIZUMAB IN PATIENTS WITH SOLID TUMORS**
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PHASE:	II
INDICATION:	Solid tumors
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of cobimetinib plus atezolizumab in patients with advanced solid tumors including the following cohorts: squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), and renal cell carcinoma (RCC). Specific objectives and corresponding endpoints for the study are outlined below.

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of cobimetinib plus atezolizumab by ORR	• Objective response, defined as a complete response or a partial response based on two consecutive tumor assessments ≥4 weeks apart, as determined by the investigator according to RECIST v1.1

ORR = objective response rate; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Objectives (cont.)	Corresponding Endpoints (cont.)
Secondary Efficacy Objective:	
• To evaluate the efficacy of cobimetinib plus atezolizumab	• OS, defined as the time from enrollment to death from any cause • PFS, defined as the time from enrollment to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first) • DOR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first) • DCR, defined as the proportion of patients with a complete response, a partial response, or stable disease at 16 weeks, as determined by the investigator according to RECIST v1.1
Exploratory Efficacy Objective:	
• To evaluate the efficacy of cobimetinib plus atezolizumab with immune-modified RECIST	• Objective response, defined as a complete response or partial response on two consecutive assessments ≥ 4 weeks apart, as determined by the investigator according to immune-modified RECIST • PFS, defined as the time from enrollment to the first occurrence of disease progression, as determined by the investigator according to immune-modified RECIST, or death from any cause (whichever occurs first) • DOR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to immune-modified RECIST, or death from any cause (whichever occurs first) • DCR, defined as the proportion of patients with a complete response, a partial response, or stable disease at 16 weeks, as determined by the investigator according to immune-modified RECIST
Safety Objective:	
• To evaluate the safety of cobimetinib plus atezolizumab	• Occurrence and severity of adverse events, with severity determined according to the NCI CTCAE v4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective:	
• To characterize cobimetinib and atezolizumab pharmacokinetics	• Plasma concentration of cobimetinib at specified timepoints • Serum concentration of atezolizumab at specified timepoints
• **Immunogenicity Objective:**	
• To evaluate the immune response to atezolizumab	• Presence of ADAs during the study relative to the presence of ADAs at baseline

• ADA = anti-drug antibody; DCR = disease control rate; DOR = duration of response; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST= Response Evaluation Criteria in Solid Tumors.

Objectives (cont.)	Corresponding Endpoints (cont.)
Exploratory Immunogenicity Objective:	
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints
Biomarker Objectives:	
• To explore biomarkers that are associated with the efficacy of cobimetinib plus atezolizumab	• Genetic alterations, such as *RAS* mutations, as measured by next generation sequencing • Baseline immune contexture, such as TIL distribution, PD-L1 expression, and immune signatures, as measured by IHC and RNA sequencing
• To explore mechanisms of acquired resistance to cobimetinib plus atezolizumab	• Genetic alterations, as measured by next generation sequencing • Changes in immune contexture, such as TIL distribution, PD-L1 expression, and immune signatures, as measured by IHC and RNA sequencing
• To assess the pharmacodynamic effects of cobimetinib plus atezolizumab treatment	• TIL distribution, CD8, PD-L1, and stromal markers as determined by IHC • Immune-signatures, pathway activation signature, and stromal signature, as determined by RNA sequencing • Changes to circulating IC prevalence and distribution during treatment and at progression

ADA = anti-drug antibody; DCR = disease control rate; DOR = duration of response; IC = immune cell; IHC = immunohistochemistry; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PD-L1 = programmed death–ligand 1; PFS = progression-free survival; PK = pharmacokinetic; RECIST= Response Evaluation Criteria in Solid Tumors; TIL = tumor-infiltrating lymphocyte.

Study Design

Description of Study

This Phase II, open-label, multicenter, non-randomized, multi-cohort study is designed to evaluate the combination of cobimetinib plus atezolizumab in patients with advanced solid tumors. The study is designed with the flexibility to open new or expand existing cohorts if the initial efficacy outcome is promising and the safety outcome is acceptable. The Sponsor may elect to suspend a particular cohort at any time. The Sponsor may elect to not open or delay enrollment of a particular cohort.

There are seven patient cohorts in the study:

- Cohort 1: patients with SCCHN who are anti–PD-1 and anti–PD-L1 treatment naive
- Cohort 2: patients with UC who are anti–PD-1 and anti–PD-L1 treatment naive
- Cohort 3: patients with RCC who are anti–PD-1 and anti–PD-L1 treatment naive
- Cohort 4: patients with SCCHN whose disease has progressed while receiving anti–PD-1 or anti–PD-L1 therapy
- Cohort 5: patients with UC whose disease has progressed while receiving anti–PD-1 or anti–PD-L1 therapy
- Cohort 6: patients with RCC whose disease has progressed while receiving anti–PD-1 or anti–PD-L1 therapy
- Cohort 7: a biopsy cohort comprising patients with solid non-melanoma, non- hematologic tumors who previously developed primary or secondary resistance to an anti–PD-1 or anti–PD-L1 agent

Number of Patients

Approximately 20 patients are planned to be enrolled in Cohorts 1–6 with possible expansion up to approximately 40 patients in each cohort. Approximately 12 patients are planned to be enrolled in Cohort 7 (biopsy cohort). Therefore, up to approximately 250 patients in total are planned to be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following general criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Ability to comply with the study protocol, in the investigator's judgment
- Eastern Cooperative Oncology group performance status of 0 to 1
- Life expectancy ≥ 3 months, as determined by the investigator
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:

  ANC ≥ 1.5×10^9/L without granulocyte colony-stimulating factor support

  Lymphocyte count ≥ 0.5×10^9/L

  Platelet count ≥ 100×10^9/L without transfusion

  Hemoglobin ≥ 90 g/L

  – Patients may be transfused to meet this criterion.

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

  – Patients with documented liver metastases: AST and ALT ≤ 5 × ULN

  Serum bilirubin ≤ 1.5 × ULN with the following exception:

  – Patients with known Gilbert disease: serum bilirubin level ≤ 3 × ULN

  Serum creatinine ≤ 1.5 × ULN *or creatinine clearance ≥50 mL/min by Cockcroft-Gault equation or 24-hour urine collection*

  Serum albumin ≥ 2.5 g/dL

  For patients not receiving therapeutic anticoagulation: INR *or* aPTT ≤ 1.5 × ULN

  For patients receiving therapeutic anticoagulation: stable anticoagulant regimen and INR ≤3.5

Cancer-Related Inclusion Criteria

Patients must meet the following cancer-related criteria for study entry:

- Patients must have measurable disease by CT or MRI scan per Response Evaluation Criteria in Solid Tumors (RECIST v1.1).
- Availability to provide a representative tumor specimen biopsy:

  Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. *For patients with SCCHN or RCC, histologic samples are required. For patients with UC, cytological or histologic samples are acceptable.* Archival tumor tissue may be submitted after Medical Monitor approval has been obtained.

  A formalin-fixed, paraffin-embedded tumor specimen in a paraffin block (preferred) or at least 15 slides (20 preferred) containing unstained, freshly cut, serial sections is recommended to be submitted along with an associated pathology report prior to study enrollment. If a limited number of slides are available, the patient may still be eligible for the study, after discussion with and approval by the Medical Monitor.
- Evidence of tumor progression on or after the last treatment regimen received and within 6 months prior to study enrollment

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a non-hormonal contraceptive method with a failure rate of $<1\%$ per year during the treatment period and for at least 5 months after the last dose of atezolizumab and within 3 months after the last dose of cobimetinib. *Women must refrain from donating eggs during this same period.*

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

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices.

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

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

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

Cohort-Specific Inclusion Criteria

SCCHN Cohort 1 (Anti–PD-1/PD-L1 Treatment-Naive)

- Patients must have histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), Stage III/IV, and are not amenable to local therapy with curative intent (surgery or radiation, with or without chemotherapy).
- Patients must have received at least one platinum-containing therapy in the recurrent or metastatic setting and up to a total of two lines of chemotherapy (including the required platinum-based regimen), in the recurrent or metastatic SCCHN.
- Patients are also eligible if they had recurrence or progression within 6 months of the last dose of platinum-containing therapy in the adjuvant (i.e., with radiation after surgery) or primary (i.e., with radiation) setting.

SCCHN Cohort 4 (Progression on Anti–PD-1/PD-L1 Therapy)

- Patients must have histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), Stage III/IV, and are not amenable to local therapy with curative intent (surgery or radiation, with or without chemotherapy).
- Progressed on prior anti–PD-1/PD-L1 therapy in the recurrent or metastatic setting

  Patients are also eligible if they had disease progression on or within 6 months of the last dose of anti–PD-1/PD-L1 therapy in the adjuvant setting
- Prior treatment with T-cell co-stimulating or immune checkpoint blockade therapies, and combinations, including anti–CTLA-4, anti–PD-1/PD-L1 therapeutic antibodies are allowed

UC Cohort 2 (Anti–PD-1/PD-L1 Treatment-Naive)

- Histologically or cytologically documented locally advanced (T4b, any N; or any T, N2–N3) or metastatic (M1, Stage IV) urothelial bladder cancer (also termed transitional cell carcinoma, urothelial carcinoma, or carcinoma the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra)

  Patients with mixed histologies are required to have a dominant transitional cell pattern.

- Locally advanced bladder cancer must be inoperable on the basis of involvement of pelvic sidewall or adjacent viscera (clinical stage T4b) or bulky nodal metastasis (N2–N3)

    Transurethral resection for bladder tumor (TURBT) specimens must contain a muscle-invasive component (i.e., T2 or greater) or the bladder tumor as verified by local pathology review. If the TURBT specimens do not contain a muscle-invasive component, then specimens obtained at the time of cystectomy, nephroureterectomy, or metastatic spread (i.e., a sample from a metastatic lesion) will be required prior to enrollment.
- Disease progression during or following treatment with at least one platinum-containing regimen for inoperable, locally advanced or metastatic urothelial bladder cancer or disease recurrence

    Patients who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment with a platinum-containing adjuvant or neoadjuvant regimen are eligible.

    Patients may have received at least one prior regimen but no more than two prior regimens of treatment (including the required platinum-based regimen) for advanced urothelial bladder cancer.

    Patients who have received one cycle of a platinum-containing regimen but discontinued because intolerable toxicity may also be eligible.

    Patients with disease progression following chemoradiotherapy must demonstrate progression outside the prior radiotherapy port.

UC Cohort 5 (Progression on Anti–PD-1/PD-L1 Therapy)

- Histologically or cytologically documented locally advanced (T4b, any N; or any T, N2–N3) or metastatic (M1, Stage IV) urothelial bladder cancer (also termed transitional cell carcinoma, urothelial carcinoma, or carcinoma the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra)

    Patients with mixed histologies are required to have a dominant transitional cell pattern.
- Locally advanced bladder cancer must be inoperable on the basis of involvement of pelvic sidewall or adjacent viscera (clinical stage T4b) or bulky nodal metastasis (N2–N3)

    Transurethral resection for bladder tumor (TURBT) specimens must contain a muscle-invasive component (i.e., T2 or greater) or the bladder tumor as verified by local pathology review. If the TURBT specimens do not contain a muscle-invasive component, then specimens obtained at the time of cystectomy, nephroureterectomy, or metastatic spread (i.e., a sample from a metastatic lesion) will be required prior to enrollment.
- Disease progression during or following treatment with at least one platinum-containing regimen for inoperable, locally advanced or metastatic urothelial bladder cancer or disease recurrence

    Patients who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment with a platinum-containing adjuvant or neoadjuvant regimen are eligible.

    Patients who have received one cycle of a platinum-containing regimen but discontinued because intolerable toxicity may also be eligible.

    Patients with disease progression following chemoradiotherapy must demonstrate progression outside the prior radiotherapy port.
- Progression while on a prior anti–PD-1/PD-L1 therapy in the recurrent or metastatic setting

    Patients are also eligible if they had disease progression on or within 6 months of the last dose of anti–PD-1/PD-L1 therapy in the adjuvant setting
- Prior treatment with T-cell co-stimulating or immune checkpoint blockade therapies, and combinations including anti–CTLA-4, anti–PD-1/PD-L1 therapeutic antibodies are allowed
- Patients are eligible if they received no more than three lines of therapy in the advanced, metastatic setting

RCC Cohort 3 (Anti–PD-1/PD-L1 Treatment-Naive)

- Histological confirmation of advanced or metastatic RCC with a clear-cell component
- Prior cytokine therapy (e.g., IL-2, IFN-α), vaccine therapy, or treatment with cytotoxic agents is allowed.
- Patients must have received at least one but no more than two total prior systemic treatment regimens in the advanced or metastatic setting.

RCC Cohort 6 (Progression while on Anti–PD-1/PD-L1 Therapy):

- Patients in RCC Cohort 6 must meet the following criteria for study entry:
- Histological confirmation of advanced or metastatic RCC with a clear-cell component
- Prior cytokine therapy (e.g., IL-2, IFN-α), vaccine therapy, or treatment with cytotoxic agents is allowed.
- Progressed while on prior anti–PD-1/PD-L1 therapy in the recurrent or metastatic setting

  Patients are also eligible if they had disease progression on or within 6 months of the last dose of anti–PD-1/PD-L1 therapy in the adjuvant setting.
- Prior treatment with T-cell co-stimulating or immune checkpoint blockade therapies, and combinations including anti–CTLA-4, anti–PD-1/PD-L1 therapeutic antibodies are allowed.
- Patients are eligible if they received no more than three lines of therapy in the advanced/metastatic setting.

Biopsy Cohort 7

- Patients must have histologically confirmed non-melanoma, non-hematologic solid tumor.
- Patients must have metastatic or locally advanced disease that is not amenable to local treatment with curative intent.
- Measurable disease according to RECIST v1.1
- Patients in this cohort must have received a minimum of two cycles of anti–PD-1 or anti–PD-L1 therapy.
- Patients in this cohort must have progressed during or after anti–PD-1 or anti–PD-L1 therapy within 12 weeks before study start.
- Patients in this cohort must meet criteria for primary or secondary resistance to an anti–PD-1 or anti–PD-L1 agent as outlined below:

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

  Secondary resistance is defined as progressive disease after initial confirmed response according to RECIST v1.1
- Patients in this cohort must have received anti–PD-1 or anti–PD-L1 therapy as the most recent treatment.
- Patients in this cohort must consent to undergo tumor biopsies of accessible lesions before and during treatment for biomarker analyses.
- Patients in this cohort must have at least two accessible lesions that are amenable to excisional or core-needle biopsy with acceptable risk of a major procedural complication. Exceptions may be made following discussion with Medical Monitor.

<u>Exclusion Criteria</u>

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

General Exclusion Criteria

- Inability to swallow medications. Other means of intake may be allowed after Medical Monitor approval has been obtained.
- Malabsorption condition that would alter the absorption of orally administered medications
- Poor peripheral venous access
- Prior treatment with cobimetinib or a MEK inhibitor

- For patients in Cohorts 1, 2, and 3 only: prior treatment with T-cell co-stimulating or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with investigational therapy within 14 days prior to initiation of study treatment
- Any anti-cancer therapy, including chemotherapy or hormonal therapy, within 2 weeks prior to initiation of study treatment
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceutical agents produced in Chinese hamster ovary cells
- Known allergy or hypersensitivity to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any component of the cobimetinib formulation
- Known allergy or hypersensitivity to any anti–PD-1/PD-L1 therapy
- History of serous retinopathy, retinal vein occlusion (RVO), or evidence of ongoing serous retinopathy or RVO at baseline
- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- Uncontrolled tumor-related pain

  Patients requiring narcotic pain medication must be on a stable regimen at study entry.

  Intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring repeated drainage more than once every 28 days

  Indwelling drainage catheters (e.g., PleurX®) are allowed.
- Uncontrolled hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected calcium greater than the ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy.

  Patients who are receiving bisphosphonate therapy for other reasons (e.g., bone metastasis or osteoporosis) and who do not have a history of clinically significant hypercalcemia are eligible for the study.
- Active or untreated CNS metastases

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

  – Evaluable or measurable disease outside the CNS
  – No metastases to midbrain, pons, medullar or within 10 mm of the optic nerves and chiasm
  – No history or evidence of intracranial hemorrhage or spinal cord hemorrhage
  – No evidence of clinically significant vasogenic edema
  – No corticosteroids for $\geq$ 2 weeks; anti-convulsant medications at a stable dose are allowed
  – No evidence of clinical and radiographic disease progression in the CNS for $\geq$ 3 weeks after radiotherapy or surgery
- Pregnancy or breastfeeding, or intending to become pregnant during the study

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

Exclusion Criteria based on Organ Function or Medical History

Cardiovascular

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

Infections

- Positive HIV test at screening
- Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening

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

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

Autoimmune Conditions and Immunomodulatory Drugs

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, anti–phospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

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

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

  – Rash must cover $<10\%$ of body surface area
  – Disease is well controlled at baseline and requires only low-potency topical corticosteroids
  – No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months
  – Disease is well controlled at baseline and only requiring low-potency steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, alclometasone dipropionate 0.05%)
- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

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

Exclusions Related to Other Medical Conditions or Medications

- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Other active malignancy or a prior malignancy within the past 3 years outside of the primary cancer being studied in this study

  Patients with completely resected basal cell carcinoma, cutaneous squamous cell carcinoma, cervical carcinoma in-situ, breast carcinoma in-situ, and patients with isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer are eligible for the study.
- Any Grade $\geq$ 3 hemorrhage or bleeding event within 28 days of Day 1 of Cycle 1
- History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to Day 1 of Cycle 1

Cohort-Specific Exclusion Criteria

SCCHN Cohorts 1 and 4

- Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx and salivary gland or of non-squamous histologies (e.g., mucosal melanoma)

End of Study

The study will end when all patients enrolled have been followed until death, withdrawal of consent, loss to follow-up, or the Sponsor decides to end the trial, whichever occurs first. Patients may continue study treatment until the development of progressive disease, unacceptable toxicity, and/or withdrawal of consent.

Length of Study

The total length of the study, from screening of the first patient to last patient, last visit is expected to be approximately 3 years.

Investigational Medicinal Products

Test Products (Investigational Drugs)

Cobimetinib

Patients will receive cobimetinib 60 mg (3 tablets of 20 mg each) orally once a day on Days 1–21 of each 28-day cycle in all cohorts.

Atezolizumab

Atezolizumab will be given at a fixed dose of 840 mg by IV infusion on Days 1 and 15 of each 28-day cycle.

Patients in the biopsy cohort, Cohort 7, will receive the first dose of atezolizumab of 840 mg by IV infusions on Day 15 of Cycle 1. Thereafter, they will receive atezolizumab 840 mg IV infusion Q2W on Days 1 and 15 of Cycle 2 and all subsequent cycles.

Statistical Methods

Primary Analysis

This study is designed to explore the preliminary efficacy, safety, pharmacokinetics, immunogenicity, and biomarker of cobimetinib plus atezolizumab in seven patient cohorts with advanced solid tumors, including SCCHN, urothelial carcinoma, and RCC.

The primary analysis will be conducted once all patients in a particular cohort have been followed for a clinically meaningful period of time of approximately 16 weeks. The statistical results will be summarized and presented by cohort.

Determination of Sample Size

The purpose of this study is for hypothesis generation only. No formal hypothesis testing or inference analysis is planned; hence, no power analysis is conducted. Approximately 20 patients are planned to be enrolled in Cohorts 1–6 with possible expansion up to approximately

40 patients in each cohort. Approximately 12 patients are planned to be enrolled in Cohort 7 (biopsy cohort). Therefore, up to approximately 250 patients in total are planned to be enrolled in this study.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
21/7	21 days on/7 days off
ADA	anti-drug antibody
CIN	chromosomal instability
CRC	colorectal cancer
CR	complete response
CT	computed tomography
DCR	disease control rate
DOR	duration of response
EC	Ethics Committee
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HPV	human papillomavirus
HR	hazard ratio
IC	immune cell
IxRS	interactive voice or Web-based response system
ICH	International Council for Harmonisation
IFN-α	interferon-alpha
Ig	immunoglobulin
IL-2	interleukin-2
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related response
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
MDSC	myeloid-derived suppressor cell

Abbreviation	Definition
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSS	microsatellite stable
MUGA	multiple-gated acquisition (scan)
NCI CTCAE v4.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
NGS	next-generation sequencing
ORR	objective response rate
OS	overall survival
PD-1	programmed death−1
PD-L1	programmed death ligand−1
PFS	progression-free survival
PK	pharmacokinetic
PO	orally (by mouth)
PR	partial response
QD	once a day
Q2W	every 2 weeks
Q3W	every 3 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RVO	retinal vein occlusion
SCCHN	squamous cell carcinoma of the head and neck
TCR	T-cell receptor
TIL	tumor-infiltrating lymphocyte
TNF-α	tumor necrosis factor−alpha
TURBT	transurethral resection for bladder tumor
UC	urothelial carcinoma
ULN	upper limit of normal
VEGFR	vascular endothelial growth factor receptor
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON SOLID TUMOR COHORTS

1.1.1 Background on Squamous Cell Carcinoma of the Head and Neck

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth most common non–skin-related cancer (Stransky et al. 2011). In 2002, head and neck cancers comprised approximately 664,000 new cases and 350,000 deaths globally (Siegel et al. 2015). In the United States, there were more than 61,000 new cases and more than 13,000 deaths from head and neck cancers in 2016, representing approximately 3.7% of all new cancer cases and 2.7% of all cancer deaths in 2016 (Siegel et al. 2016). More men are affected than women with SCCHN in a ratio of 2.5:1, and the median age at diagnosis is 60 years old (Siegel et al. 2016).

Two subclasses of SCCHN tumors have been identified: human papillomavirus (HPV)-positive and HPV-negative tumors. Of patients with SCCHN, 20% have HPV-positive tumors and have a more favorable prognosis than the remaining 80% patients with HPV-negative tumors. In addition, within the HPV-negative subclass, patients with low chromosomal instability (CIN) and high CIN have been identified on the basis of numerical genetic changes, and CIN prevalence has been estimated at 15% and 65% of SCCHN, respectively. Patients with low CIN appear to have a more favorable prognosis than patients with high CIN status; however, CIN classification is preliminary and is based on limited data (Leemans et al. 2011).

Sixty percent of SCCHN are initially diagnosed at an advanced stage, encompassing locally advanced (Stage III and IVA/B) and metastatic tumors (Stage IVC). The standard of care for patients with locally advanced SCCHN consists of multimodality therapy with surgery and/or chemoradiation, and despite 30% of patients achieving a complete response (CR), the majority of patients will relapse, with 20%–30% developing distant metastases (Vermorken and Specenier 2010). Although a minority of patients who have recurrent disease may be candidates for salvage surgery or re-irradiation, treatment options are usually limited to palliative chemotherapy or best-supportive care, depending on a patient's performance status. Platinum-containing combination therapy is considered first-line therapy in this setting. In patients with relapsing or metastatic SCCHN that is refractory to platinum-containing regimens, single-agent chemotherapy (e.g., taxanes, capecitabine, or methotrexate) or targeted agents (e.g., cetuximab) are options but have failed to demonstrate a survival benefit (NCCN 2016; Seiwert et al. 2016). The median overall survival (OS) was less than 6 months for these patients (Machiels et al. 2015; Ferris et al. 2016a).

Checkpoint inhibitors have demonstrated efficacy in SCCHN. In 2016, pembrolizumab, a programmed death–1 (PD-1) inhibitor, received accelerated approval from the U.S. Food and Drug Administration (FDA) for patients with recurrent or metastatic SCCHN with disease progression during or after platinum-containing chemotherapy. The overall response rate was 18% (95% CI: 8%, 23%) with pembrolizumab in this second-line

treatment setting for these patients, and median OS was 13.0 months (95% CI: 5 months, not reached). The most common adverse events included fatigue, pruritus, nausea, decreased appetite, and rash. Grade ≥ 3 events included increased AST and ALT, rash, fatigue, atrial fibrillation, lymphopenia, congestive heart failure, diarrhea, neck abscess, hyponatremia, and musculoskeletal pain (Bauml et al. 2016; Seiwert et al. 2016).

Nivolumab, another PD-1 inhibitor, received full approval from the FDA in 2016 for patients with recurrent or metastatic SCCHN with disease progression during or after a platinum-based therapy. Patients were randomized to receive nivolumab or investigator's choice (single-agent methotrexate, docetaxel, or cetuximab). The 1-year OS rate was 36.0% (95% CI: 28.5%, 43.4%) compared with 16.6% (95% CI: 8.6%, 26.8%), and the median OS was 7.5 months (95% CI: 5.5, 9.1 months) compared with 5.1 months (95% CI: 4.0, 6.0 months). The objective response rate (ORR) was 13.3% (95% CI: 9.3%, 18.3%) among nivolumab-treated patients compared with 5.8% (95% CI: 2.4%, 11.6%) in investigator's choice–treated patients. Overall, the safety profile of nivolumab was similar to what was reported in pembrolizumab-treated patients with SCCHN (Ferris et al. 2016a; Seiwert et al. 2016).

After progression on anti–PD-1/PD-L1 therapy, there is no standard-of-care effective therapy. Patients can receive single-agent chemotherapy such as methotrexate or taxanes or treatment with cetuximab, but these agents have been evaluated only in the anti–PD-1/PD-L1-naive setting. Currently, there are no treatment modalities that have been studied in the post–checkpoint inhibitor setting.

1.1.2 Background on Urothelial Carcinoma

Globally, urothelial carcinoma (UC) is the ninth most commonly occurring cancer. There were an estimated 429,000 new UC cases and approximately 165,000 deaths in 2012 (Ferlay et al. 2013). In the United States, there were approximately 76,960 new cases and 16,390 deaths in 2016 (Siegel et al. 2016). More men are affected than women in a ratio of 3.5:1, and the median age at diagnosis is 73 years old (Mallin et al. 2011). UC is the most prevalent in Europe, Asia, and Northern Africa (Pelucchi et al. 2006).

Of patients with newly diagnosed UC, approximately 70% present with superficial tumors, 15% with muscle-invasive tumors, and 12% present with regional or metastatic disease. Even with appropriate treatment of superficial tumors, about 50%–70% will recur, with 10%–20% presenting as muscle-invasive cancer (Kaufman et al. 2009). For muscle-invasive tumors, treatment involves radical cystectomy, with or without neoadjuvant or adjuvant chemotherapy (Kaufman et al. 2009; Clark et al. 2016). Despite treatment, approximately 50% of patients will have recurrence and ultimately will die from their disease (Grossman et al. 2003).

For patients with advanced UC, platinum-based chemotherapy has been the standard of care, with a median OS of 9–15 months (von der Maase et al. 2005; Kaufman et al.

2009). For patients with metastatic UC, almost all will progress after a first-line platinum-based therapy (von der Maase et al. 2005). Until recently, there was no standard of care for second-line therapy and treatment involved single-agent chemotherapy, such as paclitaxel, gemcitabine, and pemetrexed (Clark et al. 2016). Median OS is 5–7 months in this population (Bellmunt et al. 2009). Until the introduction of checkpoint inhibitors, no therapies prolonged survival (Sweeney et al. 2006).

In 2016, atezolizumab received accelerated approval from the FDA in patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. A Phase II study with atezolizumab in patients with advanced UC demonstrated an ORR of 15%, median progression-free survival (PFS) of 2.1 months and median OS of 7.9 months (Rosenberg et al. 2016). Study drug–related adverse events were reported in 61% of patients, with fatigue and nausea being the most common in patients treated with atezolizumab. Six percent of patients treated with atezolizumab experienced a Grade $\geq$3 adverse event.

Other checkpoint inhibitors have also been studied in this setting with similar results. Pembrolizumab was studied in patients with advanced urothelial carcinoma and showed a median PFS of 2.0 months (95% CI: 1.7, 4.0 months) and median OS of 12.7 months (95% CI: 5.0 months, not reached) (Plimack et al. 2015). In previously treated patients with metastatic urothelial carcinoma, nivolumab demonstrated a median PFS of 2.8 months (95% CI: 1.5, 5.9 months) and median OS of 9.7 months (95% CI: 7.3, 16.2 months), with confirmed investigator-assessed objective response of 24.4% (95% CI: 15.3%, 35.4%) (Sharma et al. 2016), and has received accelerated approval from the FDA.

In patients who have received checkpoint inhibitors but are chemotherapy naive, platinum-based therapy is recommended (NCCN 2018). There are no therapies that have been studied in the post–checkpoint therapy setting for patients who have previously received chemotherapy.

1.1.3 Background on Renal Cell Carcinoma

Globally, there were an estimated 338,000 new renal cell carcinoma (RCC) cases and approximately 144,000 deaths in 2012 (Ferlay et al. 2013). In the United States, there were approximately 62,700 new cases and 14,240 deaths in 2016 (Siegel et al. 2016). More men are affected than women with RCC in a ratio of 2:1. RCC is more prevalent in North America, Australia, New Zealand, and Europe (Ferlay et al. 2013).

About one-third of RCC patients have metastatic disease at the time of diagnosis, and another 30% of patients develop metastatic disease despite surgical treatment for locoregional disease (Fisher et al. 2013). For the majority of patients with metastatic RCC, treatment is palliative with systemic therapy. In the first-line setting, several

targeted therapies and immunotherapies have been approved, including sunitinib, bevacizumab plus interferon-alpha (IFN-α), high-dose interleukin-2 (IL-2), pazopanib, and temsirolimus (NCCN 2017). Sunitinib is the most commonly used in the first-line treatment setting in metastatic RCC (Hess et al. 2013); however, most patients relapse within 1 year and require second-line treatment (Motzer et al. 2007).

Nivolumab has received full approval from the FDA and European Medicines Agency (EMA); cabozantinib has received full approval from the FDA for the second-line treatment of metastatic RCC based on Phase III clinical trial results showing improvement in clinical efficacy compared with everolimus (Choueiri et al. 2015; Motzer et al. 2015). Prior to these recent approvals, no second-line therapy had shown an improvement in OS (Fisher et al. 2013).

Nivolumab is a PD-1 immune checkpoint inhibitor antibody that was studied in patients with metastatic RCC who had previously received one or two regimens of antiangiogenic therapy. The ORR was greater with nivolumab than with everolimus (25% vs. 5% [odds ratio = 5.98; 95% CI: 3.68, 9.72]), and median OS was 25 months (95% CI: 21.8 months, not evaluable) for nivolumab and 19.6 months (95% CI: 17.6, 23.1 months) for everolimus. Programmed death–ligand 1 (PD-L1) expression levels did not correlate with nivolumab benefit over everolimus. Study treatment-related adverse events of any grade occurred in 79% of patients who were treated with nivolumab, with the most common study treatment–related adverse events being fatigue, nausea, and pruritus. Grade 3 or 4 study treatment-related adverse events occurred in 19% of patients, with the most common adverse event being fatigue (2%).

Cabozantinib is a tyrosine kinase inhibitor that targets the vascular endothelial growth factor receptor (VEGFR) that was studied in patients with metastatic RCC who received at least one VEGFR-targeted tyrosine kinase inhibitor. Estimated median PFS was 7.4 months (95% CI: 5.6, 9.1 months) with cabozantinib and 3.8 months (95% CI: 3.7, 5.4 months) with everolimus. A trend toward longer OS with cabozantinib than with everolimus was observed (hazard ratio [HR] = 0.67; 95% CI: 0.51, 0.89; p = 0.005) as of the interim analysis data cutoff, but median OS is not available yet, owing to the low number of events. All patients experienced any grade adverse event, and 68% of patients experienced a Grade 3 or 4 adverse event while receiving cabozantinib. The most common adverse events (> 20%) were diarrhea (74%), fatigue (56%), nausea (50%), decreased appetite (46%), palmar–plantar erythrodysesthesia syndrome (42%), hypertension (37%), vomiting (32%), decreased weight (31%), constipation (25%), dysgeusia (24%), and stomatitis (22%). The most common Grade 3 or 4 adverse events (> 5%) were hypertension (15%), diarrhea (11%), and fatigue (9%).

No treatments have specifically been studied in the post–checkpoint inhibitor setting. The Phase III trial of cabozantinib versus everolimus in second and subsequent-line mRCC did enroll patients who previously had received nivolumab (Choueiri et. al 2016) but no therapies are currently approved in this setting.

1.2 BACKGROUND ON COBIMETINIB AND ATEZOLIZUMAB

1.2.1 The PD-L1 Pathway

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 and Dranoff 2010; Kantoff et al. 2010). Therefore, immunomodulation represents a promising new strategy for cancer therapy that may result in improved anti-tumor activity.

PD-L1 expression is prevalent in many human tumors (e.g., lung cancer, ovarian cancer, melanoma, and colon carcinoma), and its overexpression has been associated with poor prognosis in some cancers (Thompson et al. 2006; Hamanishi et al. 2007; Okazaki and Honjo 2007; Hino et al. 2010). PD-L1 is one of two ligands (PD-L1 and PD-L2) that binds to 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 monoclonal antibodies 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 immunoglobulin (Ig) G1 monoclonal antibody 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.

1.2.2 The MAPK Signaling Pathway and Regulation of the Immune Tumor Microenvironment

The MAPK signaling cascade is a key intracellular signaling network that transduces multiple proliferative and differentiating signals from the extracellular environment to the nucleus of cells to activate cellular growth and differentiation (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). Furthermore, pretreatment biopsies in which there were increased tumor-infiltrating lymphocytes (TILs) demonstrated a larger increase in TILs and PD-1 expression after treatment with a *BRAF* inhibitor and MEK inhibitor (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 targets for the inhibition of the MAPK pathway.

Cobimetinib is an orally dosed, potent and highly selective inhibitor of MEK.

1.2.3 Background on Cobimetinib Monotherapy

Cobimetinib is a reversible, potent, and highly selective inhibitor of MEK1 and MEK2, key downstream regulators of the MAPK pathway. MEK1 and MEK2 are responsible for activating ERK by phosphorylation. Cobimetinib inhibits ERK phosphorylation in xenograft tumor models to stimulate apoptosis and tumor regression. Cobimetinib has been studied alone or with other agents in more than 1000 adult cancer patients; the vast majority of patients had been treated with cobimetinib plus other agents, such as vemurafenib. The cobimetinib monotherapy trial is the first-in-human Phase I study MEK4592g, an open-label, safety, and pharmacokinetic (PK) dose-escalation study in patients with metastatic or unresectable solid tumors (Rosen et al. 2016). The recommended dose was 60 mg daily for 21 days followed by a 7-day break in dosing. As a single-agent, cobimetinib demonstrated anti-tumor activity in melanoma. In combination with other agents, cobimetinib has demonstrated anti-tumor activity in other tumor types, such as melanoma, lung, colon, and breast cancers (Larkin et al. 2014).

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

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

1.2.4 Background on Atezolizumab Monotherapy

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80),

both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

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

Atezolizumab (Tecentriq®) is approved in the United States for the treatment of locally advanced or metastatic urothelial carcinoma and for the treatment of metastatic non–small cell lung cancer.

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

1.2.5 Combined Inhibition of PD-L1 and MAPK Signaling Pathways as Potential Anti-Cancer Therapy

Although checkpoint inhibitors have shown efficacy in a variety of tumors, only a proportion of the tumors are responsive, and most patients eventually progress and die from their disease. Moreover, there are still high unmet needs for patients with tumors for which checkpoint inhibitors are ineffective.

One potential mechanism to convert cancers that are otherwise resistant to immune checkpoint inhibitors is to recruit immune cells (ICs) to the tumor sites so that 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 in tumors increases expression of the checkpoint receptor PD-L1, which could counteract the increased presentation of tumor antigens. MEK inhibition also results in increased major histocompatibility complex (MHC) class I expression and tumor antigen presentation, which acts to enhance tumor recognition by the immune system. Lastly, the MAPK pathway is known to regulate a number of cytokines and chemokines, such as VEGF, IL-6, IL-8, and granulocyte macrophage colony-stimulating factor, which may affect recruitment of vascular and other stromal cell types, including myeloid-derived suppressor cells (MDSCs), that can inhibit the anti-tumor activity of T cells (Bancroft et al. 2001, 2002; Sano et al. 2001; 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 MEK inhibitor 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. In a mouse model, the MEK inhibitor–rescued T cells appeared to be most effective in the presence of a PD-L1 blocking antibody; the MAPK axis is a key downstream pathway for the T-cell receptor (TCR) triggering. The TCR-driven death seemed to be working in parallel with the PD-1 axis (Ebert et al. 2016). The 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.

1.2.5.1 Rationale for Combining Cobimetinib and Atezolizumab for Solid Tumors after Progression on Anti–PD-1/PD-L1 Therapy

As detailed in Sections 1.1.1– 1.1.3, although anti–PD-1/PD-L1 therapies have benefited patients with certain solid tumors, response rates to anti–PD-1/PD-L1 therapies are low and patients eventually progress on treatment. Patients who do not respond or achieve disease stabilization are defined as having refractory disease or primary resistance, whereas patients whose tumors progress after initial response or stabilization are defined as having relapsed disease or secondary resistance. The molecular mechanisms of primary and secondary resistance to immunotherapy are poorly understood. However, the known effects of MAPK inhibitors, including cobimetinib, on the tumor microenvironment (see Section 1.2.5) include effects that may enable conversion to an immune-responsive phenotype, sensitize refractory tumors to anti–PD-1/PD-L1 agents, and/or re-sensitize relapsed tumors to these agents, leading researchers to the hypothesis that combining MEK inhibition with anti–PD-1/PD-L1 therapy may lead to improved efficacy.

1.2.6 Clinical Data: Cobimetinib in Combination with Atezolizumab

1.2.6.1 Phase Ib Study of Cobimetinib and Atezolizumab: Study GP28363

Study GP28363 is a Phase Ib, open-label, multicenter, global study designed to assess cobimetinib and atezolizumab administered in combination to patients with metastatic or locally advanced (unresectable) solid tumors. The study has two stages: Stage 1 (dose escalation) and Stage 2 (indication-specific expansion cohorts and serial biopsy cohort).

In Stage 1, the recommended Phase II dose was established to be 60 mg of cobimetinib by mouth (PO) once a day (QD) for 21 consecutive days of 28 days (21 days on/7 days off [21/7] schedule) and 800 mg of atezolizumab by IV infusion every 2 weeks (Q2W). In the Stage 2 (expansion cohorts), cobimetinib plus atezolizumab is being studied in a variety of solid tumors, including *KRAS*-mutant and *KRAS* wild-type metastatic colorectal cancer (CRC) and $BRAF^{V600}$ mutant and $BRAF^{V600}$ wild-type metastatic melanoma.

1.2.6.2 Preliminary Results of Study GP28363

[redacted]

[redacted]

[redacted]

Biomarker Data

Biomarker evaluation from the serial tumor biopsy cohort showed a 4-fold increase of CD8-positive T-cell infiltration in 75% of tumors as well as increases in PD-L1 and MHC-I expression (Bendell et al. 2016). The data support the hypothesis that

cobimetinib has beneficial immunomodulatory effects at the tumor site that allow for immune anti-tumor activity.

Summary of Adverse Events

The safety-evaluable population consists of 150 patients who had received at least one dose of atezolizumab. All patients received cobimetinib. Overall, 96.7% of patients experienced at least one adverse event regardless of attribution; 65.3% experienced a Grade ≥ 3 adverse event; and 44.0% experienced a serious adverse event. There were five Grade 5 adverse events (3.3%) (see Table 1).

The most common adverse events (reported in ≥ 20% of patients) were diarrhea (69.3%), fatigue (52.7%), rash (46.0%), vomiting (38.7%), nausea (34.0%), pruritus (32.7%), decreased appetite (30.0%), constipation (28.0%), peripheral edema (26.0%), pyrexia (23.3%), acneiform dermatitis (23.3%), increased CPK (22.7%), dyspnea (20.0%), and anemia (20.0%). The most common Grade ≥ 3 adverse events (≥ 5%) were fatigue (9.3%), anemia (8.7%), and diarrhea (8.0%). Overall, 44% of patients experienced a serious adverse event. [redacted]

[redacted]

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of cobimetinib plus atezolizumab in patients with advanced solid tumors, including the following seven cohorts:

- Cohort 1: patients with SCCHN who are anti–PD-1 and anti–PD-L1 treatment naive
- Cohort 2: *patients with* UC who are anti–PD-1 and anti–PD-L1 treatment naive
- Cohort 3: Patients with RCC who are anti–PD-1 and anti–PD-L1 treatment naive
- Cohort 4: Patients with SCCHN who have progressed while on anti–PD-1 or anti–PD-L1 therapy
- Cohort 5: Patients with UC who have progressed while on anti–PD-1 or anti–PD-L1 therapy
- Cohort 6: Patients with RCC who have progressed while on anti–PD-1 or anti–PD-L1 therapy
- Cohort 7: A biopsy cohort comprising patients with solid non-melanoma, non-hematologic tumors who previously developed primary or secondary resistance to an anti–PD-1 or anti–PD-L1 agent

Specific objectives and corresponding endpoints for the study are outlined in Table 2.

Table 2 Objectives and Corresponding Endpoints

Objective(s)	Corresponding Endpoint(s)
Primary Efficacy Objective:	
• To evaluate the efficacy of cobimetinib plus atezolizumab by ORR	• Objective response, defined as a complete response or a partial response based on two consecutive tumor assessments ≥4 weeks apart, as determined by the investigator according to RECIST v1.1
Secondary Efficacy Objective:	
• To evaluate the efficacy of cobimetinib plus atezolizumab	• OS, defined as the time from enrollment to death from any cause • PFS, defined as the time from enrollment to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first) • DOR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first) • DCR, defined as the proportion of patients with a complete response, a partial response, or stable disease at 16 weeks, as determined by the investigator according to RECIST v1.1

DCR=disease control rate; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1.

Table 2 Objectives and Corresponding Endpoints (cont.)

Objective(s)	Corresponding Endpoint(s)
Exploratory Efficacy Objective:	
• To evaluate the efficacy of cobimetinib plus atezolizumab with immune-modified RECIST	• Objective response, defined as a complete response or partial response on two consecutive assessments ≥ 4 weeks apart, as determined by the investigator according to immune-modified RECIST • PFS, defined as the time from enrollment to the first occurrence of disease progression, as determined by the investigator according to immune-modified RECIST, or death from any cause (whichever occurs first) • DOR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to immune-modified RECIST, or death from any cause (whichever occurs first) • DCR, defined as the proportion of patients with a complete response, a partial response, or stable disease at 16 weeks, as determined by the investigator according to immune-modified RECIST
Safety Objective:	
• To evaluate the safety of cobimetinib plus atezolizumab	• Occurrence and severity of adverse events, with severity determined according to the NCI CTCAE v4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective:	
• To characterize cobimetinib and atezolizumab pharmacokinetics	• Plasma concentration of cobimetinib at specified timepoints • Serum concentration of atezolizumab at specified timepoints
Immunogenicity Objective:	
• To evaluate the immune response to atezolizumab	• Presence of ADAs during the study relative to the presence of ADAs at baseline

ADA=anti-drug antibody; DCR=disease control rate; DOR=duration of response; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.

Table 2 Objectives and Corresponding Endpoints (cont.)

Objective(s)	Corresponding Endpoint(s)
Exploratory Immunogenicity Objectives:	
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints
Biomarker Objectives:	
• To explore biomarkers that are associated with the efficacy of cobimetinib plus atezolizumab	• Genetic alterations, such as *RAS* mutations, as measured by next generation sequencing • Baseline immune contexture, such as TIL distribution, PD-L1 expression, and immune signatures, as measured by IHC and RNA sequencing
• To explore mechanisms of acquired resistance to cobimetinib plus atezolizumab	• Genetic alterations, as measured by next generation sequencing • Changes in immune contexture, such as TIL distribution, PD-L1 expression, and immune signatures, as measured by IHC and RNA sequencing
• To assess the pharmacodynamic effects of cobimetinib plus atezolizumab treatment	• TIL distribution, CD8, PD-L1, and stromal markers as determined by IHC • Immune-signatures, pathway activation signature, and stromal signature, as determined by RNA sequencing • Changes to circulating IC prevalence and distribution during treatment and at progression

ADA=anti-drug antibody; IC=immune cell; IHC=immunohistochemistry; OS=overall survival; PD-L1=programmed death–ligand 1; PK=pharmacokinetic; TIL=tumor-infiltrating lymphocyte.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This Phase II, open-label, multicenter, non-randomized, multi-cohort study is designed to evaluate the combination of cobimetinib plus atezolizumab in patients with advanced solid tumors. The study is designed with the flexibility to open new or expand existing cohorts if the initial efficacy outcome is promising and the safety outcome is acceptable. The Sponsor may elect to suspend a particular cohort at any time. The Sponsor may elect to not open or delay enrollment of a particular cohort.

There are seven patient cohorts in the study:

- Cohort 1: patients with SCCHN who are anti–PD-1 and anti–PD-L1 treatment naive
- Cohort 2: patients with UC who are anti–PD-1 and anti–PD-L1 treatment naive
- Cohort 3: patients with RCC who are anti–PD-1 and anti–PD-L1 treatment naive
- Cohort 4: patients with SCCHN whose disease has progressed while receiving anti–PD-1 or anti–PD-L1 therapy
- Cohort 5: patients with UC whose disease has progressed while receiving anti–PD-1 or anti–PD-L1 therapy
- Cohort 6: patients with RCC whose disease has progressed while receiving anti–PD-1 or anti–PD-L1 therapy
- Cohort 7: a biopsy cohort comprising patients with solid non-melanoma, non- hematologic tumors who previously developed primary or secondary resistance to an anti–PD-1 or anti–PD-L1 agent

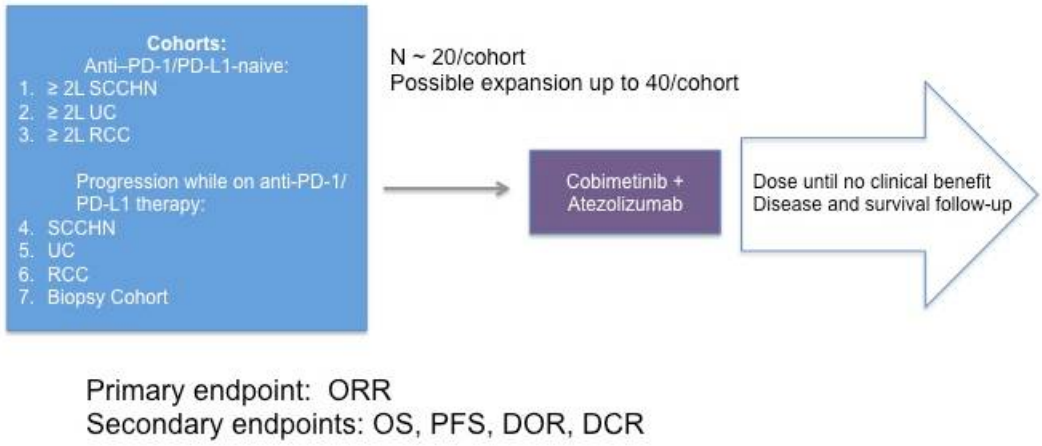
The primary objective of the study is to evaluate the efficacy of cobimetinib plus atezolizumab in different solid tumor types as measured by overall response rate. The study will be conducted globally, and approximately 20 patients will be enrolled in each cohort with the opportunity to expand up to approximately 40 patients per cohort. Approximately 12 patients will be enrolled in Cohort 7.

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.

A schedule of activities is provided in Appendix 1.

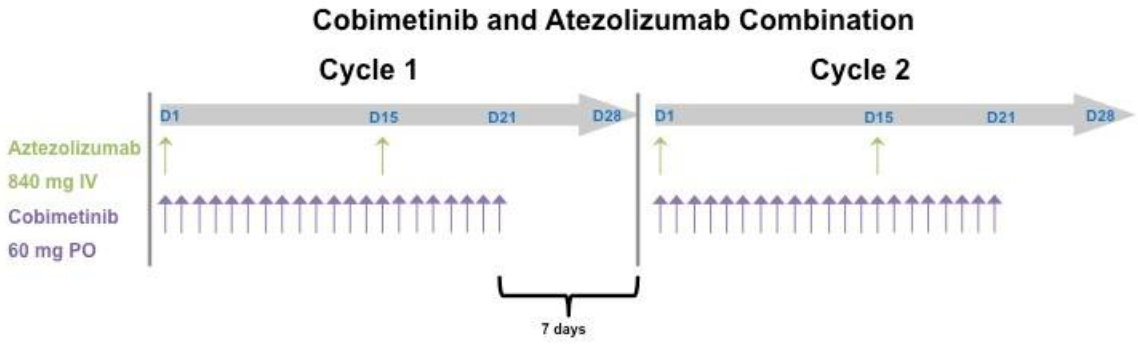
After signing informed consent, patients will undergo screening procedures that include laboratory tests (e.g., hematology, chemistries, liver function tests); left ventricular function evaluation (echocardiogram [ECHO] or multiple-gated acquisition [MUGA] scan); contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis; and ophthalmologic assessments. Patients can be rescreened.

Figure 1 Study Schema



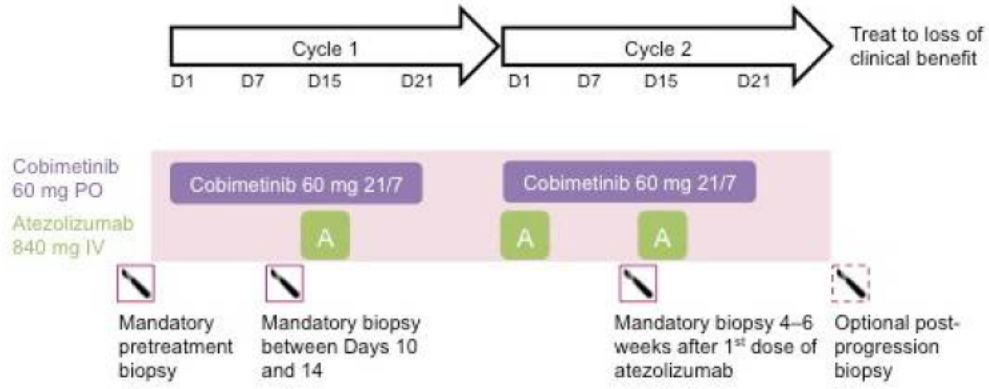
DCR = disease control rate; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCC = renal cell carcinoma; SCCHN = squamous cell carcinoma of the head and neck; UC = urothelial carcinoma.

Figure 2 Study Dosing Schema: Cohorts 1–6



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

Figure 3 Study Dosing Schema: Biopsy Cohort 7



A = atezolizumab; D = day; PO = orally (by mouth).

3.1.1.1 Cobimetinib and Atezolizumab Treatment Schedule

Cobimetinib will be administered orally at a starting dose of 60 mg QD starting on Day 1 through Day 21 followed by a 7-day rest of each 28-day cycle in all cohorts. Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle. Patients in the biopsy cohort (Cohort 7) will begin dosing cobimetinib before atezolizumab and will receive 60 mg cobimetinib alone QD, starting on Day 1 through Day 14 for Cycle 1. Atezolizumab dosing (840 mg IV) will begin on Day 15 in Cycle 1 and will continue on Days 1 and 15 of every cycle thereafter. Both study drugs will be administered until unacceptable toxicity or loss of clinical benefit, as determined by the investigator, after an integrated assessment of radiographic and biochemical data, and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). If one study drug is discontinued or temporarily withheld or dose reduced, the other study drug may be continued.

Because of the possibility of an initial increase in tumor burden caused by IC infiltration in the setting of a T-cell response (termed "pseudoprogression") with atezolizumab containing treatment, radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving cobimetinib and/or atezolizumab will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression

- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patient's written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial disease progression

After discontinuation of study treatment, patients may receive any subsequent line of therapy as directed by their treating physician. Patients will continue to be followed after discontinuation of study treatment to monitor adverse events, response and duration of response, and survival (see Section 4.6.1).

3.1.1.2 Tumor Assessments

Tumor response will be evaluated by either CT scan or MRI scan according to RECIST v1.1, as determined by the investigator (see Appendix 3). Any evaluable and measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Immune-modified RECIST will also be evaluated at the same time (see Appendix 4), as determined by the investigator. Investigators will assess tumor response at 8-week intervals, regardless of any dose delays or treatment cycles.

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 every 8 weeks 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. In patients who are treated beyond progression, tumor assessments will be performed until discontinuation of treatment.

3.1.1.3 Tumor Biopsies

3.1.1.3.1 Non-Biopsy Cohorts (Cohorts 1–6)

Baseline tumor tissue samples will be obtained from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted after Medical Monitor approval has been obtained.

These samples will be utilized for biomarker research (see [redacted] and details on tissue sample collection in Section 4.5.5).

Patients will be asked to provide an optional biopsy during treatment on Day 15 of Cycle 1 (±5 days), provided the patient's disease is easily accessible and tumor biopsies can be performed with minimal risk and discomfort. The 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).

Patients will undergo mandatory tumor biopsy sample collection, unless not clinically feasible, as assessed and documented by the investigator, at the time of first evidence of radiographic disease progression according to RECIST v1.1, within 14 days after radiographic progression, or prior to the start of new anti-cancer treatment, whichever is sooner. These samples will be analyzed to evaluate the utility of the biopsy in distinguishing pseudoprogression (caused by tumor-infiltrating lCs) from true progression. In addition, tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab may be analyzed.

For biopsies obtained during screening (fresh or archival) and during the conduct of the trial, histologic samples are required for patients with SCCHN or RCC. For patients with UC, cytological or histologic samples are acceptable.

3.1.1.3.2 Biopsy Cohort (Cohort 7)

Patients enrolled in Cohort 7, the biopsy cohort, must have at least two (preferably three) accessible lesions that meet the requirements specified in the eligibility criteria. Exceptions may be made if a patient has only one lesion that allows multiple biopsies following discussion with Medical Monitor. One pre-treatment, two on-treatment biopsies, and possibly one post-progression biopsy will be performed. If more than one biopsy will be obtained from one lesion, the lesion should be large enough to permit successive biopsies $\geq$1 cm apart. Investigators are strongly encouraged to obtain two on-treatment biopsies as described below. At a minimum, the biopsy obtained between Day 10 and 14 of Cycle 1 should be obtained to test for possible immunologic effects of cobimetinib alone.

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

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

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

3.1.2 Safety Data Review

The Sponsor's study team will review adverse events, serious adverse events, the frequency of deaths from all causes, and any other safety data in the study on an ongoing basis.

It is the responsibility of the study team to review accumulating safety data, to assess and monitor ongoing safety in patients, to evaluate potential changes to the clinical study protocol, and ultimately, to safeguard patient safety.

3.2 END OF STUDY AND LENGTH OF STUDY

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

The total length of the study, from screening of the first patient to last patient, last visit (LPLV) is expected to be approximately 3 years.

3.3 RATIONALE FOR STUDY

3.3.1 Rationale for Study Design

This Phase II study is designed to assess the efficacy and safety of cobimetinib plus atezolizumab in a variety of solid tumors. [redacted] In light of the nonclinical and clinical data, and the high unmet need of the tumors proposed in this study, the study is designed to evaluate whether this combination may benefit these patient populations.

3.3.2 Rationale for Cobimetinib and Atezolizumab Dose and Schedule

Concomitant administration of cobimetinib and atezolizumab was studied in Study GP28363. Cobimetinib and atezolizumab in combination were found to be safe and tolerable with cobimetinib on the approved dose and schedule of 60 mg QD 21/7

(Days 1–21 of a 28-day cycle), and atezolizumab 800 mg IV Q2W, which is equivalent in exposure to the approved dose and schedule for the treatment of bladder cancer of 1200 mg IV every 3 weeks (Q3W).

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

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

3.3.2.1 Rationale for the Biopsy Cohort (Cohort 7)

Cohort 7 is designed to allow assessment of the biological effects of cobimetinib on immune therapy. In this cohort, in Cycle 1 only, cobimetinib will be given for 14 days before initiation of atezolizumab treatment. Biopsies obtained before treatment start and between Days 10 and 14 of cobimetinib monotherapy period will allow elucidation of the effects of cobimetinib on tumor immune contexture. Additional biopsies taken during the combination treatment period and at radiographic progression will support evaluation of the effects of combination treatment on the tumor microenvironment and the identification of potential mechanisms of resistance to combination therapy.

During Cycle 2 and all subsequent cycles, patients in Cohort 7 will receive cobimetinib 60 mg QD 21/7 and atezolizumab 840 mg IV Q2W, the same dose and schedule as in Cohorts 1–6.

3.3.3 Rationale for Patient Population

3.3.3.1 Rationale for SCCHN

Recurrent or metastatic SCCHN is a disease of high unmet medical need for which the 5-year survival is less than 5%. In patients with recurrent or metastatic SCCHN whose disease has progressed on platinum-containing regimens, treatment options are limited and median OS is less than 6 months. Recently pembrolizumab and nivolumab, both checkpoint inhibitors, have received accelerated approval from the FDA for patients who have had disease progression during or following platinum-containing chemotherapy for recurrent or metastatic cancer; however, median OS remains short at about 8 months.

[redacted]

[redacted]

3.3.3.2 Rationale for Urothelial Carcinoma

Advanced urothelial carcinoma is a disease of high unmet medical need with an overall 5-year survival rate of < 5%. Chemotherapy with platinum-containing regimens remains the standard-of-care treatment for initial treatment of advanced disease, but median OS ranges from 9 to 15 months. Recently, atezolizumab received accelerated approval from the FDA for patients who have had disease progression during or following platinum-containing chemotherapy for advanced urothelial carcinoma, but median OS remains short at approximately 8 months. [redacted]

3.3.3.3 Rationale for RCC

Metastatic RCC is a disease of high unmet medical need with the majority of patients receiving palliative systemic therapy and dying of their disease. Nivolumab is an anti–PD-1 antibody that is approved by the FDA and the EMA for patients with metastatic RCC who have previously received one or two previous regimens of antiangiogenic therapy. [redacted]

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

In studies of immunotherapeutic agents, a CR, a PR, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by IC infiltration in the setting of a T-cell response has been termed pseudoprogression (Hales et al. 2010). [redacted] Because of the potential for a response after pseudoprogression, this study will allow all patients to continue treatment after apparent radiographic progression per RECIST v1.1, provided the benefit–risk ratio is judged to be favorable by the investigator (for the criteria, see Section 3.1.1). Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression, as determined by the investigator, after an integrated assessment of radiographic and biochemical data, biopsy results (if available), and clinical status.

3.3.5 Rationale for the Use of Immune-Modified RECIST

Increasing clinical experience indicates that traditional response criteria (e.g., RECIST v1.1 and World Health Organization criteria) may not adequately assess the activity of immunotherapeutic agents because initial radiographic evidence of disease progression does not necessarily reflect therapeutic failure. Patients can experience a response in the presence of new lesions or after an increase in tumor burden. Thus, this study will employ immune-modified RECIST for tumor assessments to account for the possible appearance of new lesions and allow radiographic progression to be confirmed at a subsequent assessment (see Appendix 4). It is required that radiographic progression be confirmed at a subsequent tumor assessment to take into account the potential for pseudoprogression (caused by IC infiltration). Given the proposed immunomodulatory mechanism of action of atezolizumab and the possibility of observing delayed responses, use of immune-modified RECIST criteria will allow for the capture of a greater proportion of potential responses and allow patients to derive maximum clinical benefit.

3.3.6 Rationale for Pharmacokinetic Sample Collection Schedule

The proposed PK sampling scheme for assessment of cobimetinib and atezolizumab concentrations, together with available data from other clinical studies, will be used to investigate the impact of concomitant administration on PK parameters (e.g., maximum and minimum concentrations [C_{max} and C_{min}]) of each compound.

[redacted]

The pharmacokinetics of each compound will be compared with single-agent data for each molecule from previous studies. Plasma samples will be collected as outlined in Appendix 2.

[redacted]

[redacted]

[redacted]

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 20 patients in each cohort of advanced solid tumors will be enrolled in this study with a possibility of expanding to approximately 40 patients in each cohort. Approximately 12 patients are planned to be enrolled in Cohort 7. The seven cohorts of patients are described in Section 2.

4.1.1 Inclusion Criteria

4.1.1.1 General Inclusion Criteria

Patients must meet the following general criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Ability to comply with the study protocol, in the investigator's judgment
- ECOG performance status of 0 to 1 (see Appendix 5)
- Life expectancy ≥ 3 months, as determined by the investigator
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:

  ANC $\geq 1.5 \times 10^9$/L without granulocyte colony-stimulating factor support

  Lymphocyte count $\geq 0.5 \times 10^9$/L

  Platelet count $\geq 100 \times 10^9$/L without transfusion

Hemoglobin ≥ 90 g/L

- Patients may be transfused to meet this criterion.

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

- Patients with documented liver metastases: AST and ALT ≤ 5 × ULN

Serum bilirubin ≤ 1.5 × ULN with the following exception:

- Patients with known Gilbert disease: serum bilirubin level ≤ 3 × ULN

Serum creatinine ≤ 1.5 × ULN *or creatinine clearance ≥ 50 mL/min by Cockcroft-Gault equation or 24-hour urine collection*

Serum albumin ≥ 2.5 g/dL

For patients not receiving therapeutic anticoagulation: INR *or* aPTT ≤ 1.5 × ULN

For patients receiving therapeutic anticoagulation: stable anticoagulant regimen and INR ≤ 3.5

4.1.1.2 Cancer-Related Inclusion Criteria

Patients must meet the following cancer-related criteria for study entry (for cohort-specific inclusion criteria, see Section 4.1.3):

- Patients must have measurable disease by CT or MRI scan per RECIST v1.1.
- Availability to provide a representative tumor specimen biopsy:

  Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. *For patients with SCCHN or RCC, histologic samples are required. For patients with UC, cytological or histologic samples are acceptable.* Archival tumor tissue may be submitted after Medical Monitor approval has been obtained.

  A formalin-fixed, paraffin-embedded tumor specimen in a paraffin block (preferred) or at least 15 slides (20 preferred) containing unstained, freshly cut, serial sections is recommended to be submitted along with an associated pathology report prior to study enrollment. If a limited number of slides are available, the patient may still be eligible for the study, after discussion with and approval by the Medical Monitor.
- Evidence of tumor progression on or after the last treatment regimen received and within 6 months prior to study enrollment
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a non-hormonal contraceptive method with a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab and within 3 months after the last dose of cobimetinib. *Women must refrain from donating eggs during this same period.*

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

Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices.

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

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

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

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

4.1.2 Exclusion Criteria

4.1.2.1 General Exclusion Criteria

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

- Inability to swallow medications. Other means of intake may be allowed after Medical Monitor approval has been obtained.
- Malabsorption condition that would alter the absorption of orally administered medications
- Poor peripheral venous access
- Prior treatment with cobimetinib or a MEK inhibitor
- For patients in Cohorts 1, 2, and 3 only: prior treatment with T-cell co-stimulating or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with investigational therapy within 14 days prior to initiation of study treatment
- Any anti-cancer therapy, including chemotherapy or hormonal therapy, within 2 weeks prior to initiation of study treatment
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceutical agents produced in Chinese hamster ovary cells
- Known allergy or hypersensitivity to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any component of the cobimetinib formulation

- Known allergy or hypersensitivity to any anti–PD-1/PD-L1 therapy
- History of serous retinopathy, retinal vein occlusion (RVO), or evidence of ongoing serous retinopathy or RVO at baseline
- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- Uncontrolled tumor-related pain

  Patients requiring narcotic pain medication must be on a stable regimen at study entry.

  Intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring repeated drainage more than once every 28 days

  Indwelling drainage catheters (e.g., PleurX®) are allowed.
- Uncontrolled hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected calcium greater than the ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy.

  Patients who are receiving bisphosphonate therapy for other reasons (e.g., bone metastasis or osteoporosis) and who do not have a history of clinically significant hypercalcemia are eligible for the study.
- Active or untreated CNS metastases

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

  – Evaluable or measurable disease outside the CNS
  – No metastases to midbrain, pons, medullar or within 10 mm of the optic nerves and chiasm
  – No history or evidence of intracranial hemorrhage or spinal cord hemorrhage
  – No evidence of clinically significant vasogenic edema
  – No corticosteroids for $\geq$ 2 weeks; anti-convulsant medications at a stable dose are allowed
  – No evidence of clinical and radiographic disease progression in the CNS for $\geq$ 3 weeks after radiotherapy or surgery
- Pregnancy or breastfeeding, or intending to become pregnant during the study

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

4.1.2.2 Exclusion Criteria based on Organ Function or Medical History

Cardiovascular

Patients who meet the following cardiovascular exclusion criterion will be excluded from study entry:

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

Infections

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

- Positive HIV test at screening
- Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening

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

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

4.1.2.3 Autoimmune Conditions and Immunomodulatory Drugs

Patients who meet any of the following exclusion criteria for autoimmune conditions and immunomodulatory drugs will be excluded from study entry:

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, anti–phospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 6 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

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

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

- Rash must cover $<$10% of body surface area
- Disease is well controlled at baseline and requires only low-potency topical corticosteroids
- No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months
- Disease is well controlled at baseline and only requiring low-potency steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, alclometasone dipropionate 0.05%)

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

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

4.1.2.4 Exclusions Related to Other Medical Conditions or Medications

Patients who meet any of the following exclusion criteria related to other medical conditions or medications will be excluded from study entry:

- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Other active malignancy or a prior malignancy within the past 3 years outside of the primary cancer being studied in this study

  Patients with completely resected basal cell carcinoma, cutaneous squamous cell carcinoma, cervical carcinoma in-situ, breast carcinoma in-situ, and patients with isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer are eligible for the study.
- Any Grade $\geq$ 3 hemorrhage or bleeding event within 28 days of Day 1 of Cycle 1
- History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to Day 1 of Cycle 1

4.1.3 Cohort-Specific Inclusion and Exclusion Criteria

4.1.3.1 SCCHN Cohorts

Inclusion Criteria for SCCHN Cohort 1 (Anti–PD-1/PD-L1 Treatment-Naive Patients):

Patients in SCCHN Cohort 1 must meet the following criteria for study entry:

- Patients must have histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), Stage III/IV, and are not amenable to local therapy with curative intent (surgery or radiation, with or without chemotherapy).
- Patients must have received at least one platinum-containing therapy in the recurrent or metastatic setting and up to a total of two lines of chemotherapy (including the required platinum-based regimen), in the recurrent or metastatic SCCHN.
- Patients are also eligible if they had recurrence or progression within 6 months of the last dose of platinum-containing therapy in the adjuvant (i.e., with radiation after surgery) or primary (i.e., with radiation) setting.

Inclusion Criteria for SCCHN Cohort 4 (Progression while on Anti–PD-1/PD-L1 Therapy)

- Patients in SCCHN Cohort 4 must meet the following criteria for study entry:
- Patients must have histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), Stage III/IV, and are not amenable to local therapy with curative intent (surgery or radiation, with or without chemotherapy).
- Progressed on prior anti–PD-1/PD-L1 therapy in the recurrent or metastatic setting

  Patients are also eligible if they had disease progression on or within 6 months of the last dose of anti–PD-1/PD-L1 therapy in the adjuvant setting
- Prior treatment with T-cell co-stimulating or immune checkpoint blockade therapies, and combinations, including anti–CTLA-4, anti–PD-1/PD-L1 therapeutic antibodies are allowed

Exclusion Criteria for SCCHN Cohorts 1 and 4:

Patients in the SCCHN cohorts who meet the following exclusion criterion will be excluded from study entry:

Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx and salivary gland or of non-squamous histologies (e.g., mucosal melanoma)

4.1.3.2 UC Cohorts

Inclusion Criteria for UC Cohort 2 (Anti–PD-L1/PD-1 Treatment-Naive Patients):

Patients in UC Cohort 2 must meet the following criteria for study entry:

- Histologically or cytologically documented locally advanced (T4b, any N; or any T, N2–N3) or metastatic (M1, Stage IV) urothelial bladder cancer (also termed transitional cell carcinoma, urothelial carcinoma, or carcinoma the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra)

Patients with mixed histologies are required to have a dominant transitional cell pattern.

- Locally advanced bladder cancer must be inoperable on the basis of involvement of pelvic sidewall or adjacent viscera (clinical stage T4b) or bulky nodal metastasis (N2–N3)

  Transurethral resection for bladder tumor (TURBT) specimens must contain a muscle-invasive component (i.e., T2 or greater) or the bladder tumor as verified by local pathology review. If the TURBT specimens do not contain a muscle-invasive component, then specimens obtained at the time of cystectomy, nephroureterectomy, or metastatic spread (i.e., a sample from a metastatic lesion) will be required prior to enrollment.

- Disease progression during or following treatment with at least one platinum-containing regimen for inoperable, locally advanced or metastatic urothelial bladder cancer or disease recurrence

  Patients who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment with a platinum-containing adjuvant or neoadjuvant regimen are eligible.

  Patients may have received at least one prior regimen but no more than two prior regimens of treatment (including the required platinum-based regimen) for advanced urothelial bladder cancer.

  Patients who have received one cycle of a platinum-containing regimen but discontinued because intolerable toxicity may also be eligible.

  Patients with disease progression following chemoradiotherapy must demonstrate progression outside the prior radiotherapy port.

Inclusion Criteria for UC Cohort 5 (Progression while on Anti–PD-1/PD-L1 Therapy):

- Patients in UC Cohort 5 must meet the following criteria for study entry:
- Histologically or cytologically documented locally advanced (T4b, any N; or any T, N2–N3) or metastatic (M1, Stage IV) urothelial bladder cancer (also termed transitional cell carcinoma, urothelial carcinoma, or carcinoma the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra)

  Patients with mixed histologies are required to have a dominant transitional cell pattern.

- Locally advanced bladder cancer must be inoperable on the basis of involvement of pelvic sidewall or adjacent viscera (clinical stage T4b) or bulky nodal metastasis (N2–N3)

  Transurethral resection for bladder tumor (TURBT) specimens must contain a muscle-invasive component (i.e., T2 or greater) or the bladder tumor as verified by local pathology review. If the TURBT specimens do not contain a muscle-invasive component, then specimens obtained at the time of cystectomy, nephroureterectomy, or metastatic spread (i.e., a sample from a metastatic lesion) will be required prior to enrollment.

- Disease progression during or following treatment with at least one platinum-containing regimen for inoperable, locally advanced or metastatic urothelial bladder cancer or disease recurrence

    Patients who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment with a platinum-containing adjuvant or neoadjuvant regimen are eligible.

    Patients who have received one cycle of a platinum-containing regimen but discontinued because intolerable toxicity may also be eligible.

    Patients with disease progression following chemoradiotherapy must demonstrate progression outside the prior radiotherapy port.

- Progression while on a prior anti–PD-1/PD-L1 therapy in the recurrent or metastatic setting

    Patients are also eligible if they had disease progression on or within 6 months of the last dose of anti–PD-1/PD-L1 therapy in the adjuvant setting

- Prior treatment with T-cell co-stimulating or immune checkpoint blockade therapies, and combinations including anti–CTLA-4, anti–PD-1/PD-L1 therapeutic antibodies are allowed
- Patients are eligible if they received no more than three lines of therapy in the advanced, metastatic setting

4.1.3.3 RCC Cohorts

Inclusion Criteria for RCC Cohort 3 (Anti–PD-1/PD-L1 Treatment-Naive Patients):

Patients in RCC Cohort 3 must meet the following criteria for study entry:

- Histological confirmation of advanced or metastatic RCC with a clear-cell component
- Prior cytokine therapy (e.g., IL-2, IFN-α), vaccine therapy, or treatment with cytotoxic agents is allowed.
- Patients must have received at least one but no more than two total prior systemic treatment regimens in the advanced or metastatic setting.

Inclusion Criteria for RCC Cohort 6 (Progression while on Anti–PD-1/PD-L1 Therapy):

- Patients in RCC Cohort 6 must meet the following criteria for study entry:
- Histological confirmation of advanced or metastatic RCC with a clear-cell component
- Prior cytokine therapy (e.g., IL-2, IFN-α), vaccine therapy, or treatment with cytotoxic agents is allowed.
- Progressed while on prior anti–PD-1/PD-L1 therapy in the recurrent or metastatic setting

    Patients are also eligible if they had disease progression on or within 6 months of the last dose of anti–PD-1/PD-L1 therapy in the adjuvant setting.

- Prior treatment with T-cell co-stimulating or immune checkpoint blockade therapies, and combinations including anti–CTLA-4, anti–PD-1/PD-L1 therapeutic antibodies are allowed.
- Patients are eligible if they received no more than three lines of therapy in the advanced/metastatic setting.

4.1.3.4 Biopsy Cohort 7

- Patients must have histologically confirmed non-melanoma, non-hematologic solid tumor.
- Patients must have metastatic or locally advanced disease that is not amenable to local treatment with curative intent.
- Measurable disease according to RECIST v1.1
- Patients in this cohort must have received a minimum of two cycles of anti–PD-1 or anti–PD-L1 therapy.
- Patients in this cohort must have progressed during or after anti–PD-1 or anti–PD-L1 therapy within 12 weeks before study start.
- Patients in this cohort must meet criteria for primary or secondary resistance to an anti–PD-1 or anti–PD-L1 agent as outlined below:

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

  Secondary resistance is defined as progressive disease after initial confirmed response according to RECIST v1.1
- Patients in this cohort must have received anti–PD-1 or anti–PD-L1 therapy as the most recent treatment.
- Patients in this cohort must consent to undergo tumor biopsies of accessible lesions before and during treatment for biomarker analyses.
- Patients in this cohort must have at least two accessible lesions that are amenable to excisional or core-needle biopsy with acceptable risk of a major procedural complication. Exceptions may be made following discussion with Medical Monitor.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label trial. After written informed consent has been obtained and eligibility has been established, each patient will be assigned an identification number and be enrolled to the appropriate cohort through use of an interactive voice or Web-based response system (IxRS).

4.3 STUDY TREATMENT

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

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Cobimetinib

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

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

4.3.1.2 Atezolizumab

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

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

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Cobimetinib

Patients will receive cobimetinib 60 mg (3 tablets of 20 mg each) orally QD on Days 1–21 of each 28-day cycle in all cohorts. 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, patients may resume dosing with the next scheduled dose.

Guidelines for dosage modification and treatment interruption or discontinuation of cobimetinib are provided in Section 5.1.3.1.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.4.4.

4.3.2.2 Atezolizumab

Atezolizumab will be given at a fixed dose of 840 mg by IV infusion on Days 1 and 15 of each 28-day cycle. A 28-day period is considered a treatment cycle.

Patients in the biopsy cohort, Cohort 7, will receive the first dose of atezolizumab of 840 mg by IV infusions on Day 15 of Cycle 1. Thereafter, they will receive atezolizumab 840 mg IV infusion Q2W on Days 1 and 15 of Cycle 2 and all subsequent cycles.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to

manage potentially serious reactions. For anaphylaxis precautions, see Appendix 7. Atezolizumab infusions will be administered per the instructions outlined in Table 3.

Table 3 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
Premedication is not allowed.	If patient experienced IRR during any previous infusion, pre-medication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the treating physician.
Record vital signs (pulse rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion.	Record patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion.
Infuse atezolizumab (one vial in 250 mL of NaCl) over 60 (±15) minutes.	If the patient tolerated the first infusion well without infusion-associated adverse events, the second infusion may be delivered over 30 (±10) minutes.
Record vital signs (pulse rate, respiratory rate, blood pressure, and temperature) during the infusion or after the infusion if clinically indicated.	If the patient had an IRR during the previous infusion, the subsequent infusion must be delivered over 60 (±15) minutes.
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 (pulse rate, respiratory rate, blood pressure, and temperature) during the infusion or after the infusion if clinically indicated or if the patient experienced symptoms during the previous infusion. If no reaction occurs, continue subsequent infusions over 30 (±10) minutes using the same schedule for recording vital signs.

IRR = infusion-related reaction; NaCl = sodium chloride.

Dose modifications to atezolizumab are not permitted. Guidelines for treatment interruption of atezolizumab are provided in Section 5.1.3.3, and the management of specific adverse events associated with cobimetinib and atezolizumab are provided in Section 5.1.3.4. For information regarding management of atezolizumab-associated adverse events, refer to *Appendix 8*.

For anaphylaxis precautions, see Appendix 7.

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

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.4.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (cobimetinib and atezolizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

4.3.4 Post-Trial Access to Cobimetinib and Atezolizumab

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

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

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

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

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or 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 the particular solid tumor depending on the cohort.
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for the particular solid tumor, depending on the cohort.
- 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

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

4.4.1 Permitted Therapy

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

- Hormonal therapy with gonadotropin-releasing hormone agonists for prostate cancer
- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin). However, caution should be used in patients on anticoagulation therapy because of the risk of hemorrhage events with cobimetinib.
- Inactivated influenza vaccinations
- Megestrol administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Palliative radiotherapy (e.g., treatment of known bone metastases or symptomatic relief of pain) as outlined below:

    Palliative radiotherapy is permitted, provided it does not interfere with the assessment of the tumor target lesions.

- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.

  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

  – Anti-convulsant therapy, if required, is administered at a stable dose.

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

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 7).

4.4.2 Cautionary and Prohibited Therapy

4.4.2.1 Corticosteroids and Tumor Necrosis Factor–Alpha Inhibitors

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

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

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

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

Strong and moderate CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, and phenobarbital) should be avoided during cobimetinib treatment because they increase the metabolism of cobimetinib. Strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product with no or minimal potential to induce CYP3A4 should be considered.

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

4.4.2.3 Prohibited Therapy

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

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited during study treatment.
- Treatment with live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

- Systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents) are prohibited within 2 weeks of Cycle 1, Day 1 and during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.
- Systemic corticosteroids may not be administered as premedication to patients with an allergy to contrast agents used for tumor scans (see Appendix 3 for information on tumor scans for patients with contrast allergies).

4.4.2.4 Prohibited Food and Herbal Supplements

Consumption of potent CYP3A4 enzyme inhibitors such as grapefruit juice and potent CYP3A4 enzyme inducers such as St. John's wort are prohibited starting 7 days prior to Day 1 of Cycle 1, during the study, and for 30 days after the last dose of study treatment.

4.5 STUDY ASSESSMENTS

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

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

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, prior surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, 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 treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity. Baseline disease characteristics data will include ECOG performance status, date of diagnosis of first metastatic disease, site of primary disease, *RAS* status, history of metastectomy, and location of metastasis at enrollment.

4.5.3 Physical Examinations

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

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

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

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and blood pressure while the patient is in a seated position (after a 5-minute rest period), and temperature (measured in degrees Centigrade).

Vital signs will be measured and recorded at the timepoints outlined in the schedule of activities (see Appendix 1).

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

4.5.5 Tumor and Response Evaluations

All measurable and non-measurable lesions must be documented at screening (within 28 days prior to initiation of study treatment) and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator based on CT or MRI scans, using RECIST v1.1, and immune-modified RECIST (see Appendix 3 and Appendix 4). An objective response should be confirmed by repeat assessments $\geq$4 weeks after initial documentation. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Assessments should be performed by the same evaluator to ensure internal consistency across visits.

Radiographic scans should include chest, abdomen, and pelvic scans; radiographic scans of the head and/or neck should be included in the SCCHN cohort or if clinically indicated. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

It is possible that the CT and MRI scans might be collected, sent to and reviewed by an independent review committee for response assessments.

4.5.6 Laboratory, Biomarker, and Other Biologic Samples

4.5.6.1 Screening (Local Laboratory)

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

- Hematology: WBC count, RBC count, CBC, hemoglobin, hematocrit, count with differential (neutrophils, eosinophils, basophils, monocytes, and lymphocytes)
- Serum chemistry panel: glucose, BUN or urea, creatinine, sodium, potassium, magnesium, calcium, phosphorus, total bilirubin, ALT, AST, ALP, CPK, albumin, and others per the schedule of activities (see Appendix 1)
- Coagulation (INR and aPTT)
- Urinalysis (includes dipstick [pH, specific gravity, glucose, protein, ketones, and blood] and microscopic examination [sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria])
- Serum pregnancy test for women of childbearing potential, including women who have had a tubal ligation

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

  HBV DNA should be obtained prior to enrollment 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 enrollment if patient tests positive for anti-HCV.
- HIV testing

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

4.5.6.2 Treatment (Local Laboratory)

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

- Hematology: WBC count, RBC count, CBC, hemoglobin, hematocrit, count with differential (neutrophils, eosinophils, basophils, monocytes, and lymphocytes)

- Serum chemistry panel: glucose, BUN or urea, creatinine, sodium, potassium, magnesium, calcium, phosphorus, total bilirubin, ALT, AST, ALP, CPK, and others according to the schedule of activities (see Appendix 1)
- Urine pregnancy test for women of childbearing potential
- Thyroid function test

4.5.6.3 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. Serum samples collected for PK and immunogenicity (anti-drug antibody [ADA]) analysis may be needed for additional PK and ADA assay development and validation, and additional immunogenicity characterization; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed. The schedule for sampling is presented in Appendix 2.

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

- Serum samples for immunogenicity (ADA) assessment

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

  Serum samples will be assayed for atezolizumab concentration with use of a validated immunoassay.
- Plasma samples for PK analysis

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

[redacted]

- Blood sample for DNA extraction to enable analysis via next-generation sequencing (NGS) and/or optional whole genome sequencing (WGS)
- Tumor tissue sample collected during the study for exploratory research on biomarkers (see Table 2) and for DNA extraction to enable analysis via NGS

[redacted]

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

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

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

- Plasma and serum samples collected for PK analysis and/or immunogenicity analysis will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Optional blood samples collected for WGS will be stored until they are no longer needed or until they are exhausted.
- Blood, plasma, peripheral blood mononuclear cell, urine, and tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

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

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

4.5.7 Samples for Optional Whole Genome Sequencing

At participating sites, blood samples will be collected for DNA extraction to enable WGS [redacted] The blood samples may be sent to one or more laboratories for analysis.

Collection and submission of WGS samples is contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not

been granted approval for WGS sampling, this section of the protocol (Section 4.5.7) will not be applicable at that site.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. [redacted]

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

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

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

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

4.5.8 Left Ventricular Ejection Fraction

For patients receiving cobimetinib, evaluations of LVEF are required.

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

- Screening
- Day 1 of Cycle 2 ($\pm$1 week)
- At least every 3 months or as clinically indicated
- 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.

- After restarting treatment with a dose reduction of cobimetinib

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

Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF assessment. Evaluation of LVEF must be performed using the same method (ECHO or MUGA scan) for each patient. It is strongly encouraged that the same laboratory and operator perform each ECHO or MUGA scan for each individual patient. Investigators must be aware of local institution regulations regarding repeat MUGA scans.

4.5.9 Ophthalmologic Examinations

Patients receiving cobimetinib are required to undergo ophthalmologic examinations because of the risk of serous retinopathy.

An ophthalmologic examination must be performed at the following timepoints:

- Screening
- Day 1 of Cycle 2 ($\pm$1 week)
- Day 1 of Cycles 5, 8, and 11 (every three treatment cycles; $\pm$2 weeks)
- Day 1 of Cycles 15, 19, and 23 (every four treatment cycles; $\pm$2 weeks)
- Day 1 of Cycles 29, 35, 41, 47, and so on (every six treatment cycles; $\pm$2 weeks)
- Treatment discontinuation visit

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

The objective of baseline ophthalmologic examination is to evaluate for evidence of retinal pathology. Ophthalmologic examination must be performed by a qualified optometrist or ophthalmologist.

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Disease progression (see Section 3.1.1 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-specified anti-cancer therapy
- 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 and patients will remain in the study for safety follow-up.

Patients who discontinue study treatment prematurely will not be replaced.

4.6.2 Patient Discontinuation from Study

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

- Patient withdrawal of consent at any time
- 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. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

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

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

The safety plan is based on results from nonclinical studies, completed and ongoing clinical studies, and published data on similar molecules. Refer to the Atezolizumab Investigator's Brochure for a complete summary of atezolizumab 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. Refer to the Cobimetinib Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients who participate in this study. 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 two different study drugs as the toxicities and management guidelines are distinct for the two different drugs. Refer to the specific guidelines for each drug individually.

5.1 SAFETY PLAN

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

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2 –5.6.

5.1.1 Risks Associated with Cobimetinib

Information related to risks attributed to cobimetinib is based on safety data from Studies GO28141 and NO25395 (cobimetinib and vemurafenib) and Study MEK4592g (cobimetinib monotherapy). For additional information regarding clinical safety, refer to the current Cobimetinib Investigator's Brochure.

5.1.1.1 Important Identified Risks Associated with Cobimetinib

5.1.1.1.1 Hemorrhage

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

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

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

Instructions for dose modification for hemorrhagic events are included in Section 5.1.3.4.

5.1.1.1.2 Serous Retinopathy

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

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

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

Guidelines for management of patients who develop Grade ≥ 2 visual disorders or retinopathy are provided in Section 5.1.3.

5.1.1.1.3 Left Ventricular Dysfunction

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

Left ventricular dysfunction has been characterized in Study GO28141. The study incorporated prospective serial LVEF evaluations in all patients. With active surveillance, measured reductions in LVEF were observed more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (8.5% vs. 3.7%, respectively, of Grade 2 or 3 decreased LVEF). Of the patients treated with cobimetinib plus vemurafenib, 2 patients (0.8%) had symptomatic reduction in LVEF and the remaining patients were asymptomatic. Most LVEF reduction events in patients treated with cobimetinib plus vemurafenib improved or resolved with management according to dose modification guidelines (see Section 5.1.3).

5.1.1.1.4 Rhabdomyolysis and Creatine Phosphokinase Elevations

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

In Study GO28141, elevated CPK was reported as an adverse event more frequently in patients treated with cobimetinib plus vemurafenib (32.4% all grades, 11.3% Grade ≥3 events) than placebo plus vemurafenib (8.1% all grades, no patients with Grade ≥3 events).

CPK will be monitored at baseline and monthly during treatment or as clinically indicated. Instructions for dose modification for elevated CPK and rhabdomyolysis are included in Section 5.1.3.

5.1.1.1.5 Pneumonitis

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

5.1.1.2 Potential Risks Associated with Cobimetinib

5.1.1.2.1 Liver Laboratory Abnormalities and Severe Hepatotoxicity

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

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

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

5.1.1.2.2 Impaired Female Fertility

There is a potential for effects on fertility based on results from nonclinical studies.

Although no dedicated fertility studies have been conducted with cobimetinib in animals, degenerative changes observed in reproductive tissues included increased apoptosis and 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 treatment.

5.1.1.2.3 Teratogenicity and Developmental Toxicity

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

5.1.1.3 Other Risks with Cobimetinib

5.1.1.3.1 Rash

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

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

5.1.1.3.2 Gastrointestinal Toxicity

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

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

Nausea and vomiting have been reported in association with cobimetinib. Most nausea and vomiting events were considered to be non-serious and of low severity grade. In Study GO28141, nausea and vomiting events were reported more frequently in the active cobimetinib arm than the control arm (nausea, 41.3% vs. 25.2%; vomiting, 24.3% vs. 12.6%). However, of the 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 events and none were reported for vomiting.

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

5.1.1.3.3 Hypersensitivity

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

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

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

5.1.2 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as IRRs and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis*, and nephritis*. In addition, systemic immune activation 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.

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 Management of Patients Who Experience Specific Adverse Events

5.1.3.1 Cobimetinib Dose Modifications

Cobimetinib dose modifications are provided in Table 4.

Table 4 Recommended Cobimetinib Dose Modifications

Grade (NCI CTCAE v4.0)	Recommended Cobimetinib Dose
Grade 1 or Grade 2 (tolerable)	No dose reduction. Maintain cobimetinib at the same dose of 60 mg QD (3 tablets).
Grade 2 (intolerable) or Grade 3 or 4 (any)	
First appearance	Interrupt treatment until Grade ≤ 1, restart treatment at 40 mg QD (2 tablets).
Second appearance	Interrupt treatment until Grade ≤ 1, restart treatment at 20 mg QD (1 tablet).
Third appearance	Consider permanent discontinuation.

NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; QD = once a day.

Note: Cobimetinib dose re-escalation is permitted on a case-by-case basis after discussion with the Medical Monitor or [redacted] *designee.*

5.1.3.2 Atezolizumab Dose Modifications

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

5.1.3.3 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, 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.

5.1.3.4 Guidelines for Management of Patients Who Experience Adverse Events

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

Refer to Table 5 for management of cobimetinib- and atezolizumab-specific toxicities, including gastrointestinal toxicity, hepatotoxicity, dermatologic toxicity, pulmonary toxicity, potential eye toxicity, LVEF reduction, rhabdomyolysis and elevated CPK, hemorrhage, and systemic immune activation. Refer to Appendix 8 for detailed management guidelines for atezolizumab-specific adverse events.

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab)

Event	Action to Be Taken
General guidance for dose modifications and treatment delays and discontinuation	• There will be no dose modifications for atezolizumab. • If atezolizumab is withheld and corticosteroids are initiated for an atezolizumab-related toxicity, corticosteroids must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. [a, b] The dose of cobimetinib can be reduced by 20 mg (1 dose level) up to 2 times (i.e., from 60 mg to 40 mg and then from 40 mg to 20 mg). If further dose reduction is indicated after two dose reductions, the patient must discontinue cobimetinib but may continue treatment with atezolizumab at the investigator's discretion. • If atezolizumab is discontinued, treatment with cobimetinib may be continued at the investigator's discretion and after discussion with the Medical Monitor. • If cobimetinib is withheld for > 28 days because of toxicity, the patient should be discontinued from cobimetinib, unless resumption of treatment is approved by the Medical Monitor after discussion with the investigator.
IRRs, anaphylaxis, and hypersensitivity reaction	• Guidelines for management of IRRs are provided in Appendix 8. • For anaphylaxis precautions, see Appendix 7. • For severe hypersensitivity reactions, permanently discontinue all study treatment.

IRR = infusion-related reaction.

[a] 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.

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

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

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

GI = gastrointestinal; LLN = lower limit of normal.

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea, Grade 2 (intolerable) or Grade 3	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 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 GI specialist for evaluation and confirmatory biopsy if symptoms persist for >7 days.

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

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

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

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

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 2	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 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 3	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.

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

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

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

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

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

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

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

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

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

Event	Action to Be Taken
Dermatologic toxicity	
General guidance	• A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.
Dermatologic event, Grade 1 or 2	• Continue atezolizumab and cobimetinib. • Initiate supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve, consider treatment with higher-potency topical corticosteroids. • For Grade 2 rash, consider referral to dermatologist. **Acneiform rash:** • Consider topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) as clinically indicated.
Dermatologic event, Grade 3	• Withhold atezolizumab and cobimetinib. • Refer patient to dermatologist. A biopsy should be performed if appropriate. • Consider initiating treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 2 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib. [a, b] • Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c] • If event resolves to Grade 2 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. **Acneiform rash:** • Consider continuation of topical corticosteroids (e.g., 2.5% alclometasone) and oral antibiotics (e.g., minocycline, doxycycline, or antibiotics covering skin flora) when restarting cobimetinib.
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor. [c]

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

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

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

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

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

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

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

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

[c] Atezolizumab may be withheld for a period of time beyond 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.

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

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

LFT = liver function test; TNF-α = tumor necrosis factor–alpha; ULN = upper limit of normal.

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

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

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

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

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

BAL = bronchoscopic alveolar lavage; IVIg = intravenous immunoglobulin.

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

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

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

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

Event	Action to Be Taken
Ocular toxicity	
General guidance	• An ophthalmologist should evaluate visual complaints. • Uveitis or episcleritis and other immune–mediated ocular disease may be associated with atezolizumab and may be treated with topical corticosteroid eye drops. Atezolizumab should be permanently discontinued for immune-related ocular event that is unresponsive to local immunosuppressive therapy. • Serous retinopathy is associated with cobimetinib. In clinical trials, most events were Grade 1 (asymptomatic) or 2 (symptomatic). Most events in clinical trials resolved or improved to asymptomatic Grade 1 following dose interruption or reduction. If serous retinopathy is diagnosed, cobimetinib should be withheld until visual symptoms improve to Grade ≤ 1. Serous retinopathy can be managed with treatment interruption, dose reduction, or treatment discontinuation. • RVO has been reported in patients treated with MEK inhibitors other than cobimetinib.
Serous retinopathy Severity grade assessment based on NCI CTCAE v4.0 "Eye Disorders–Other" scale [a, b, c, d]	**Serous retinopathy, Grade 1 [a] or 2 [b] (tolerable):** • Continue cobimetinib and atezolizumab without dose change. • Follow the monitoring schedule **Serous retinopathy, Grade 2 [b] (intolerable) or Grade 3 or 4:[c, d]** • Interrupt cobimetinib until Grade ≤ 1. • Continue atezolizumab as clinically indicated. • Consult ophthalmology and undergo complete ophthalmologic examination, which includes visual acuity testing, intra-ocular pressure measurements, slitlamp ophthalmoscopy, indirect ophthalmoscopy, visual field, and OCT. Consider a fluorescein angiogram and/or indocyanine green angiogram, if clinically indicated. • Follow the monitoring schedule detailed in Section 4.5.9. • The dose of cobimetinib should be reduced by one dose level when restarting. • Consider permanent discontinuation of cobimetinib if serous retinopathy recurs despite two dose level reductions.

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

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

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

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

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

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

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

RVO = retinal vein occlusion.

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

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

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

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

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

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events (Cobimetinib and Atezolizumab) (cont.)

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

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

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

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

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and 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 National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 [NCI CTCAE v4.0]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

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

- Severe hepatic events

  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)

  Hepatitis, including AST or ALT $> 10 \times$ ULN
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Pneumonitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hypothyroidism or hyperthyroidism
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome, myasthenia gravis, and meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, systemic inflammatory response syndrome, or systemic immune activation

- Ocular toxicities
    - Uveitis or retinitis
    - Serous retinopathy, including events of retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment, and central serous chorioretinopathy
    - Retinal vein occlusion
- Myositis
- Cardiac disorders
    - Grade ≥ 2 atrial fibrillation, myocarditis, or pericarditis
    - Symptomatic heart failure or Grade ≥ 3 LVEF reduction
- Vasculitis
- Rhabdomyolysis, Grade ≥ 3 CPK elevation, or myopathies
- Grade ≥ 3 hemorrhage or any grade cerebral hemorrhage
- Grade ≥ 3 rash
- Grade ≥ 3 diarrhea
- Colitis

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study drug.

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 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE v4.0.

Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

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

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

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

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

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

5.3.5.8 Deaths

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

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Events 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 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 or immune-modified RECIST. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

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

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

  The patient has not experienced an adverse event

  Hospitalization due solely to progression of the underlying cancer

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

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted], M.D. (Primary)

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical

Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 30 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

Instructions for reporting serious adverse events that occur >30 days after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of 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. 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 cobimetinib. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to 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

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

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

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

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

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

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

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

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

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

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

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

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

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

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

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 30 days after the last dose of study drug), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF. In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- Cobimetinib Investigator's Brochure
- Atezolizumab Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This study is designed to explore the preliminary efficacy, safety, pharmacokinetics, immunogenicity, and biomarker of cobimetinib plus atezolizumab in seven patient cohorts with advanced solid tumors, including SCCHN, urothelial carcinoma, and RCC.

The primary analysis will be conducted once all patients in a particular cohort have been followed for a clinically meaningful period of time of approximately 16 weeks. The statistical results will be summarized and presented by cohort.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is for hypothesis generation only. No formal hypothesis testing or inference analysis is planned; hence, no power analysis is conducted. Approximately 20 patients are planned to be enrolled in Cohorts 1–6 with possible expansion up to approximately 40 patients in each cohort. Approximately 12 patients are planned to be enrolled in Cohort 7 (biopsy cohort). Therefore, up to approximately 250 patients in total are planned to be enrolled in this study.

[redacted]

6.2 SUMMARIES OF CONDUCT OF STUDY

For all enrolled patients, enrollment, eligibility violations, and patient disposition will be summarized. Study treatment administration will be summarized for treated patients only.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patient demographics, baseline, and disease characteristics will be summarized descriptively using mean (standard deviation), median (interquartile range), or number and percent.

6.4 EFFICACY ANALYSES

The analysis population for efficacy will include all patients enrolled in the study who received at least one dose of both study drugs.

6.4.1 Primary Efficacy Endpoint

ORR is the primary endpoint for all cohorts. Objective response is defined as a CR or a PR on two consecutive tumor assessments $\geq$4 weeks apart, as determined by the investigators using RECIST v1.1.

The number of patients included in the analysis and the number of patients with a CR or a PR will be summarized by cohort. The cohort-specified ORR and the corresponding 95% Clopper-Pearson CIs will be calculated.

6.4.2 Secondary Efficacy Endpoints

OS, defined as the time from enrollment to death from any cause, will be analyzed for all cohorts. The cohort specific results will be summarized as median survival times obtained using Kaplan-Meier methods and their corresponding 95% CIs for median constructed using the Brookmeyer and Crowley method.

PFS, DOR, and DCR will be summarized. PFS is defined as the time from enrollment to the first occurrence of disease progression as determined by the investigator(s) using RECIST v1.1 or to death from any cause, whichever occurs first. DOR is defined as the time from the first occurrence of a documented, confirmed objective response to disease progression as determined by the investigator using RECIST v1.1 or to death from any cause, whichever occurs first. DCR is defined as the proportion of patients with a CR, a PR, or stable disease at 16 weeks as determined by the investigator using RECIST v1.1. For PFS and DOR, cohort-specified median PFS and DOR will be obtained using Kaplan-Meier method, and the corresponding 95% CIs for median will be constructed using the Brookmeyer and Crowley method. Cohort-specified DCR will be summarized as frequency and percentages and the corresponding 95% Clopper-Pearson Cis will be reported.

6.4.3 Exploratory Efficacy Endpoints

For patients with measurable disease in each cohort, ORR, PFS, DOR, and DCR as determined by the investigator according to immune-modified RECIST will be analyzed using the same methods as described above.

6.5 SAFETY ANALYSES

The safety population will include all enrolled patients who received at least one dose of study drug. The number of patients for safety population will be specified by cohort.

Adverse events, changes in vital signs, changes in laboratory test results, and study treatment exposure will be summarized by cohort.

For each cohort, the occurrence of all adverse events observed during or after the first study drug dose, their severity and verbatim description will be summarized by mapped terms and appropriate thesaurus levels and graded according to NCI CTCAE v4.0. In addition, the incidence and percentages as well as exposure adjusted event rates will be reported for serious adverse events, severe adverse events (Grades ≥ 3), adverse events of special interest, and adverse events leading to study drug discontinuation or interruption within each cohort. If a patient experiences the same event several times, the occurrence of the event will be counted once at the maximum severity. The causality of all adverse events in relation to the study drug as determined by investigator will also be summarized.

For each cohort, study drug exposure, including treatment duration, number of doses, and dose intensity, will be summarized descriptively.

All deaths and causes of death will be reported as frequency and percentages.

Relevant laboratory data and vital signs will be summarized over time. Abnormal values for laboratory and vital sign data will be identified and summarized.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients with sufficient data to enable estimation of key parameters, with patients grouped according to treatment received.

PK samples will be collected in this study as outlined in Appendix 2. Cobimetinib and atezolizumab maximum and minimum concentration data (C_{max} and C_{min}, respectively) will be tabulated and summarized by study day, as data permit. Summary statistics will include mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation, as appropriate.

Additional PK and pharmacodynamic analyses will be conducted, as appropriate, based on available data.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with any ADA assessment, with patients grouped according to treatment received.

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

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

6.8 BIOMARKER ANALYSES

Descriptive statistics will be used to explore the biomarkers and their relations to response or escape of combined treatment in patients, [redacted]

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered on the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve

as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal

Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

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

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IIND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the

course of the study and for 1 year after completion of the study (i.e., see definition of end of study in Section 3.2.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This study is sponsored by F. Hoffmann-La Roche Ltd. Approximately 20 study centers will participate in this study globally and enroll up to approximately 250 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 enroll patients in the study. For patients not previously tested for tumor mutational status, testing will be performed at screening. Plasma and serum will be sent to a central laboratory for analysis and sample storage. Routine sample analysis will be performed by an accredited external vendor or the center's local laboratory; central and local laboratory ranges will be collected.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to

eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Assessment/Procedure (Day Window)	Screening [a]	Cycle 1		Cycle 2		Cycle ≥ 3		Tx Discon [b]	ADA Visit [c]	Survival FU [d]
	Days –28 to –1	Day 1 (±3)	Day 15 (±3)	Day 1 (±3)	Day 15 (±3)	Day 1 (±3)	Day 15 (±3)	< 30 Days *(+3)* after Last Dose	> 90 *(−3)* Days after Last Dose	Every 3 Months *(±3 days)*
Informed consent [e]	x									
Demographic data	x									
Medical and cancer history	x									
Vital signs [f, g]	x	x	x	x	x	x	x	x		
ECOG Performance Status	x	x		x		x				
Weight	x									
Height	x									
Complete physical examination	x							x		
Limited physical examination		x [h]		x		x				
Hematology [i]	x	x		x		x		x		
Coagulation (INR and aPTT)	x									
PK sample for cobimetinib		Refer to Appendix 2								
PK and ADA samples for atezolizumab		Refer to Appendix 2								
Chemistry [j]	x	x		x		x				

Appendix 1
Schedule of Activities (cont.)

Assessment/Procedure (Day Window)	Screening [a]	Cycle 1		Cycle 2		Cycle ≥ 3		Tx Discon [b]	ADA Visit [c]	Survival FU [d]
	Days –28 to –1	Day 1 (±3)	Day 15 (±3)	Day 1 (±3)	Day 15 (±3)	Day 1 (±3)	Day 15 (±3)	< 30 *(+3)* Days after Last Dose	>90 Days *(−3)* after Last Dose	Every 3 Months *(±3 days)*
ECHO or MUGA scan [k]	x			x		x [k]				
Optional WGS		x								
Tumor assessments [l]	x	Tumor assessments occur every 8 weeks.								
Serology [m]	x									
Thyroid function [n]	x	x		x		x [n]		x		
Ophthalmologic exam [o]	x			x		x [o]		x		
Pregnancy test [p]	x	x		x		x [p]		x		
Urinalysis [q]	x									
Concomitant medications [r]	x [r]	x [r]		x		x		x [r]		
Adverse events [s]	x [s]	x [s]	x	x	x	x	x	x [s]		x [s]
Tumor biopsy (Cohorts 1–6) [t]	x		x					x		
Tumor biopsy (Cohort 7 only)	x [u]		x [v]		x [w]			x [x]		
Biomarker blood samples [y]		x	x	x		x		x		
Biomarker PBMC samples [y]		x	x	x		x		x		
Biomarker plasma samples [y]		x				x		x		
Biomarker urine samples [y, z]		x				x		x		
Atezolizumab administration [aa]		x [bb]	x	x	x	x [aa]	x			
Dispense cobimetinib [cc]		x		x		x				
Survival and anti-cancer therapy follow-up										x [d]

Appendix 1
Schedule of Activities (cont.)

ADA = anti-drug antibody; Discon = discontinuation; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; FU = follow-up; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IRR = infusion-related reactions; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; Tx = treatment; WGS = whole genome sequencing.

Notes: All assessments should be performed within ±3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. On treatment days, pre-infusion laboratory samples should be drawn 0–4 hours before the start of infusion, and post-infusion laboratory samples should be drawn 0–30 minutes after the end of infusion, unless otherwise specified.

Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit *within* 30 (+ 3) days *after the last dose*. The visit at which response assessment shows progressive disease may be used as the study discontinuation visit.

[c] Visit not specified by the protocol. Assessments should be performed as clinically indicated.

[d] Required follow-up information will be collected via telephone calls and/or clinic visits every 3 months until death, loss to follow-up, or study termination by the Sponsor.

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained up to 28 days before initiation of study treatment.

[f] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] Vital signs will be recorded within 60 minutes prior to the infusion and otherwise as clinically indicated during or after the infusion.

[h] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. If physical examinations are assessed within 7 days of the Day 1, Cycle 1 visit, they do not have to be repeated on Day 1.

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

[j] Chemistry panel (serum) includes sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, magnesium, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, CPK, and uric acid. Albumin will be assessed at screening only.

Appendix 1
Schedule of Activities (cont.)

[k] Evaluation of LVEF by ECHO or MUGA scan must be performed at the following timepoints only for patients on cobimetinib: at screening; on Day 1 of Cycle 2 (±1 week); on Day 1 of Cycles 5, 8, 11, 14, 17, and every 3 treatment cycles thereafter (i.e., Cycles 20, 23, 26, etc.; ±2 weeks for each); and at treatment discontinuation visit evaluation (unless evaluation performed within the previous 12 weeks showed no clinically significant findings and/or changes from baseline).

[l] Tumor assessments will continue until disease progression per RECIST v1.1 or immune-modified RECIST unless patient continued treatment, loss of clinical benefit (for patients who continue treatment after disease progression according to RECIST v1.1 or immune-modified RECIST), withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first. Patients who discontinue treatment for reasons other than disease progression (e.g. toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first.

[m] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the study. HBV serology will include HBsAg, antibodies against HBsAg, and total HBcAb antibody (anti-HBcAb). HBV DNA should be obtained prior to enrollment 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 enrollment if patient tests positive for anti-HCV.

[n] Thyroid-function testing (thyroid-stimulating hormone, free T3 [or total T3 for sites where free T3 is not performed], and free T4) collected on Day 1 of Cycles 1–5, and every 2 cycles thereafter (i.e., Day 1 of Cycles 7, 9, 11, etc.) for patients on atezolizumab.

[o] Ophthalmologic examination must be performed at the following timepoints only for patients on cobimetinib: at screening; on Day 1 of Cycle 2 (± 1 week); on Day 1 of Cycles 5, 8, and 11 (every 3 treatment cycles; ±2 weeks); on Day 1 of Cycles 15, 19, and 23 (every 4 treatment cycles; ±2 weeks); on Day 1 of Cycles 29, 35, 41, 47, and every 6 treatment cycles thereafter (i.e., Cycles 53, 59, 65, etc.; ±2 weeks for each); and at treatment discontinuation visit evaluation (unless evaluation performed within the previous 12 weeks showed no clinically significant findings and/or changes from baseline).

[p] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed on Day 1 (±2 weeks) of every cycle. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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

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

[s] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events or adverse events of special interest considered to be related to study drug or trial-related procedures until a final outcome can be reported.

Appendix 1
Schedule of Activities (cont.)

[t] Biopsy schedule for patients in Cohorts 1–6. Please see different biopsy schedule listed in the table for the biopsy cohort (Cohort 7). Fresh baseline tumor tissue collected during screening (or archival if fresh tumor biopsy cannot be performed); optional on-treatment biopsy at Cycle 1, Day 15 (±5 days); mandatory biopsy at progression if clinically feasible.

[u] Mandatory pre-treatment biopsy

[v] Biopsy Cohort 7, mandatory tumor biopsy done between Days 10 and 14 of Cycle 1.

[w] Biopsy Cohort 7, second (mandatory) on-treatment biopsy will be done during Cycle 2, approximately 4–6 weeks after the first dose of atezolizumab.

[x] Biopsy Cohort 7, optional post-treatment biopsy at the time of radiographic progression.

[y] Biomarkers are collected until Cycle 3, Day 1 (including that visit) and then at treatment discontinuation.

[z] Urine samples will be collected for urothelial carcinoma patients only: screening on Day 1 of Cycle 1; on Day 1 of Cycle 3; and at treatment discontinuation visit only.

[aa] The initial dose of atezolizumab will be delivered over 60 (±15) minutes. If the first infusion is well tolerated, all subsequent infusions will be delivered over 30 (±10) minutes until loss of clinical benefit. Study drug administration may be ±7 days.

[bb] For patients in Cohorts 1–6 only.

[cc] All patients will receive cobimetinib at a dose of 60 mg (three 20-mg tablets) orally once a day on Days 1–21 of each 28-day cycle. At least 7 days off cobimetinib are required prior to starting a new treatment cycle. Cobimetinib should be taken approximately the same time each day, and no later than 4 hours after the scheduled time.

Appendix 2
Schedule of Pharmacokinetic and Immunogenicity Samples

Visit	Timepoint	Sample Type(s)
Day 1 of Cycle 1 (Cohorts 1–6 only)	Prior to atezolizumab infusion	Atezolizumab PK and ADA (serum)
	30 (±10) minutes following end of atezolizumab infusion	Atezolizumab PK (serum)
Day 15 of Cycle 1 (Cohort 7 only)	Prior to atezolizumab infusion	Atezolizumab PK and ADA (serum)
	30 (±10) minutes following end of atezolizumab infusion	Atezolizumab PK (serum)
Day 1 of Cycles 2, 4, 8, 12, and 16	Prior to atezolizumab infusion	Atezolizumab PK and ADA (serum)
Day 15 of Cycle 3	Prior to atezolizumab infusion	Atezolizumab PK and ADA (serum)
	Prior to cobimetinib dose	Cobimetinib PK (plasma)
	30 (±10) minutes following end of atezolizumab infusion	Atezolizumab PK and ADA (serum)
	2–4 hours after cobimetinib dose	Cobimetinib PK (plasma)
Atezolizumab treatment discontinuation visit	At visit	Atezolizumab PK and ADA (serum)
>90 days after last atezolizumab infusion	At visit	Atezolizumab PK and ADA (serum)

ADA=anti-drug antibody; NA=not applicable; PK=pharmacokinetic.

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

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (Eisenhauer et al. 2009), are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

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

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

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

DEFINITION OF NON-MEASURABLE LESIONS

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

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

Cystic Lesions:

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

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

METHODS FOR ASSESSING LESIONS

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

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

CLINICAL LESIONS

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

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new

lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

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

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

ASSESSMENT OF TUMOR BURDEN

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

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

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

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

as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but $<$ 15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$ 10 mm are considered non-pathological and should not be recorded or followed.

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

CALCULATION OF SUM OF DIAMETERS

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

Measuring Lymph Nodes

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

Measuring Lesions That Become Too Small to Measure

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

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

assigned in this circumstance as well and "too small to measure" should also be ticked).

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

Measuring Lesions That Split or Coalesce on Treatment

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

EVALUATION OF NON-TARGET LESIONS

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

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

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

- CR: Disappearance of all target lesions

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

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

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

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

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

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

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

Patients with Non-Measurable Disease Only

For patients with non-measurable disease only, the same general concepts apply as noted above. However, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-measurable 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. 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 PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

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

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Non-Target Lesions Only

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

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

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; 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 measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

REFERENCE

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47. doi: 10.1016/j.ejca.2008.10.026.

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

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

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

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

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

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

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

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

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

DEFINITION OF NON-MEASURABLE LESIONS

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

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

Bone Lesions:

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

Cystic Lesions:

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

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

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

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

CLINICAL LESIONS

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

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

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

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

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

<u>ASSESSMENT OF TUMOR BURDEN</u>

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

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

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

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

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

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

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

NEW LESIONS

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

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

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

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline as a measure of tumor burden. At each subsequent tumor assessment, a sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions plus measurable new lesions (up to five new lesions, with a maximum of two new lesions per organ) that have emerged after baseline. Hence, each net percentage change in tumor burden per assessment accounts for the size and growth kinetics of both old lesions and new lesions as they appear.

Measuring Lymph Nodes

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

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

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

Measuring Lesions That Become Too Small to Measure

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

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

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

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly

coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS AND NON-MEASURABLE NEW LESIONS

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

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

RESPONSE CRITERIA

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

- CR: Disappearance of all lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), taking as reference the baseline sum of diameters, in the absence of CR
- PD: At least a 20% increase in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), taking as reference the smallest sum of diameters on study (including baseline)

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

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

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

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

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

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

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

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

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

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

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions, as well as new lesions, as shown in Table 2.

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

REFERENCES

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Appendix 5
Eastern Cooperative Oncology Group Performance Status Scale

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

Appendix 6
Preexisting Autoimmune Diseases and Immune Deficiencies

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias for whom the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty about autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

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

Appendix 7
Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

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

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

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

PULMONARY EVENTS

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

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

Management guidelines for pulmonary events are provided in Section 5.1.3.4.

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

HEPATIC EVENTS

Immune-related hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Section 5.1.3.4.

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

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

GASTROINTESTINAL EVENTS

Immune-related colitis has been associated with the administration of atezolizumab. Management guidelines for gastrointestinal events are provided in Section 5.1.3.4.

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.

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 1.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and

magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 1 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-related hyperthyroidism. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

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

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

Table 1 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

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

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

Table 1 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-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 2.

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

Table 2 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

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

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

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

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

IMMUNE-RELATED MYOCARDITIS

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 3.

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

Table 3 Management Guidelines for Immune-Related Myocarditis

Event	Management
Immune-related myocarditis, Grade 1	• Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.
Immune-related myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-related myocarditis, Grade 3-4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

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

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

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

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

INFUSION-RELATED REACTIONS

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

Guidelines for medical management of IRRs during Cycle 1 are provided in Table 4. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table 4 Management Guidelines for Infusion-Related Reactions

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

IRR = infusion-related reaction.

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

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

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 5.

Table 5 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.

Table 5 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.

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 Section 5.1.3.4.

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 6.

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

Table 6 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.

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 7.

Table 7 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.

RENAL EVENTS

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 8.

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

Table 8 Management Guidelines for Renal Events

Event	*Management*
Renal event, Grade 1	• *Continue atezolizumab.* • *Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.*
Renal event, Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to renal specialist.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [c]
Renal event, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact Medical Monitor.* • *Refer patient to renal specialist and consider renal biopsy.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

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

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

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