Official Title: Atezolizumab in Combination With Bevacizumab in Patients With Unresectable Locally Advanced or Metastatic Mucosal Melanoma

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PROTOCOL

TITLE:	**ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB IN PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC MUCOSAL MELANOMA**
PROTOCOL NUMBER:	ML41186
VERSION NUMBER:	5
EUDRACT NUMBER:	NA
IND NUMBER:	NA
TEST PRODUCT:	Atezolizumab, Bevacizumab
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
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FINAL PROTOCOL APPROVAL

PROTOCOL AMENDMENT, VERSION 5

Comparison with Version 4:

SUMMARY OF CHANGES

1. Updated the risk associated with atezolizumab (including addition of AEs of special interest for atezolizumab: facial paresis and myelitis) and management guidelines (Section 5.1.1 and Section 5.2.3.1 and Appendix 9) due to the update of safety information for atezolizumab
2. Additional minor changes were made to ensure clarity and consistency.

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PROTOCOL ACCEPTANCE FORM

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

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

PROTOCOL SYNOPSIS

TITLE:	**ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB IN PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC MUCOSAL MELANOMA**
PROTOCOL NUMBER:	ML41186
VERSION NUMBER:	**5**
EUDRACT NUMBER:	NA
IND NUMBER:	NA
TEST PRODUCT:	Atezolizumab, Bevacizumab
PHASE:	Phase II
INDICATION:	Mucosal Melanoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of atezolizumab in combination with bevacizumab (atezo + bev) in patients with unresectable locally advanced or metastatic mucosal melanoma. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Efficacy Objective

- Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Secondary Efficacy Objective

- Progression-free survival (PFS), defined as the time from the date of first treatment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
- Overall survival (OS), defined as the time from the date of first treatment to death from any cause
- Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
- Disease control rate (DCR) (defined as the sum of a complete or partial response or stable disease rates) as determined by the investigator according to RECIST v1.1.

Safety Objective

The primary safety objective for this study is to evaluate the safety of atezolizumab + bevacizumab on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0)
- Changes in vital signs, physical examination findings, and clinical laboratory results during and following study treatment

Study Design

Description of Study

This is an open-label, multicenter, single arm, phase II study exploring the efficacy and safety of atezo + bev in patients with unresectable locally advanced or metastatic mucosal melanoma.

The trial will consist of a Screening Period (Day –28 to −1), a Treatment Period, a Treatment Discontinuation Visit occurring when atezolizumab and bevacizumab are both discontinued for any reason and a Survival Follow-Up Period until death, loss to follow-up, or study termination. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments.

The study is divided into 2 stages. Stage I of the study is completed when 22 patients with measurable disease have been enrolled and completed ORR evaluation. If the number of responders in Stage I is more than 3, another 16 patients may be enrolled to Stage II.

Considering a drop-out rate of 10%, a total number of 25 subjects (if stops at the first stage) or 43 subjects (if runs into the second stage) will need to be enrolled in this study.

Atezolizumab and/or bevacizumab 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 (e.g., LDH level), local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

Patients who transiently withhold or permanently discontinue either atezolizumab or bevacizumab may continue on single-agent therapy as long as the patients are experiencing clinical benefit in the opinion of the investigator.

Number of Patients

The study will enroll 38 subjects that fully evaluable for ORR (approximately 43 patients in total considering 10% dropout rate), including study Stages I and II.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Age ≥ 18 and ≤75 years at time of signing Informed Consent Form
3. Ability to comply with the study protocol, in the investigator's judgment
4. Histologically confirmed unresectable locally advanced(stage III) or metastatic(Stage IV) mucosal melanoma
5. May have received prior systemic treatment or treatment naive at enrollment
6. Measurable disease per RECIST v1.1
7. ECOG Performance Status of 0-1
8. Life expectancy ≥ 12 weeks
9. Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
    1) ANC ≥ 1.5×10^9/L (1500/μL) without granulocyte colony-stimulating factor support, G-CSF may be administered until 2 weeks prior to Cycle 1, Day 1
    2) Lymphocyte count ≥ 0.5×10^9/L (500/μL)
    3) Platelet count ≥ 100×10^9/L (100,000/μL) without transfusion, transfusion may be administered until 2 weeks prior to Cycle 1, Day 1
    4) Hemoglobin ≥ 90 g/L (9 g/dL)
        i. Patients may be transfused to meet this criterion.

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

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

   ii. Patients with documented liver or bone metastases: ALP ≤ 5 × ULN

6) Serum bilirubin ≤ 1.5 × ULN with the following exception:

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

7) Serum creatinine ≤ 1.5 × ULN

8) Serum albumin ≥ 25 g/L (2.5 g/dL)

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

10. Negative HIV test at screening

11. Negative hepatitis B surface antigen (HBsAg) test at screening

12. Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by quantitative hepatitis B virus (HBV) DNA<500 IU/mL at screening

13. Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

    1) The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

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

    1) Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the final dose of atezolizumab, or 6 months after the final dose of bevacizumab, whichever is longer. Women must refrain from donating eggs during this same period.

    2) 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). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

    3) Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

    4) 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.

15. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:
    1) With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for 6 months after the final dose of bevacizumab. Men must refrain from donating sperm during this same period.
    2) With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of bevacizumab to avoid exposing the embryo.
    3) The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

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

1. Symptomatic or actively progressing central nervous system (CNS) metastases
    1) Asymptomatic patients with treated or untreated CNS lesions are eligible, provided that all of the following criteria are met:
        i. Measurable disease, per RECIST v1.1, must be present outside the CNS.
        ii. The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
        iii. The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment.
        iv. The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anticonvulsant therapy at a stable dose is permitted.
        v. Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
        vi. There is no evidence of interim progression between completion of CNS-directed therapy (if administered) and initiation of study treatment.
    2) Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.
2. History of leptomeningeal disease
3. Uncontrolled tumor-related pain
    1) Patients requiring pain medication must be on a stable regimen at study entry.
    2) Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment.

Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

3) Asymptomatic metastatic lesions that would likely cause functional deficits or 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.

4. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

   1) Patients with indwelling catheters are allowed.

5. Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN)

6. 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, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

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

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

   3) 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:

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

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

      iii. 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

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

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

8. Active tuberculosis

9. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina

   1) Patients with known coronary artery disease, arrhythmias, congestive heart failure not meeting the above criteria must be on a stable medical regimen that is optimized in the

opinion of the treating physician, in consultation with a cardiologist if appropriate. Baseline evaluation of left ventricular ejection fraction (LVEF) should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease or where low LVEF is suspected

2) Patients with known LVEF < 40%

10. 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
11. History of malignancy other than melanoma within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>$ 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
12. 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
13. Prior allogeneic stem cell or solid organ transplantation
14. 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
15. Current treatment with anti-viral therapy for HBV
16. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
17. Current, recent (within 28 days prior to initiation of study treatment) or planned treatment with any other investigational agent or participation in another clinical study with anti-cancer therapeutic intent
18. Prior treatment with immune checkpoint agonists, including CD137 agonists and TLR9 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
19. Prior treatment with anti-angiogenic therapies
20. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment as well as prior cancer vaccines and cellular immunotherapy
21. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents, as well as T and B cell targeting biologic agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

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

2) Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

22. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
23. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
24. Known allergy or hypersensitivity to any component of the bevacizumab formulation
25. Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of atezolizumab, 6 months after the final dose of bevacizumab
    1) Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
26. Inadequately controlled hypertension (defined as systolic blood pressure $>$ 150 mmHg and/or diastolic blood pressure $>$ 100 mmHg)
    1) Anti-hypertensive therapy to achieve these parameters is allowable.
27. Prior history of hypertensive crisis or hypertensive encephalopathy
28. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Cycle 1, Day 1
29. Patients with a baseline ECG demonstrating a QTc > 460 msec (calculated with use of the Fridericia method)
30. History of Grade ≥ 2 hemoptysis (defined as ≥ 2.5 mL of bright red blood per episode) within 1 month prior to screening
31. History of stroke or transient ischemic attack within 6 months prior to Cycle 1, Day 1
32. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
33. Prophylactic or therapeutic use of low molecular weight heparin (e.g., enoxaparin), direct thrombin inhibitors, or warfarin are permitted, provided, where appropriate anticoagulation indices are stable. Patients should have been on a stable dose (for therapeutic use) for at least 2 weeks (or until reaching steady state level of the drug) prior to the first study treatment
34. Current or recent (< 10 days prior to initiation of study treatment) use of aspirin (> 325 mg/day), clopidogrel (> 75 mg/day) or treatment with dipyramidole, ticlopidine, or cilostazol
    1) Note: The use of full-dose oral or parenteral anticoagulants for therapeutic purpose is permitted as long as the INR and/or aPTT is within therapeutic limits (according to institution standards) within 7 days prior to initiation of study treatment and the patient has been on a stable dose of anticoagulants for ≥ 2 weeks prior to initiation of study treatment. Prophylactic use of anticoagulants is allowed.
35. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 calendar days prior to the first dose of bevacizumab

36. History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to Cycle 1, Day 1
37. Clinical signs or symptoms of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding
38. Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
39. Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
40. Proteinuria, as demonstrated by urinalysis or $>$ 1.0 g of protein in a 24-hour urine collection
    1) All patients with $\geq$ 2+ protein on urinalysis at baseline must undergo a 24-hour urine collection for protein.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs. The end of the study is expected to occur 20 months after the last patient is enrolled. In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 2 years and 9 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

The dose of atezolizumab in this study will be 1200 mg administered by intravenous infusion every 3 weeks.

The dose of bevacizumab in this study will be 7.5 mg/kg administered by intravenous infusion every 3 weeks.

Statistical Methods

The efficacy analyses will be performed on the Full Analysis Set (FAS) population, defined as all enrolled patients who receive any amount of study treatment and evaluable for efficacy endpoints.

The safety analysis will be performed on the safety-evaluable population, defined as all enrolled patients who receive at least one dose of any study treatment.

Other analyses (Demography, Baseline Characteristics, .etc.) will be performed on the basis of all enrolled patients (the ITT population), regardless of whether they receive any assigned study drug.

Primary Analysis

The primary efficacy endpoint is ORR, as assessed by the Investigator using RECIST, v1.1.

Number and percentage of responders with corresponding Clopper-Pearson 95% confidence intervals will be provided.

Estimates for the time-to-event variables, such as PFS, OS, DOR, will be obtained by using the Kaplan-Meier (KM) approach together with associated 95% CI.

Determination of Sample Size

The sample size calculation was based on a Simon two-stage design, and the primary endpoint was ORR (H_0 = 20%, H_1 = 40%). Two-sided alpha is set to be 0.05 and statistical power is set to be 80%.

22 fully evaluable subjects will be included at the first stage, and if the study continues another 16 fully evaluable subjects will be included in the second stage. Thus, considering a drop-out rate of 10%, a total number of 25 subjects (if stops at the first stage) or 43 subjects (if runs into the second stage) will need to be finally enrolled in this study.

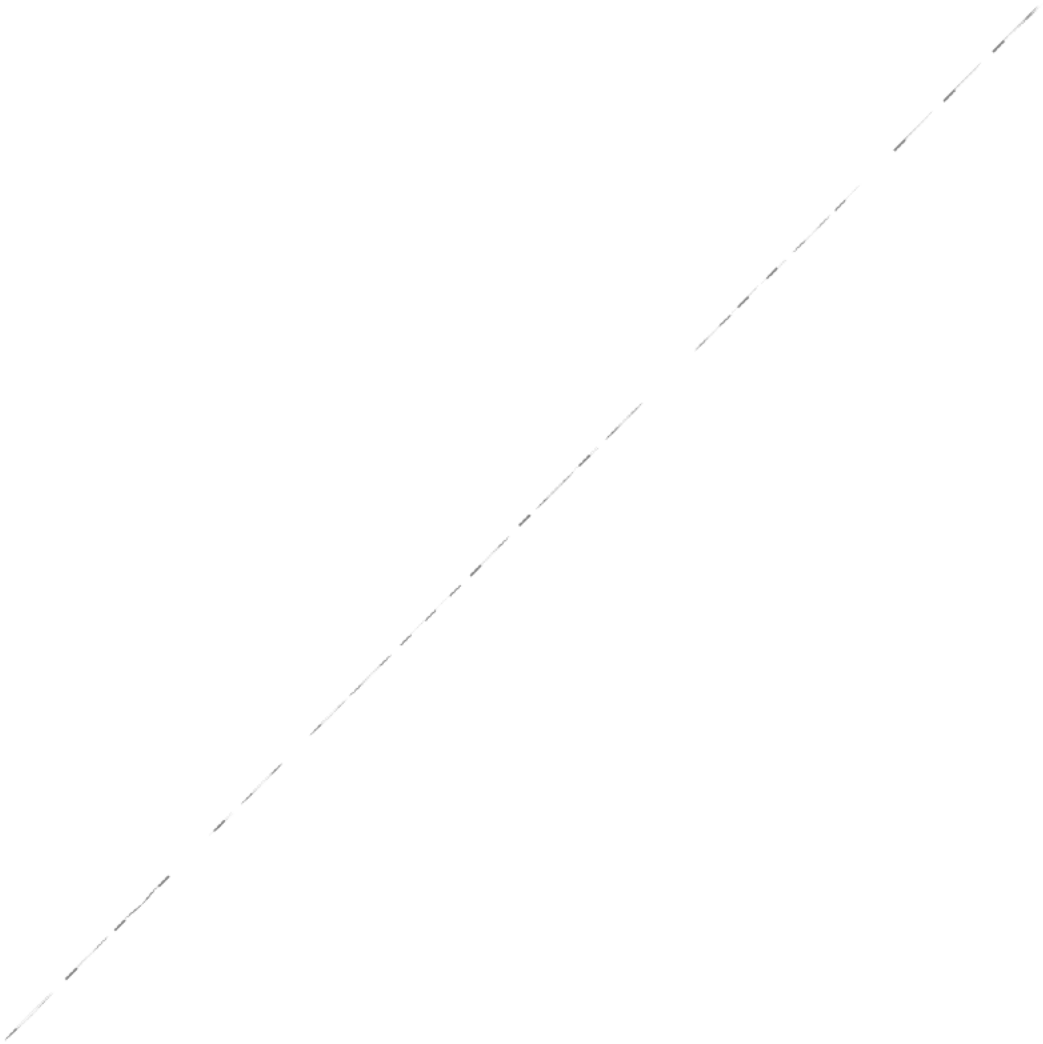
Interim Analyses

One interim analysis is planned. The interim analysis will be performed for futility at the time of 22 subjects completes ORR evaluation. According to preplanned stopping rules of Simon 2-

stage design, further testing of Atezolizumab and Bevacizumab would be halted if the number of subjects that respond in the first evaluable 22 patients (stage 1) is less or equal than 3. This study has a probability of 33.2% to terminate at the first stage. The optimal or minimax are not used because of their high probability of termination at the first stage.

At the end of the study, if more than 12 patients out of 38 patients have responses, we can conclude that the therapy is statistically significant in improving the ORR in curing mucosal melanoma.

The sample size and stopping rule are calculated with SAS 9.4



LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event Of Special Interest
ALM	Acral Lentiginous Melanoma
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATE	Arterial Thromboembolism
BRAF	V-Raf Murine Sarcoma Viral Oncogene Homolog B1
BUN	Blood Urea Nitrogen
CHF	Congestive Heart Failure
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CRC	Carcinoma Of The Colon Or Rectum
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria For Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
DCR	Disease Control Rate
DLT	Dose Limited Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration Of Response
EC	Ethics Committee
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EORTC	European Organisation For Research And Treatment Of Cancer
EOC	Epithelial Ovarian Cancer
EU	European Union
FAS	Full Analysis Set
FTC	Fallopian Tube Cancer

GBM	Glioblastoma Multiforme
GI	Gastrointestinal
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IC	Tumor-Infiltrating Immune Cell
ICF	Informed Consent Form
ICH	International Council For Harmonisation
IgG1	Immunoglobulin G1
IL-2	Interleukin 2
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
IV	Intravenous
LDH	Lactate Dehydrogenase
LPLV	Last Patient, Last Visit
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary For Regulatory Activities
MEK	Mitogen-Activated Protein Kinase (MAPK) Or Extracellular Signal—Regulated Kinase (ERK) Kinase
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PPC	Primary Peritoneal Cancer
PR	Partial Response
Q3W	Every 3 Weeks
RBC	Red Blood Cell

RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SD	Stable Disease
TNF	Tumor Necrosis Factor
ULN	Upper Limit Of Normal
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell
5-FU	5-Fluorouracil

1. BACKGROUND

1.1 BACKGROUND ON MUCOSAL MELANOMA

Melanoma most commonly arises from melanocytes present in cutaneous primary locations (cutaneous melanoma), but it can also arise from melanocytes located within the mucosal surfaces of the body (mucosal melanoma) and the uvea of the eye (uveal melanoma)(Kuk, et al. 2016).

Worldwide, about 232,100 (1.7%) cases of all newly diagnosed primary malignant cancers (excluding non-melanoma skin cancer) are cases of cutaneous melanoma, and about 55 500 cancer deaths (0.7% of all cancer deaths) are cases of cutaneous melanoma. The incidence and mortality rates of cutaneous melanoma differ widely by country. In 2012, the age-standardized (world standard population) incidence of cutaneous melanoma ranged from 0.2 per 100 000 person-years in South-East Asia to 7.7 per 100 000 person-years in the Americas. In 2012, the estimated age-standardized mortality rates of cutaneous melanoma ranged from 0.1 per 100 000 person-years in South-East Asia to 1.5 per 100 000 person-years in the European Union (EU). In China, the age-standardized incidence and mortality of cutaneous melanoma is 0.6 and 0.3 per 100 000 person-years, respectively (GLOBOCAN 2012).

There have been few epidemiologic and natural history studies about mucosal melanoma, primarily because of its extremely low incidence as 1% of all melanoma patients in Caucasian (McLaughlin, et al. 2005). But in Asia, it is the second common subtype after acral lentiginous melanoma (ALM), with a percentage incidence of 22–27% (Chi, et al 2011 Bai, et al. 2017).

Because of its hidden location and rich vascularization, mucosal melanoma is more often diagnosed at an advanced stage of disease and is associated with worse outcomes (McLaughlin, et al. 2005). While the 5-year overall survival rate for cutaneous melanoma is 80%, the rate for mucosal melanoma is only 25% (Chang AE, et al. 1998). In addition to having an inferior survival from the time of diagnosis, patients with mucosal melanoma

may have a poorer stage-matched survival than other melanoma subtypes from the time of development of clinical metastatic disease (Shoushtari, et al. 2017).

1.2 TREATMENT FOR MUCOSAL MELANOMA

Since 2011, the treatment of cutaneous melanoma has been revolutionized by targeted therapy against BRAF and MEK and immunotherapy against immune-checkpoints.

Although National Comprehensive Cancer Network (NCCN) guidelines suggest that the treatment of mucosal melanoma can refer to cutaneous melanoma, responses to treatment differ significantly between mucosal and cutaneous melanoma.

In a pooled analysis of 889 patients from 5 studies who received nivolumab monotherapy in clinical studies, median progression-free survival was 3.0 months (95% Confidence Interval (CI), 2.2 to 5.4 months) and 6.2 months (95% CI, 5.1 to 7.5 months) for mucosal and cutaneous melanoma, with objective response rates (ORR)of 23.3% (95% CI, 14.8% to 33.6%) and 40.9% (95% CI, 37.1% to 44.7%), respectively (D'Angelo, et al. 2016).

Results from other studies also showed the efficacy of immune-checkpoint inhibitors is inferior in mucosal melanoma than in cutaneous melanoma (Del vecchio, et al.2014 Shoushtari, et al 2016 Butler, et al. 2017).

BRAF mutation rate is relatively low as 10.7% in mucosal melanoma (Bai, et al. 2017).There have been few reports of BRAF inhibitors specifically in this population. In one study, ORR was 20% with PFS and overall survival (OS) of 4.4 (95%CI 0.8-12.7) months and 8.2 (95%CI 6.6-19.9) months, respectively (Bai, et al. 2017).

KIT (commonly known as c-KIT) mutations have been associated most commonly with mucosal and acral subtypes of melanoma (Curtin, et al. 2006). Phase II studies testing imatinib in patients with KIT-mutation or KIT amplified metastatic melanoma (46%-71% mucosal) demonstrated 20% to 30% ORR (Guo, et al. 2011 Carvajal, et al. 2011 Hodi, et al. 2013).

Therefore, alternative treatment options that yield higher responses and enhance PFS and OS remain an important focus of research.

1.3 BACKGROUND ON ATEZOLIZUMAB

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 is approved for the treatment of urothelial carcinoma, non-small cell lung cancer (NSCLC), triple-negative breast cancer (TNBC), and small cell lung cancer (SCLC)

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

1.4 BACKGROUND ON BEVACIZUMAB

Avastin (bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in in vitro and in vivo assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF, and has an approximate molecular weight of 149 kD. Bevacizumab is produced in a mammalian Chinese hamster ovary cell line.

Bevacizumab was first granted marketing approval in the United States on 26 February 2004 (international birth date) in combination with IV 5-fluorouracil (5-FU)–based chemotherapy for the first-line treatment of patients with metastatic carcinoma of the colon or rectum (CRC). As of November 2016, bevacizumab has been approved for use in over a 100 countries worldwide in a variety of indications, including locally recurrent or metastatic breast cancer; advanced, metastatic, or recurrent NSCLC; advanced and/or metastatic renal cell cancer (RCC); newly diagnosed glioblastoma multiforme (GBM) and GBM after relapse or disease progression; persistent, recurrent, or metastatic cervical cancer; front-line treatment of epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC); and treatment of platinum-sensitive and platinum-resistant recurrent EOC, PPC, or FTC.

1.5 RATIONALE FOR TESTING ATEZOLIZUMAB + BEVACIZUMAB COMBINATION

Experience to date with atezolizumab in mucosal melanoma is from Study PCD4989g, in which atezolizumab monotherapy only demonstrated limited efficacy in this population. Study PCD4989g is an ongoing Phase Ia, open-label, dose-escalation trial to assess the safety, pharmacokinetics and efficacy of atezolizumab administered as a single agent to patients with solid tumors. As of 1 Jan 2014, a total of 45 patients with melanoma have been treated with atezolizumab monotherapy with a minimum follow up of 15 months. The confirmed ORR by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

was 28% in all efficacy-evaluable patients, 20% in 5 mucosal melanoma patients. Median PFS was 4.2 months (range, 0.9-19.6+ months) among all efficacy-evaluable melanoma patients(Hodi, et al. 2014).

Beyond its known anti-angiogenic effects (Ferrara, et al. 2004), bevacizumab has been shown to give immunomodulatory effects in combination with check-point inhibitors. Bevacizumab stimulates dendritic cell maturation which promotes T cell priming and activation (Gabrilovich, et al. 1996 Oyama, et al. 1998). The normalization effect of bevacizumab on tumor vasculature increases T-cell tumor infiltration (Motz, et al. 2014 Wallin, et al. 2016). Bevacizumab establishes an immune-permissive tumor microenvironment by decreasing myeloid-derived suppressor cells and regulatory T-cell populations (Roland, et al. 2009, Facciabene, et al. 2011).

Currently there is no preclinical data or prior clinical experience of the combination of atezolizumab + bevacizumab available in mucosal melanoma. However there is sufficient rationale for exploring the efficacy and safety of atezolizumab + bevacizumab in patients with mucosal melanoma. To address the ongoing high unmet medical need for patients with mucosal melanoma, this study aims to evaluate the efficacy and safety of atezolizumab + bevacizumab in patients with locally advanced or metastatic mucosal melanoma.

In the setting of the COVID-19 pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from COVID-19. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of COVID-19.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD 1/PD L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from COVID-19 is altered by cancer immunotherapy.

Severe COVID-19 appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS CoV-2 infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from COVID-19.

There may be potential synergy or overlap in clinical and radiologic features for immune mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for COVID-19-related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of atezolizumab in combination with bevacizumab (atezo+bev) in patients with unresectable locally advanced or metastatic mucosal melanoma. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., atezolizumab and bevacizumab).

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of atezo + bev on the basis of the following endpoint:

- Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1).

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of atezo + bev on the basis of the following endpoints:

- Progression-free survival (PFS), defined as the time from the date of first treatment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1.
- Overall survival (OS), defined as the time from the date of first treatment to death from any cause.
- Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1.
- Disease control (defined as the sum of the CR, PR and stable disease (SD) rates) as determined by the investigator according to RECIST v1.1

2.2 SAFETY OBJECTIVE

The primary safety objective for this study is to evaluate the safety of atezo + bev on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0)
- Changes in vital signs, physical examination findings, and clinical laboratory results during and following study treatment

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is an open-label, multicenter, single arm, phase II study exploring the efficacy and safety of atezo + bev in patients with unresectable locally advanced or metastatic mucosal melanoma.

The study will enroll approximately 43 patients (38 patients fully evaluable for ORR) at approximately 3 centers, including study Stages I and II.

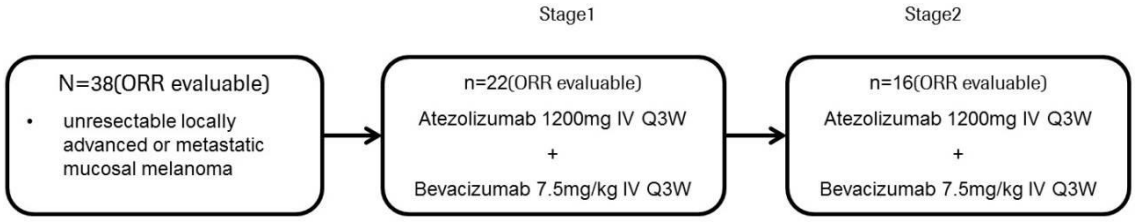
The trial will consist of a Screening Period (Day –28 to −1), a Treatment Period, an Treatment Discontinuation Visit occurring when atezolizumab and bevacizumab are both discontinued for any reason and a Survival Follow-Up Period until death, loss to follow-up, or study termination. Day 1 of the study (baseline) will be defined as the first day a patient receives atezo + bev. One cycle of therapy will be defined as 21 days of treatment. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments.

The study is divided into 2 stages. Stage I of the study is completed when 22 patients with measurable disease have been enrolled and completed ORR evaluation. If the number of responders in Stage I is more than 3, another 16 fully evaluable patients may be enrolled to Stage II.

Considering a drop-out rate of 10%, a total number of 25 subjects (if stops at the first stage) or 43 subjects (if runs into the second stage) will need to be enrolled in this study.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



IV = intravenous; Q3W= every 3 weeks

Atezolizumab and/or bevacizumab 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 (e.g., LDH level), local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudoprogression) with atezolizumab treatment, radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 will be permitted to continue 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

Patients who transiently withhold or permanently discontinue either atezolizumab or bevacizumab may continue on single-agent therapy as long as the patients are experiencing clinical benefit in the opinion of the investigator (i.e., patients temporarily withdrawn from bevacizumab due to adverse effects may continue atezolizumab monotherapy and vice versa).

Patients will undergo tumor assessments at scheduled intervals during the study (see Section 4.4 and Appendix 1 for details).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs. The end of the study is expected to occur 20 months after the last patient is enrolled. In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 2 years and 9 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no DLTs were observed at any dose. The fixed dose

of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

3.3.2 Rationale for Bevacizumab Dose and Schedule

Bevacizumab will be administered at a dose of 7.5 mg/kg Q3W (7.5 mg/kg on Day 1 of each 21-day cycle), which is the approved dosage for bevacizumab (Avastin® U.S. and China Package Insert).

Bevacizumab is approved for use (in combination) at 7.5 mg/kg Q3W and 5mg/kg Q2W in metastatic colorectal cancer. Both dosing regimens were selected on the basis of nonclinical studies and available clinical pharmacokinetic, efficacy and safety data (refer to the Bevacizumab / Avastin® Investigator's Brochure for details). The former dosing regimen (7.5 mg/kg Q3W) was chosen in the current study, to more easily accommodate the Q3W dosing pattern for atezolizumab, thereby streamlining study design and simplifying administration of the combination for the investigators (and potentially future clinicians).

3.3.3 Rationale for Open-Label Single-Arm Study

The primary objective of this study is to assess the efficacy profile of atezolizumab +bevacizumab in a non-comparative fashion. Thus, as all patients are pre-specified to receive active treatment, the study will have an open-label and non-randomized design.

3.3.4 Rationale for Atezolizumab Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response, partial response, 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 immune-cell infiltration in the setting of a T-cell response has been termed pseudoprogression (Hales et al. 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed ICs and no viable cancer cells. 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 (see criteria in Section 3.1.1). Patients should be discontinued for unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1.1 for details).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 38 patients that fully evaluable for ORR and with unresectable locally advanced or metastatic mucosal melanoma will be enrolled in this study, including study Stages I and II. Considering 10% dropout rate, approximately 43 subjects will be included.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Age ≥ 18 and ≤75 years at time of signing Informed Consent Form (ICF)
3. Ability to comply with the study protocol, in the investigator's judgment
4. Histologically confirmed unresectable locally advanced(stage III) or metastatic (Stage IV) mucosal melanoma
5. May have received prior systemic treatment or treatment naive at enrollment
6. Measurable disease per RECIST v1.1
7. ECOG Performance Status of 0-1
8. Life expectancy ≥ 12 weeks
9. Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
    1) ANC ≥ 1.5×10^9/L (1500/μL) without granulocyte colony-stimulating factor support, G-CSF may be administered until 2 weeks prior to Cycle 1, Day 1
    2) Lymphocyte count ≥ 0.5×10^9/L (500/μL)
    3) Platelet count ≥ 100×10^9/L (100,000/μL) without transfusion, transfusion may be administered until 2 weeks prior to Cycle 1, Day 1
    4) Hemoglobin ≥ 90 g/L (9 g/dL)
        i. Patients may be transfused to meet this criterion.
    5) AST, ALT, and alkaline phosphatase (ALP) ≤ 2.5 × upper limit of normal (ULN), with the following exceptions:
        i. Patients with documented liver metastases: AST and ALT ≤ 5× ULN
        ii. Patients with documented liver or bone metastases: ALP ≤ 5 ×ULN
    6) Serum bilirubin ≤ 1.5 × ULN with the following exception:
        i. Patients with known Gilbert disease: serum bilirubin level ≤ 3 ×ULN
    7) Serum creatinine ≤ 1.5 × ULN
    8) Serum albumin ≥ 25 g/L (2.5 g/dL)
    9) For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 × ULN

10. Negative HIV test at screening
11. Negative hepatitis B surface antigen (HBsAg) test at screening
12. Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by quantitative hepatitis B virus (HBV) DNA<500 IU/mL at screening
13. Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening
    1) The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
14. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:
    1) Women must remain abstinent or use contraceptive methods with a failure rate of $<$ 1% per year during the treatment period and for 5 months after the final dose of atezolizumab, or 6 months after the final dose of bevacizumab, whichever is longer. Women must refrain from donating eggs during this same period.
    2) A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.
    3) Examples of contraceptive methods with a failure rate of $<$ 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
    4) 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.
15. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:
    1) With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<$ 1% per year during the treatment period and for 6 months after the final dose of bevacizumab. Men must refrain from donating sperm during this same period.
    2) With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of bevacizumab to avoid exposing the embryo.

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

4.1.2 Exclusion Criteria

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

1. Symptomatic or actively progressing central nervous system (CNS) metastases
    1) Asymptomatic patients with treated or untreated CNS lesions are eligible, provided that all of the following criteria are met:
        i. Measurable disease, per RECIST v1.1, must be present outside the CNS.
        ii. The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
        iii. The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment.
        iv. The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anticonvulsant therapy at a stable dose is permitted.
        v. Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
        vi. There is no evidence of interim progression between completion of CNS-directed therapy (if administered) and initiation of study treatment.
    2) Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.
2. History of leptomeningeal disease
3. Uncontrolled tumor-related pain
    1) Patients requiring pain medication must be on a stable regimen at study entry.
    2) Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.
    3) Asymptomatic metastatic lesions that would likely cause functional deficits or 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.
4. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
    1) Patients with indwelling catheters are allowed.

5. Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN)
6. 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, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
    1) Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
    2) Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
    3) 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:
        i. Rash must cover < 10% of body surface area
        ii. Disease is well controlled at baseline and requires only low-potency topical corticosteroids
        iii. 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
7. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan
    1) History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
8. Active tuberculosis
9. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
    1) Patients with known coronary artery disease, arrhythmias, congestive heart failure not meeting the above criteria must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate. Baseline evaluation of left ventricular ejection fraction (LVEF) should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease or where low LVEF is suspected
    2) Patients with known LVEF < 40%
10. 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

11. History of malignancy other than melanoma within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>$ 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
12. 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
13. Prior allogeneic stem cell or solid organ transplantation
14. 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
15. Current treatment with anti-viral therapy for HBV
16. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
17. Current, recent (within 28 days prior to initiation of study treatment) or planned treatment with any other investigational agent or participation in another clinical study with anti-cancer therapeutic intent
18. Prior treatment with immune checkpoint agonists, including CD137 agonists and TLR9 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
19. Prior treatment with anti-angiogenic therapies
20. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment as well as prior cancer vaccines and cellular immunotherapy
21. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents, as well as T and B cell targeting biologic agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
    1) Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor approval has been obtained.
    2) Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

22. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
23. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
24. Known allergy or hypersensitivity to any component of the bevacizumab formulation
25. Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of atezolizumab, 6 months after the final dose of bevacizumab
    1) Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
26. Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg)
    1) Anti-hypertensive therapy to achieve these parameters is allowable.
27. Prior history of hypertensive crisis or hypertensive encephalopathy
28. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Cycle 1, Day 1
29. Patients with a baseline ECG demonstrating a QTc > 460 msec (calculated with use of the Fridericia method)
30. History of Grade ≥ 2 hemoptysis (defined as ≥ 2.5 mL of bright red blood per episode) within 1 month prior to screening
31. History of stroke or transient ischemic attack within 6 months prior to Cycle 1, Day 1
32. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
33. Prophylactic or therapeutic use of low molecular weight heparin (e.g., enoxaparin), direct thrombin inhibitors, or warfarin are permitted, provided, where appropriate anticoagulation indices are stable. Patients should have been on a stable dose (for therapeutic use) for at least 2 weeks (or until reaching steady state level of the drug) prior to the first study treatment
34. Current or recent (< 10 days prior to initiation of study treatment) use of aspirin (> 325 mg/day), clopidogrel (> 75 mg/day) or treatment with dipyramidole, ticlopidine, or cilostazol
    1) Note: The use of full-dose oral or parenteral anticoagulants for therapeutic purpose is permitted as long as the INR and/or aPTT is within therapeutic limits (according to institution standards) within 7 days prior to initiation of study treatment and the patient has been on a stable dose of anticoagulants for ≥ 2 weeks prior to initiation of study treatment. Prophylactic use of anticoagulants is allowed.
35. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 calendar days prior to the first dose of bevacizumab

36. History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to Cycle 1, Day 1
37. Clinical signs or symptoms of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding
38. Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
39. Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
40. Proteinuria, as demonstrated by urinalysis or $>$ 1.0 g of protein in a 24-hour urine collection
    1) All patients with $\geq$ 2+ protein on urinalysis at baseline must undergo a 24-hour urine collection for protein.

4.2 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMP) for this study are atezolizumab and bevacizumab.

4.2.1 Study Treatment Formulation, Packaging, and Handling

The packaging and labeling of the study medication will be in accordance with Roche standards and local regulations.

All investigational products must be kept in a secure place under appropriate storage conditions.

For further details, see the investigator brochure.

4.2.1.1 Atezolizumab

The atezolizumab Drug Product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

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

4.2.1.2 Bevacizumab

The Bevacizumab Drug Product will be supplied by the Sponsor as a clear to slightly opalescent, colorless to pale brown, sterile liquid for IV infusion in single-use vials, which are preservative-free. Bevacizumab will be supplied in 20-mL glass vials with a 16-mL fill (400 mg, 25 mg/mL).

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

4.2.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.

Refer to 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.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 8, Appendix 9 and Appendix 10.

Atezolizumab will be administered first, followed by bevacizumab, with a minimum of 5 minutes between dosing.

4.2.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1.1 for details).

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 1.

Table 1 Administration of First and Subsequent Atezolizumab Infusions

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

Guidelines for medical management of infusion-related reactions (IRRs) are provided in the Appendix 9.

No dose modification for atezolizumab is allowed.

4.2.2.2 Bevacizumab

Bevacizumab will be administered by IV infusion at a dose of 7.5 mg/kg on Day 1 of each 21-day Cycle until unacceptable toxicity or loss of clinical benefit (see Table 2).

Administration of bevacizumab 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. Bevacizumab infusions will be administered per the instructions outlined in Table 2. Guidelines for dosage modification and treatment interruption or discontinuation because of toxicities are provided in Appendix 10.

Body weight at baseline should be used to calculate the required dose of bevacizumab. If a weight change of > 10% from baseline is observed, the treatment dosage should be modified accordingly (i.e., this becomes the new weight for dose calculation). No other dose modification is allowed for bevacizumab.

A rounding up or down of the dose is acceptable to allow practical ease of administration. Rounding of the dose is optional, and if the treating physician decides to round the total dose of bevacizumab, it should be rounded to the nearest 5 mg.

Table 2 Administration of First and Subsequent Bevacizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the Bevacizumab infusion. • Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Bevacizumab should be infused over 90 (± 15) minutes. • Vital signs should be at the end of infusion and 2 (± 1) hours after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Bevacizumab should be infused over 60 (± 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 90 (± 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (± 15) minutes thereafter. • Vital signs should be at the end of infusion and 2 (± 1) hours after the infusion.

4.2.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab+bevacizumab) will be provided by the Sponsor where required by local regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied 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 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

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

4.3.1 Permitted Therapy

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

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic low-molecular-weight heparin
- Inactivated influenza vaccinations
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy. Treatment with bevacizumab should be suspended during palliative radiotherapy.
- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment after Medical Monitor approval has been obtained. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

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

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.3.2 to 4.3.4) 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).

4.3.2 Cautionary Therapy for Atezolizumab-Treated Patients

4.3.2.1 Corticosteroids and TNF-α Inhibitors

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

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 7 and Appendix 9 for details).

4.3.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.3.4) may be used during the study at the discretion of the investigator.

4.3.3 Cautionary Therapy Specific to Bevacizumab

Anticoagulants

The use of full-dose oral or parenteral anticoagulants is permitted during the trial as long as the INR and/or aPTT is within therapeutic limits (according to the medical standard of the treating institution). Prophylactic use of anticoagulation at baseline and during study treatment is permitted. Bevacizumab or anticoagulation treatment will be stopped if there is any evidence of tumor invasion into major blood vessels on any CT scan.

Aspirin

Owing to a possible risk of bleeding during treatment with bevacizumab, patients should not take more than 325 mg of aspirin daily (or more than 75 mg of clopidogrel daily, or equivalent), at least until discontinuation of bevacizumab treatment.

4.3.4 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 for various time periods prior to starting study treatment, depending on the agent (see

Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see Section 4.3.1 for details).

- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines are prohibited within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the final 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, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.

4.3.5 Continued Access to Atezolizumab and Bevacizumab

Currently, the Sponsor does not have any plans to provide Roche IMPs (atezolizumab and bevacizumab) or any other study treatments to patients who have completed the study. The Sponsor may evaluate whether to continue providing atezolizumab and bevacizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

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

4.4 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should 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.

4.4.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). 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. Patients who fail their first screening for study eligibility may qualify for one re-screening opportunity (for a total of two screenings per patient) at the investigator's discretion. All re-screening requests will require approval by the Medical Monitor or designee.

4.4.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, will be recorded at baseline. 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.

4.4.3 Physical Examinations

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

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. 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.

4.4.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, 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.

Vital signs are to be measured before, during, and after infusions as outlined in Table 3, and at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

Table 3 Timing for Vital Sign Measurements for First and Subsequent Infusions

Drug	Timing for Vital Sign Measurements	
	First Infusion	Subsequent Infusions
Atezolizumab	• Within 60 minutes prior to the atezolizumab infusion • Record patient's vital signs during or after the infusion if clinically indicated.	• Within 60 minutes prior to the atezolizumab infusion • Record patient's vital signs during or after the infusion if clinically indicated
Bevacizumab	• Within 60 minutes prior to the bevacizumab infusion • At the end of infusion and 2 (± 1) hours after the infusion	• Within 60 minutes prior to the bevacizumab infusion • At the end of infusion and 2 (± 1) hours after the infusion

4.4.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 54 weeks following treatment initiation, and every 12 weeks (±1 week) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 or (for patients who continue atezolizumab and/or bevacizumab after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening.

Screening assessments must include CT scans (with oral or IV contrast) or magnetic resonance imaging (MRI) scans of the chest, abdomen, pelvis, and head. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and head should be performed. A CT scan with contrast or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

All measurable and evaluable lesions identified at baseline should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Objective response at a single timepoint will be determined by the investigator according to RECIST v1.1 (see Appendix 2). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

4.4.6 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology: white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, glucose, blood urea nitrogen (BUN) or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, and Lactate dehydrogenase (LDH)
- Coagulation: INR, and aPTT
- 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)
- HIV serology
- HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

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

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

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

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

- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

4.4.7 Electrocardiograms

An ECG is required at screening and when clinically indicated. Clinically indicated situation include when investigators consider it necessary to monitor ECG. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

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

4.5 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.5.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (atezolizumab and bevacizumab) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details)

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment after he or she has completed at least 1 post baseline tumor assessment will not be replaced. In other situations, patients can be replaced only after approval has been documented by both the investigator(or an appropriate delegate) and the Medical Monitor.

Patients will return to the clinic for a treatment discontinuation visit $\leq$30 days after the final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities (see Appendix 1).

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study).

4.5.2 Patient Discontinuation from the 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 patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation 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 prior to receiving study drug will be replaced. Patients who have received any dose of study drug and withdraw from the study after he or she has completed at least 1 post baseline tumor assessment will not be replaced. In other situations, patients can be replaced only after approval has been documented by both the investigator(or an appropriate delegate) and the Medical Monitor.

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.

4.5.3 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.

4.5.4 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

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with atezolizumab and bevacizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Section 5.1.1 and Section 5.1.2).

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 and bevacizumab 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. Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Appendix 8, Appendix 9 and Appendix 10. Refer to Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator

judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis,facial paresis, myelitis, meningoencephalitis, myocarditis, nephritis, and myositis, and severe cutaneous adverse reactions.In addition,immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis. Refer to Appendix 9 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: GI perforation, hemorrhage, arterial thromboembolic events, fistulae, wound-healing complications, hypertension, venous thromboembolism, and proteinuria.

Refer to Appendix 10 of the protocol and Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for bevacizumab.

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) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- 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 treatment
- 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 treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

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

- 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)
- Suspected transmission of an infectious agent by the study treatment, 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 study treatment is suspected.

5.2.3.1 Adverse Events of Special Interest for Atezolizumab

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, hypothyroidism and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness and systemic inflammatory response syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

- Myelitis
- Facial paresis

5.2.3.2 Adverse Events of Special Interest for Bevacizumab

Adverse events of special interest for bevacizumab are as follows:

- Grade ≥ 3 hypertension
- Grade ≥ 3 proteinuria
- Any grade GI perforation, abscesses, or fistulae
- Grade ≥ 3 wound-healing complication
- Hemorrhage
  - Any grade CNS bleeding
  - Grade ≥ 2 hemoptysis
  - Other Grade ≥ 3 hemorrhagic event
- Any grade arterial thromboembolic event
- Grade ≥ 3 venous thromboembolic event
- Any grade posterior reversible encephalopathy syndrome (PRES; also known as reversible posterior leukoencephalopathy syndrome or RPLS)
- Grade ≥ 3 CHF/left ventricular systolic dysfunction
- Grade ≥ 2 non-GI fistula or abscess

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special

interest will continue to be reported until 3 months after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), 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 study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 5):

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

Table 5 Causal Attribution Guidance

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

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 treatment administration and are judged to be related to study treatment 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 treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

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

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

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of mucosal melanoma 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 treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Mucosal Melanoma

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

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

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

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

5.3.5.12 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (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
- 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.

Special situations are not in themselves adverse events, but may result in adverse events. 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). For atezolizumab and bevacizumab, 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.
- 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.

In addition, all special situations associated with atezolizumab and bevacizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRFas described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- 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.

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

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 treatment:

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

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

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor/Roche Medical Responsible: [redacted] (Primary)

Telephone No.:

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 Treatment Initiation

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

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 3 months after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

Instructions for reporting serious adverse events that occur after the reporting period 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 final dose of atezolizumab, or within 6 months after the final dose of bevacizumab, whichever is longer. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6

months after the final dose of bevacizumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the 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 treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all

serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

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

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

5.5.2 Sponsor Follow-Up

For serious adverse events, 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 reporting period for serious adverse events and adverse events of special interest (defined as 3 months after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event/AESI that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- Atezolizumab Investigator's Brochure
- Bevacizumab 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 is an open-label, single-arm study.

Analysis populations

This study will include the following analysis populations:

- Full Analysis Set (FAS) population: defined as all enrolled patients who receive any amount of study treatment and evaluable for efficacy endpoints. The efficacy analyses will be performed on the FAS population.
- Safety population: defined as all enrolled patients who receive any amount at least one dose of any study treatment. The safety analysis will be performed on the safety population.
- ITT population: defined as all enrolled patients regardless of whether they receive any assigned study drug. The ITT population will be used for other analyses (Demography, Baseline Characteristics, etc.).

All major deviations (at study entry and on study) will be summarized and reported.

General Analysis Methods

Unless otherwise stated, all statistical analyses specified in the subsequent sections will be based on the following general methods.

All qualitative data will be presented in contingency tables, using absolute and relative frequencies, unless otherwise stated. Percentages will be rounded to the first decimal place and, therefore, may not always add up to 100%. When applicable, 95% confidence intervals (CIs) will be presented with estimates of proportions.

All quantitative data will be summarized via relevant descriptive statistics, such as number of observations with available measurements, mean, standard deviation, median, first and third quartiles (Q1and Q3) when applicable, minimum and maximum.

Time to event data will be summarized via Kaplan-Meier (KM) estimates/curves and median with corresponding 95% CI.

Timing of Analyses

The primary analysis and reporting of the study will occur 12 months after the last patient has been enrolled. The long-term follow-up will be reported in a subsequent report following the end of study.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size calculation was based on a Simon two-stage design (Simon 1989).

In this Phase II study, an ORR of 20% is a level of activity that is not of interest for further clinical development, whereas an ORR of 40% is of clinical interest.

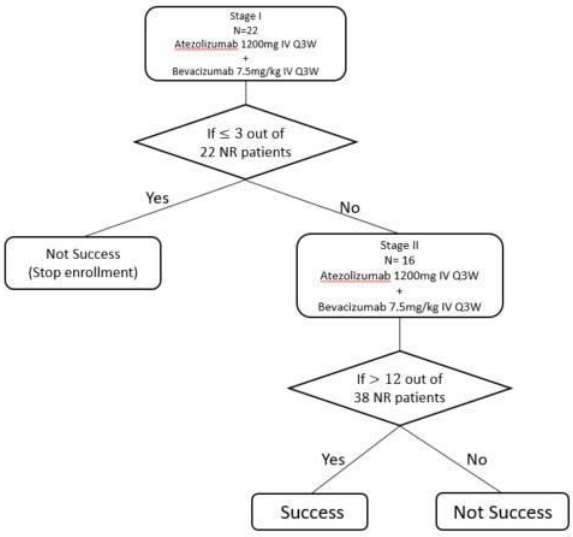
The study hypotheses are:

H_0: $\pi \leq n_O$
H_1: $\pi > n_1$

Where n_O= 20% and the assumed ORR under the alternative n_1= 40%.

The type I error will be 5% and the study will have 80% power to reject the null hypothesis when the true ORR is 40%.

Figure 2 Sample Size Allocation



NR: Non-Response; ORR: Overall Response Rate

Assumptions: H_0= ORR 20%; H_1= ORR 40%; Power=80%; alpha=5% (two-sided)

The Simon design in this study requires 22 fully evaluable patients for the first stage. If at the end of first stage there are less than or equal to 3 patients with ORR, the enrollment in to the study will be terminated. Otherwise, if more than 3 patients with ORR are observed at the end of the stage I, an additional 16 fully-evaluable patients may be enrolled into stage II.

Thus, considering a drop-out rate of 10%, a total number of 25 subjects (if stops at the first stage) or 43 subjects (if runs into the second stage) will need to be enrolled in this study.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study drug administration, and discontinuation from the study will be summarized. The reasons for study drug discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be listed.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, medical history and prior treatment, etc.) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented descriptively using the ITT population.

6.4 EFFICACY ANALYSES

The efficacy analyses will be performed on the FAS population, defined as all enrolled patients who receive any amount of study treatment and evaluable for efficacy endpoints.

6.4.1 Primary Efficacy Endpoint

The primary analysis will be based on Objective response rate (ORR), defined as the proportion of patients with a CR or PR on two consecutive occasions $\geq$ 4 weeks apart, as determined by the investigator according to RECIST v1.1. Patients treated with study drug who have no post-baseline tumor assessment (per protocol mandated timelines), and enrolled patients who do not receive any dose of study drug will be replaced. This endpoint will be assessed at Stage I and Stage II. The number and proportion of responders will be presented with the corresponding Clopper-Pearson 95% CI.

Enrollment into the cohort may continue into Stage II if more than 3 patients (out of 22) with ORR are observed at the end of Stage I. In the Stage II, if more than 12 patients out of 38 patients have responses and there is no unacceptable toxicity, we can conclude that the therapy is statistically significant in improving the ORR in curing mucosal melanoma.

6.4.2 Secondary Efficacy Endpoints

- Progression-free survival (PFS), defined as the time from the date of first treatment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1. A patient without a PFS event will be censored at the time of the last evaluable tumor assessment. Patients with no tumor assessment after the baseline visit will be censored at the time of the first day of study treatment plus 1 day.
- Overall survival (OS), defined as the time from the date of first treatment to death from any cause. Patients for whom no death is captured on the clinical database will be censored at the most recent date they were known to be alive.

- Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1. For patients who do not die or experience disease progression before the end of the study or who are lost to follow-up, duration of objective response will be censored at the day of the last tumor assessment.
- Disease control rate (DCR) (defined as the sum of a complete or partial response or stable disease rates.) as determined by the investigator according to RECIST v1.1. DCR will be presented along with the 95% Clopper-Pearson CI.

6.5 SAFETY ANALYSES

The safety analysis will be performed on the safety population, defined as all enrolled patients who receive at least one dose of any study treatment.

Verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0.

Other safety variables studied will include:

- Drug exposure (treatment duration, number of doses, dose intensity and dose modifications/discontinuations, with reasons)
- All AEs
- SAEs
- AEs (Grade 3–5)
- AESIs
- AEs leading to study drug discontinuation or interruption
- Changes in vital signs from baseline
- Changes in physical findings from baseline
- Changes in selected laboratory parameters from baseline
- Deaths and cause of death
- Concomitant medications

The incidence of AEs will be summarized by frequency tables. Corresponding 95% Clopper-Pearson CIs will be presented, as applicable.

Treatment exposure, discontinuation rate, and cause of death will be analyzed by frequency tables. When appropriate, median time on treatment and 95% CI will be estimated by the Kaplan-Meier approach or using univariate statistics, presenting mean, median, quartiles, minimum, maximum and standard deviation.

Changes in vital signs and physical findings from baseline will be tabulated and presented graphically when applicable. Worst grades for laboratory parameters, newly

occurring Grade 3 and 4 laboratory values during treatment, and concomitant medications will be summarized by frequency tables.

6.6 INTERIM ANALYSIS

One interim analysis is planned. The interim analysis will be performed for futility at the time of 22 subjects completes ORR evaluation. According to preplanned stopping rules of Simon 2-stage design, further testing of Atezolizumab and Bevacizumab would be halted if the number of subjects that respond in the first evaluable 22 patients (stage 1) is less or equal than 3. This study has a probability of 33.2% to terminate at the first stage. The optimal or minimax are not used because of their high probability of termination at the first stage. All decisions above will be made by the Sponsor in discussion with the stud team members.

The sample size and stopping rule are calculated with SAS 9.4, and all the tables, listings and figures will be generated using SAS 9.4.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will approve eCRF specifications developed by a contract research organization (CRO) for this study. A contract research organization (CRO) 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 CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used 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 at the CRO and records retention for the study data will be consistent with the CRO'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 that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 25 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 study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an 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.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

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

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

8.4 CONFIDENTIALITY

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

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

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

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

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

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

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

Approximately 3 sites in China will participate to enroll approximately 43 patients (38 subjects that fully evaluable for ORR).

Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 DISSEMINATION 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, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared

with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

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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	Screening Period [a]	Treatment Period	Treatment Discontinuation [b]	Follow-Up
	Days –28 to –1	Day 1 (±3 days) of each 3-week treatment cycle	≤ 30 Days after Final Dose	(every 3 months)
Informed consent [c]	x [c]			
Demographic data	x			
Medical history and baseline conditions	x			
Vital signs [d]	x	x	x	
Weight	x	x	x	
Height	x			
Complete physical examination [e]	x		x	
Limited physical examination [f]		x		
ECOG Performance Status	x	x	x	
ECG [g]	x	x [k]		
LVEF [h]	x			
Hematology [i]	x [j]	x [k]	x	
Chemistry [l]	x [j]	x [k]	x	
Pregnancy test [m]	x [j]	x [k]		
Coagulation (INR, aPTT)	x [j]		x	
TSH, free T3 (or total T3), free T4 [n]	x	x [k, n]	x	
Viral serology [o]	x			
Urinalysis [p]	x [j]	x [q]		
Tumor response assessments	x [r]	x [s, t]	x [s, t]	x [s, t]
Concomitant medications [u]	x [u]	x	x	
Adverse events [v]	x [v]	x [v]	x	x [v]
Study treatment administration [w]		x		

Survival follow-up and anti-cancer treatment				X [x]

eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; NA = not applicable; RECIST = Response Evaluation Criteria in Solid Tumors; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone;

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

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 treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after their final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

c Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

d Includes respiratory rate, pulse rate, systolic and diastolic blood pressure, 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.

e Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

f Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

g ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Clinically indicated situation include when investigators consider it necessary to monitor ECG. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

h Baseline evaluation of left ventricular ejection fraction (LVEF) should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease or where low LVEF is suspected

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

j Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

k If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

l Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, and LDH.

m All women of childbearing potential will have a serum pregnancy test at screening, within 14 days prior to initiation of study treatment. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

n TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every four cycles thereafter (i.e., Cycles 5, 9, 13, etc.).

o At screening, patients will be tested for HIV, HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection. Patients with a positive quantitative HBV DNA at screening (must be <500 IU/mL per the eligibility criteria) will undergo additional HBV DNA tests at Cycle 4 Day 1, Cycle 8 Day 1 and at treatment discontinuation visit (±7 days). Study treatment and procedures may proceed while HBV DNA is being processed, but results should be reviewed by the investigator as soon as they are available. If HBV DNA increases to ≥500 IU/mL, consultation with the Medical Monitor is required prior to continuation of study treatment and consultation with a hepatologist or gastroenterologist with specialty in hepatitis B is recommended.

p Includes pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted.

q Urinalysis should be performed as clinically indicated during study treatment. Clinically indicated situation include when investigators consider it necessary to monitor urinalysis.

r All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with oral or IV contrast) or MRI scans of the chest, abdomen, pelvis, and head. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and head should be performed. A CT scan with contrast or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

s Patients will undergo tumor assessments at baseline, every 6 weeks($^{\pm}$1 week) for the first 54 weeks following treatment initiation, and every 12 weeks($^{\pm}$1 week) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 or (for patients who continue treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy.

t All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

u Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

v After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 3 months after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the investigator should report any SAEs or AESIs believed to be related to prior study drug treatment. The investigator should follow each AE 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 SAEs considered to be related to study drug or study-related procedures until a final outcome can be reported.

w The initial infusion of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. The initial dose of bevacizumab will be delivered over 90 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 (± 10) minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes.

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

Appendix 2
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 ≤ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

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

[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.

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.

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

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

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used 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 should 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 $\geq$ 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 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 CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

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

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

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

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

CRITERIA FOR NON-TARGET LESIONS

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

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

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

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

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

NEW LESIONS

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

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

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

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 6 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 6 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

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

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

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 6.

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.

REFERENCES

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

Appendix 3
New York Heart Association Functional Classification

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity (e.g., shortness of breath when walking, climbing stairs, etc.)
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity (e.g., walking short distances [20–100 m]). Comfortable only at rest
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients

Appendix 4
ECOG Performance Status

Zubrod-ECOG-WHO	
Grade	Performance status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Death

Appendix 5
Corticosteroid Dose Equivalents

Equivalent Dose	Steroid
1.2 mg	Betamethasone (long-acting)
1.5 mg	Dexamethasone (long-acting)
8 mg	Methylprednisolone (intermediate-acting)
8 mg	Triamcinolone (intermediate-acting)
10 mg	Prednisone (intermediate-acting)
10 mg	Prednisolone (intermediate-acting)
40 mg	Hydrocortisone (short-acting)
50 mg	Cortisone (short-acting)

http://emedicine.medscape.com/article/2172042-overview.

Appendix 6
Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life–threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anti-cancer agent. Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmue myelitis • 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, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

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

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

Appendix 8
Overall Guidelines for Management of Patients Who Experience Adverse Events

DOSE MODIFICATIONS

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

The bevacizumab dose will be based on the patient's weight at C1D1 and will remain the same throughout the study, unless there is a weight change of ≥ 10% from C1D1. It is not necessary to correct dosing on the basis of ideal weight, unless warranted per institutional guidelines/standard. Management of bevacizumab may be performed according to the label. If adverse events occur that necessitate holding bevacizumab, the weight-based dose in mg/kg will remain unchanged after treatment resumes.

TREATMENT INTERRUPTION

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

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level. Patients who develop Grade 4 toxicities related to bevacizumab for > 21 days should permanently discontinue bevacizumab.

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

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-mediated 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-mediated 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-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Guidelines for managing patients who experience selected adverse events are provided in the following sections. Management guidelines are presented by adverse event severity based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) and in some instances may vary by CTCAE version (4.0 vs. 5.0).

For patients developing a new autoimmune disease not listed in this Appendix or for patients having been enrolled in the study with an autoimmune disease who develop a flare, the following dosing guidance should be applied:

- Grade 1 event: atezolizumab dosage should be maintained
- Grade 2 or 3 event: atezolizumab should be suspended until the subject responds to treatment of the autoimmune disease and the disease becomes stable (see rules above regarding maximum suspended time). The subject should be referred to an appropriate specialist
- Grade 4 event: atezolizumab should be permanently discontinued and the

subject should be referred to an appropriate specialist

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in table 7.

Table 7 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.\ • For Grade 1 pneumonitis, consider withholding atezolizumab.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL with or without transbronchial biopsy. • Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c,d] • For recurrent events or events with no improvement after 48–72 hours of corticosteroids,, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL=bronchoscopic alveolar lavage. CTCAE= Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[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 based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[d] In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.

HEPATIC EVENTS

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in table 8.

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

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 8 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

LFT = liver function tests.

CTCAE= Common Terminology Criteria for Adverse Events; LFT=liver function tests; NCI=National Cancer Institute.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0, except where indicated.

[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 based on the investigator's benefit□risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed..

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on the investigator's benefit□risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 8 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function tests.

CTCAE= Common Terminology Criteria for Adverse Events; LFT=liver function tests; NCI=National Cancer Institute.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0, except where indicated.

[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 based on the investigator's benefit□risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed..

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on the investigator's benefit□risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed .

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in table 9.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 9 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[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 based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 9 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] • Refer patient to gastrointestinal specialist for evaluation and confirmation biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[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 based on the investigator's benefit□risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in table 10.

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 10 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Grade 2 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.
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer to an endocrinologist. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status). • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism. [c]
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH < 0.1 mU/L:** • Follow guidelines for Grade 2 hyperthyroidism. • Consider patient referral to endocrinologist.
Grade 2 hyperthyroidism	• Consider withholding 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.
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

CTCAE=Common Terminology Criteria for Adverse Events; MRI=magnetic resonance imaging; TSH=thyroid-stimulating hormone; NCI=National Cancer Institute.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[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 based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed..

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 10 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	**CTCAE v4.0 guidelines** • Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control. **CTCAE v5.0 guidelines** • Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

CTCAE=Common Terminology Criteria for Adverse Events; MRI=magnetic resonance imaging; TSH=thyroid-stimulating hormone; NCI=National Cancer Institute.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[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 based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 10 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.[a] • 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.[a] • Initiate hormone replacement if clinically indicated.

CTCAE=Common Terminology Criteria for Adverse Events; MRI=magnetic resonance imaging; TSH=thyroid-stimulating hormone; NCI=National Cancer Institute.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[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 based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in table 11.

Table 11 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.

CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute.
Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[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 based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED CARDIAC EVENTS

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated 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-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on pericardial disorders below) and should be managed accordingly.

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 12.

IMMUNE-MEDIATED PERICARDIAL DISORDERS

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 12 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2-4 Immune-mediated pericardial disorders, Grades 2-4	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If 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.

CTCAE= Common Terminology Criteria for Adverse Events; ECMO= extracorporeal membrane oxygenation; NCI=National Cancer Institute; VAD= ventricular assist device.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0, except where indicated.

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

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

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in table 13.

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Table 13 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 [a] fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 [a] fever [b] with hypotension not requiring vasopressors **and/or** hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact the Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Medical Monitor.

Grade 3 [a] fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, nonrebreather mask, or Venturi-mask	• Permanently discontinue atezolizumab and contact the Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.

Event	Management
Grade 4 [a] fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact the Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP=bi-level positive airway pressure; CAR=chimeric antigen receptor; CPAP=continuous positive airway pressure; CRS=cytokine-release syndrome; CTCAE=Common Terminology Criteria for Adverse Events; eCRF=electronic Case Report Form; HLH=hemophagocytic lymphohistiocytosis; ICU=intensive care unit; IRR=infusion-related reaction; MAS=macrophage activation syndrome; NCCN National Cancer Comprehensive Network; NCI=National Cancer Institute.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature $\geq$ 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, antipyretic medications, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at $\leq$ 6 L/min, and high flow is defined as oxygen delivered at $>$ 6 L/min.

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit–risk ratio.

[f] Refer to Riegler et al. (2019).

PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup 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 14.

Table 14 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**CTCAE v4.0 guidelines** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., >3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **CTCAE v5.0 guidelines** **Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1-2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0, except where indicated.

[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 based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 14 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0, except where indicated.

[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 based the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

DERMATOLOGIC EVENTS

Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in table 15.

Table 15 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy.. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]
Stevens Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens Johnson syndrome or toxic epidermal necrolysis, permanently discontinue atezolizumab.

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[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 based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor

is available to advise as needed.

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in table 16, with specific guidelines for myelitis provided in table 17.

Table 16 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist.. • Initiate treatment as per institutional guidelines. • For general immune-mediated neuropathy: – 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 facial paresis: – If event resolves fully, resume atezolizumab [b] – If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • 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.

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[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 $\leq$ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 17 Management Guidelines for Immune-Mediated Myelitis

Event	Management
Immune-mediated myelitis, Grade 1	• Continue atezolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness.
Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in table 17.

Table 18 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor. • 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.

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Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

RENAL EVENTS

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 19.

Table 19 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 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]
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.

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[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 based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in table 20.

Table 20 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[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 based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed. [b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 20 Management Guidelines for Immune-Mediated Myositis (cont.)

Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] **CTCAE v4.0 guidelines** • For recurrent events permanently discontinue atezolizumab and contact Medical Monitor. [c] **CTCAE v5.0 guidelines** • For recurrent events, treat as a Grade 4 event. Permanently discontinue atezolizumab and contact the Medical Monitor. c
Immune-mediated myositis, Grade 4 **(CTCAE v5.0 guidelines only)**	**CTCAE v5.0 guidelines** • Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[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 based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS). Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged. Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)

- At least two of the following:
  - Platelet count $\leq 181 \times 10^9$/L (181,000/μL)
  - AST $\geq$ 48 U/L
  - Triglycerides $>$ 1.761 mmol/L (156 mg/dL)
  - Fibrinogen $\leq$ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in table 21.

Table 21 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact the Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over $\geq$ 1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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Appendix 10
Guidelines for Management of Patients Who Experience SpecificAdverse Events with Atezolizumab+Bevacizumab

Event	Action to Be Taken
IRRs, anaphylaxis, and hypersensitivity reactions	• Guidelines for management of IRRs for atezolizumab are provided in Appendix 9. • Guidelines for management of IRRs for bevacizumab are provided below. • For anaphylaxis precautions, see Appendix 7. • For hypersensitivity reactions and allergic reactions, permanently discontinue the causative agent.
IRR to bevacizumab, Grade 1	• Systemic intervention is not indicated. Continue bevacizumab.
IRR to bevacizumab, Grade 2	• Reduce infusion rate to ≤ 50% or interrupt infusion at the discretion of the investigator per medical judgment. • If the infusion is interrupted, it may be resumed at ≤ 50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.
IRR to bevacizumab, Grade 3 or 4	• Stop infusion and permanently discontinue bevacizumab. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen) if clinically indicated.

IRR = infusion-related reaction.

Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity	
GI perforation, any grade	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • Initiate treatment per institutional guidelines. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a]
Bowel obstruction, Grade 2	• Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab for partial obstruction requiring medical intervention. • Bevacizumab may be restarted upon complete resolution of event.
Bowel obstruction, Grade 3 or 4	• Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab until complete resolution. • If surgery is necessary, patient may restart bevacizumab after full recovery from surgery and at the investigator's discretion.
Posterior reversible encephalopathy syndrome	
Posterior reversible encephalopathy syndrome, any grade confirmed by magnetic resonance imaging	• Withhold atezolizumab. Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a]

GI = gastrointestinal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit and the Medical Monitor is in agreement.

Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab (cont.)

Hypertension [a]	
General guidance	• Treat with antihypertensive medication as needed.
Hypertension, Grade 1	• Continue atezolizumab and bevacizumab. • Consider inceased BP monitoring.
Hypertension, Grade 2	• Continue atezolizumab. • If asymptomatic, begin or modify baseline anti-hypertensive therapy and continue bevacizumab. • If symptomatic, start or adjust anti-hypertensive therapy.
Hypertension, Grade 3	• Continue atezolizumab. • Modify existing anti-hypertensive therapy (more than one drug or more intensive therapy than previously indicated). • Withold bevacizumab until symptoms resolve AND BP $<$ 160/90 mmHg
Hypertension, Grade 4	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Hemorrhage	
Hemorrhage, Grade 3 or 4 (excluding cerebral hemorrhage)	• Continue atezolizumab. • Permanently discontinue bevacizumab.
CNS hemorrhage, any grade	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Grade $\geq$ 2 hemoptysis ($\geq$ 2.5 mL of bright red blood per episode)	• Continue atezolizumab. • Permanently discontinue bevacizumab.
Bleeding in patients on full-dose anticoagulant therapy	• Continue atezolizumab. • Permanently discontinue bevacizumab.

BP = blood pressure.

[a] Vascular disorders (including hypertension and hypotension) are possible adverse events of atezolizumab, considering the mechanism of action.

Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab (cont.)

Event	Action to Be Taken
Thromboembolic events	
Venous thromboembolic event, Grade 3	• Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be withheld until the full-dose anticoagulation period is over. The use of direct oral anticoagulants is not recommended. • If the planned duration of full-dose anticoagulation is > 2weeks, bevacizumab may be resumed during full-dose anticoagulation IF all of the criteria below are met: – The patient must not have pathological conditions that carry high risk of bleeding (e.g., tumor involving major vessels or other conditions). – The patient must not have had hemorrhagic events Grade > 2 while on study. – The patient must be on stable dose of heparin, low-molecular-weight heparin, or have an in-range INR (usually 2–3) on a stable dose of warfarin prior to restarting bevacizumab. • If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab.
Venous thromboembolic event, Grade 4	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Arterial thromboembolic event, any grade	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.

Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab (cont.)

Event	Action to Be Taken
Proteinuria	
Proteinuria, Grade 1 (1+ by dipstick; urinary protein < 1.0 g/24 hours)	• Continue atezolizumab and bevacizumab.
Proteinuria, Grade 2 (2+ and 3 + by dipstick; urinary protein 1.0–3.4 g/24 hours)	• Continue atezolizumab. • For 2+ dipstick: Continue bevacizumab and collect 24-hour urine protein prior to subsequent bevacizumab administration. • For 3+ dipstick: Obtain 24-hour urine prior to administering bevacizumab. • Withhold bevacizumab for urinary protein ≥ 2 g/24 hours. • If bevacizumab is withheld and urine protein improves to < 2 g/24 hours ≤ 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab.
Proteinuria, Grade 3 (4 + by dipstick; urinary protein ≥ 3.5 g/24 hours) with no diagnosis of nephrotic syndrome	• Atezolizumab may be continued at the discretion of the investigator. • Withhold bevacizumab. • If urine protein improves to < 2 g/24 hours ≤ 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab.
Nephrotic syndrome, Grade 3 or 4	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Fistula	
Tracheoesophageal fistula, any grade	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a]
Fistula (non-tracheoesophageal), Grade 4	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit and the Medical Monitor is in agreement.

Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab+Bevacizumab (cont.)

Event	Action to Be Taken
Wound dehiscence	
Wound dehiscence, any grade requiring medical or surgical therapy	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Congestive heart failure	
Congestive heart failure, Grade 3 or 4	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Bevacizumab-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab and bevacizumab.
Grade 3	• Continue atezolizumab. Withhold bevacizumab. • If event resolves to Grade 2 or better ≤ 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]
Grade 4	• Withhold atezolizumab and bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab. [a] • If event resolves to Grade 2 or better ≤ 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 9. • Continue bevacizumab.
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 9. • Withhold bevacizumab. • If event resolves to Grade 2 or better ≤ 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit and the Medical Monitor is in agreement.

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