Official Title: An Open Label, Single arm, Multicenter, Safety Study of Atezolizumab in Locally Advanced or Metastatic Urothelial or Non-Urothelial Carcinoma of the Urinary Tract

NCT Number: NCT02928406

Document Dates: Protocol Version 15: 17-December-2021

PROTOCOL

TITLE:	**AN OPEN LABEL, SINGLE ARM, MULTICENTER, SAFETY STUDY OF ATEZOLIZUMAB IN LOCALLY ADVANCED OR METASTATIC UROTHELIAL OR NON-UROTHELIAL CARCINOMA OF THE URINARY TRACT**
PROTOCOL NUMBER:	MO29983
VERSION NUMBER:	15
EUDRACT NUMBER:	2016-002625-11
IND NUMBER:	120827
TEST PRODUCT:	Atezolizumab (MPDL3280A; RO5541267)
MEDICAL MONITOR:	Dr. [redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
16-Dec-2021 19:20:23	[redacted] EU QPPV	[redacted]
17-Dec-2021 18:24:05	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol		Associated Country and/or Region-Specific Protocols		
Version	**Date Final**	**Country and/or Region**	**Version**	**Date Final**
15	See electronic date stamp on title page	Canada	16	TBD
13	3 March 2021	Canada	14	4 March 2021
11	22 October 2019	Canada	12	22 October 2019
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7	22 February 2018	Canada	8	7 March 2018
5	19 May 2017	Canada	6	6 July 2017
3	23 November 2016	Canada	4	31 January 2017
2	25 August 2016	—		—
1	22 July 2016	—		—

PROTOCOL AMENDMENT, VERSION 15:
RATIONALE

- Protocol MO29983 has been primarily amended to align with Atezolizumab Investigator's Brochure Version 18 and update the document with the recent Roche Atezolizumab protocol template. Changes to the protocol, along with rationale for each change, are summarized below.
- Benefit–risk assessment and guidance on concomitant administration of coronavirus disease 2019 vaccines with atezolizumab has been added (Sections 1.4 and 4.4.1).
- Language has been added to indicate that sites can confirm that appropriate temperature conditions have been maintained during IMP transit either by time monitoring (shipment arrival date and time) or temperature monitoring (Section 4.3.3).
- If a patient withdraws from the study, public information source may be used to obtain information about survival status (Section 4.6.1)
- The document has been updated to align with the current Roche Atezolizumab protocol template in Section 1.3, 4 and 5.
- The Roche Global Policy on Continued Access to Investigational Medicinal Product for eligible patients has been added (Section 4.3.4).
- The responsibilities of the Principal Investigator and the role of the Medical Monitor during study conduct have been clarified (Section 5.1.2, Appendix 5 and Appendix 11).
- The serious adverse events and adverse events of special interest reporting timelines after the final dose of study drug or until initiation of new systemic anti-cancer therapy is corrected in Section 5.4.2.2 and 5.6.
- Language has been clarified that study adverse event reports will not be derived from patient reported outcome (PRO) data by the Sponsor; sites are not expected to review the PRO data for adverse events (Section 5.3.5.13).
- Language has been added for consistency with Roche's current data retention policy and to accommodate more stringent local requirements (if applicable) (Section 7.5).
- Language has been added to indicate that the study will comply with applicable local, regional, and national laws (Section 8.1).
- The language regarding the informed consent form revision and the re-consenting in accordance with the local applicable laws and IRB/EC policy has been clarified (Section 8.2).
- The language regarding the study data management, sharing and application has been added (Sections 8.4 and 9.6).
- The guidelines for management of suspected anaphylactic reaction has been updated in Appendix 6.

- The medical term “primary biliary cirrhosis” has been replaced by the term “primary biliary cholangitis” to align with the updated preferred term in MedDRA (Appendix 8).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 18 (Appendix 11).
- The study synopsis has been simplified by deleting information regarding IMP preparation, administration, and concomitant therapy, because the relevant information already is available in the main body of the protocol.

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

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PROTOCOL ACCEPTANCE FORM

TITLE:	**AN OPEN LABEL, SINGLE ARM, MULTICENTER, SAFETY STUDY OF ATEZOLIZUMAB IN LOCALLY ADVANCED OR METASTATIC UROTHELIAL OR NON-UROTHELIAL CARCINOMA OF THE URINARY TRACT**
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MEDICAL MONITOR:	Dr. [redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
PHASE:	IIIB

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

(Name)
(Address)

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN LABEL, SINGLE ARM, MULTICENTRE, SAFETY STUDY OF ATEZOLIZUMAB IN LOCALLY ADVANCED OR METASTATIC UROTHELIAL OR NON-UROTHELIAL CARCINOMA OF THE URINARY TRACT**
PROTOCOL NUMBER:	MO29983
VERSION NUMBER:	15
EUDRACT NUMBER:	2016-002625-11
IND NUMBER:	120827
TEST PRODUCT:	Atezolizumab (MPDL3280A; RO5541267)
PHASE:	IIIB
INDICATION:	Advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study is being conducted to evaluate the safety of atezolizumab as second-line treatment for locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract. The study will also evaluate treatment efficacy and explore potential tumor biomarkers related to atezolizumab. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective

The primary objective of this study is to evaluate the safety of atezolizumab based on the following endpoints:

- Nature, severity, duration, frequency and timing of adverse events (AEs)
- Changes in vital signs, physical findings, and clinical laboratory results during and following atezolizumab administration

Secondary Objectives

The secondary objectives of the study include evaluation of the efficacy of atezolizumab based on the following disease response endpoints:

- Overall survival (OS), defined as the time from initiation of study treatment to death from any cause
- Progression-free survival (PFS), defined as the time from initiation of study treatment to the first occurrence of disease progression or death from any cause, whichever occurs first. PFS will be calculated based on disease status evaluated by the investigator according to RECIST v1.1, and also by disease status evaluated by the investigator according to modified RECIST
- Overall response rate (ORR), defined as the proportion of patients with a best overall response of either complete response (CR) or partial response (PR). ORR will be calculated based on disease status evaluated by the investigator according to RECIST v1.1, and also by disease status evaluated by the investigator according to modified RECIST

- Disease control rate (DCR), defined as the sum of the CR, PR and stable disease (SD) rates. DCR will be calculated based on disease status evaluated by the investigator according to RECIST v1.1, and also by disease status evaluated by the investigator according to modified RECIST
- Duration of response (DoR), defined as the time from first occurrence of a documented response to disease progression or death from any cause, whichever occurs first. Duration of response will be calculated based on disease status evaluated by the investigator according to RECIST v1.1, and also by disease status evaluated by the investigator according to modified RECIST

Additional secondary study objectives include the evaluation of efficacy of atezolizumab according to the following patient-reported outcomes (PROs; Appendix 4):

- Change from baseline in health-related quality of life (HRQoL), as assessed using the EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30)
- EuroQol EQ-5D-5L-assessed utility

Exploratory Objectives

Exploratory study objectives may include evaluations of atezolizumab efficacy according to additional efficacy endpoints.

Biomarker Objectives

The biomarker objectives of the study are as follows:

- To evaluate PD-L1 prevalence based on retrospective evaluation of PD-L1 expression in tumor tissue measured by IHC. PD-L1 testing may be conducted on a subset of samples at local laboratories for inter-laboratory concordance evaluation
- The study also includes exploratory biomarker objectives to examine centrally assessed biomarkers and biomarker profiles in tumor tissue, and to correlate these with safety and/or efficacy outcomes. Biomarkers and biomarker profiles may be assessed using various methodologies including, but not limited to, IHC (single and multiplex, e.g., PD-L1 expression and immune cell infiltration analyses), RNA and DNA analysis (e.g., mutation and expression analyses)

Study Design

Description of Study

Study MO29983 is an open label, single-arm, multicenter study of the safety of atezolizumab as second-line treatment for patients with locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract. The study includes evaluation of the efficacy of atezolizumab and potential tumor biomarkers associated with atezolizumab. An overview of study design is shown in the Synopsis Figure.

Study screening will take place within 28 days prior to initiation of study treatment. Eligible patients will be enrolled and begin treatment with 1200 mg atezolizumab IV every 3 weeks. The single agent study treatment will continue until investigator-assessed loss of clinical benefit, unacceptable toxicity, investigator or patient decision to withdraw from therapy, or death (whichever occurs first).

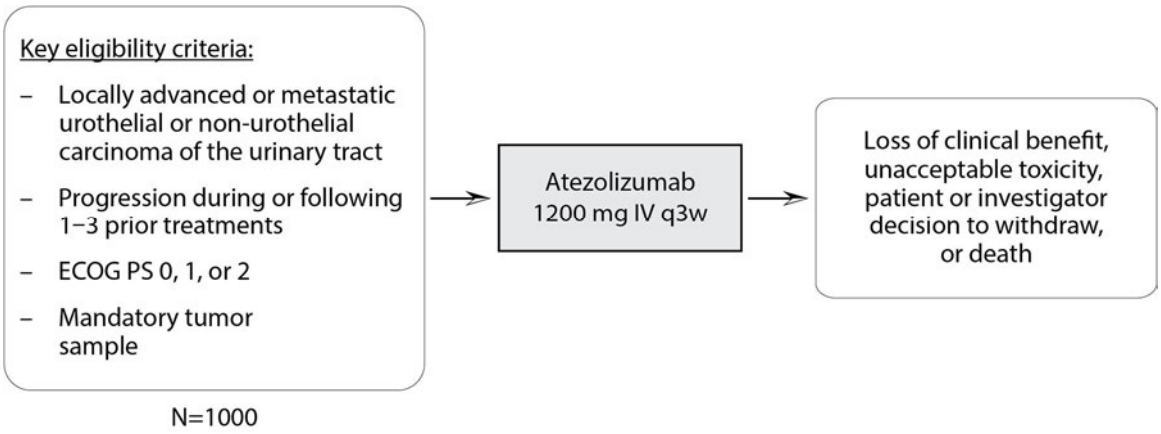
During the study treatment period, patients will be followed for safety based on AE assessments including vital signs, physical findings and clinical laboratory test results. Efficacy will be evaluated by the investigator according to both RECIST v1.1 (Appendix 3) and modified RECIST (Appendix 2). Exploratory biomarker analyses will be conducted based on primary tumor tissue or biopsied metastatic tumor tissue collected at baseline and an optional tumor sample collected at the second study treatment cycle.

Following discontinuation of study treatment, safety assessments will be conducted 30 days after the last study drug administration or until initiation of other anti-cancer therapy (whichever occurs first). Thereafter, patients will be followed for disease progression (unless this has

already occurred), SAEs, AEs of special interest, anti-cancer therapy and survival. Follow-up will continue for up to four years after the last patient is enrolled in the study.

An iDMC established for the study will review all AEs, SAEs and AEs of special interest and cumulative safety data.

Synopsis Figure. Study Schema



ECOG PS, Eastern Cooperative Oncology Group performance status; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; GC, gemcitabine and cisplatin.

Number of Patients

Approximately 1000 patients with locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract who progressed on one to three prior combination lines of systemic therapy for inoperable, locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract will be enrolled in this study. Patients who discontinue the study prior to study treatment initiation will not be replaced.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed informed consent form
2. Age ≥ 18 years
3. Is, according to the investigator's judgment, able to comply with the study protocol
4. Histologically documented locally advanced (T4b, any N; or any T, N 2−3) or metastatic (M1, Stage IV) urothelial or non-urothelial carcinoma of the urinary tract
   - Urinary tract carcinoma includes carcinoma of the bladder, ureter, urethra, and renal pelvis
   - Primary non-urothelial carcinoma includes all sub-types listed in the WHO classification (see Appendix 8)

     Bellini collecting duct tumors are allowed if independently reviewed by two expert pathologists from different sites

   - Lymphoma, sarcoma, and renal cell carcinoma are excluded
5. Patients with measurable and/or non-measurable disease according to RECIST v1.1 are allowed

6. Must have progressed during or following treatment with at least one (and not more than 3) prior treatments for inoperable, locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract
   - Patients who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment will be considered as having a first line of treatment for metastatic disease
   - Patients who were intolerant to prior systemic treatment are allowed as long as they had received at least 2 treatment cycles
   - Platinum- or non-platinum-based chemotherapy regimens are allowed
   - Low-dose chemotherapy given as radiosensitizer for curative treatment of localized disease does not count as a line of systemic chemotherapy

7. Representative formalin-fixed paraffin-embedded (FFPE) tumor specimen block available for submission
   - Only tissue from core needle (with ≥ 3 cores), punch, incisional, excisional, or forceps biopsies will be accepted. Fine-needle aspiration, brushing, bone tissue, and lavage samples are not acceptable
   - If an appropriate tumor specimen is not available, a sample will be collected by biopsy during the study screening period
   - ONLY at sites where local laws and regulations prohibit the sending of tumor specimen blocks to an outside central laboratory, specimen slides are acceptable. A minimum of 15 unstained serially-cut sections must be prepared and sent per tumor sample. For details, please refer to the Sample Handling Manual

8. Eastern Cooperative Oncology Group (ECOG) Performance Status 0, 1 or 2
9. Life expectancy ≥ 12 weeks
10. Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 2 weeks prior to the first study treatment:
    - Absolute neutrophil count ≥ 1500 cells/μL (without granulocyte colony-stimulating factor support within 2 weeks prior to the first study treatment)
    - White blood cell count > 2500/μL
    - Lymphocyte count ≥ 500/μL
    - Platelet count ≥ 100,000/μL (without transfusion within 2 weeks prior to the first study treatment)
    - Hemoglobin ≥ 9.0 g/dL (patients may be transfused or receive erythropoietic treatment to meet this criterion)
    - Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase ≤ 2.5 times the upper limit of normal (ULN), with the following exceptions:

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

      Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 × ULN

    - Serum bilirubin ≤ 1.5 ×ULN. Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled
    - Calculated creatinine clearance ≥ 15 mL/min (Cockcroft-Gault formula)
    - International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 ×ULN. This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation must be on a stable dose

11. Patients with treated, asymptomatic central nervous system (CNS) metastases are eligible, provided they meet all of the following criteria:
    - Evaluable disease outside the CNS

- No history of intracranial or spinal cord hemorrhage
- No evidence of significant vasogenic edema
- No stereotactic radiation within 7 days or whole-brain radiation or neurosurgical resection within 2 weeks before the start of study treatment
- Have had a screening CNS radiography ≥ 2 weeks since completion of radiotherapy or surgical resection
- Radiographic demonstration of interim stability (i.e. no progression) between the completion of CNS-directed therapy and the screening radiographic study

Note: Patients on stable doses of anticonvulsants or on prednisone doses (or dose equivalents) of ≤ 20 mg/day are allowed

12. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 5 months after the last dose of atezolizumab
    - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus)
    - Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception

<u>Exclusion Criteria</u>

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

1. Treatment with more than three prior lines of systemic therapy for inoperable, locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract
2. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 4 weeks prior to study treatment initiation
    - Patients who were in another clinical trial with therapeutic intent within 4 weeks of study treatment initiation but were not on active drug in that prior trial are eligible
    - Patients who were in another clinical trial with therapeutic intent within 4 weeks of study treatment initiation but were in the follow-up phase of that prior trial and had stopped receiving active drug 4 or more weeks before study treatment initiation are eligible
3. Treatment with chemotherapy within 2 weeks prior to study treatment initiation
4. Treatment with radiotherapy ongoing at the time of study entry (for CNS-directed radiotherapy, please refer to Inclusion Criterion 11)
5. Pregnant or lactating, or intending to become pregnant during the study
    - Women who are not postmenopausal (postmenopausal defined as ≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 2 weeks prior to initiation of study drug
6. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)

7. Malignancies other than the one studied in this protocol within 5 years prior to Cycle 1, Day 1
   - Patients with localized low risk prostate cancer (defined as Stage ≤ pT2b, Gleason score ≤ 7, and prostate-specific antigen [PSA] at prostate cancer diagnosis ≤ 20 ng/mL) treated with curative intent and without PSA recurrence are eligible
   - Patients with pre-existing low risk prostate cancer (defined as Stage T1/T2a, Gleason score ≤ 6, and PSA ≤ 10 ng/mL) who are treatment-naive and undergoing active surveillance are eligible
   - Patients with malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death < 5% at 5 years) are eligible provided they meet all of the following criteria:

     Malignancy treated with expected curative intent (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent)

     No evidence of recurrence or metastasis by follow-up imaging and any disease-specific tumor markers

8. Significant cardiovascular disease, such as New York Heart Association cardiac disease ≥ Class III, myocardial infarction within 3 months, unstable arrhythmias, or unstable angina
   - Patients with known coronary artery disease or left ventricular ejection fraction < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate

9. Significant renal disorder indicating a need for renal transplant
10. Signs or symptoms of severe infection within 2 weeks prior to initiation of study treatment, including but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
11. Major surgical procedure within 4 weeks prior to study treatment initiation or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis
12. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
13. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
14. History of autoimmune disease (Appendix 5) are allowed if controlled and on stable treatment (i.e., same treatment, same dose) for the last 12 weeks, with the exception of:
   - Patients taking concurrent abatacept or belatacept treatment, unless therapy has been withdrawn for > 8 weeks
   - Patients with a history of serious or life threatening immune-related events
   - No more than 1 concomitant autoimmune disease at the time of study entry is allowed unless one of them is:

     Autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone

     Controlled Type I diabetes mellitus on a stable dose of insulin regimen

     A medical history of such entities as atopic disease or childhood arthralgias, where the clinical suspicion of autoimmune disease is low. 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)

     Vitiligo

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

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

17. Patients with active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C
    - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible
    - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA

18. Active tuberculosis
19. Administration of a live, attenuated vaccine within 4 weeks prior to study treatment initiation
    - Influenza vaccination should be given during influenza season only (e.g., approximately October to March in the Northern Hemisphere and April through September in the Southern Hemisphere) and must not be a live, attenuated vaccine.
    - Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to study treatment initiation or at any time during the study treatment, and so for 5 months thereafter

20. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti−CTLA-4, anti−PD-1, and anti−PD-L1 therapeutic antibodies
    - Patients who have received prior treatment with anti-CTLA-4 may be enrolled provided at least 5 half-lives (approximately 75 days) have elapsed from the last dose of anti−CTLA-4 to the first dose of atezolizumab and there was no history of severe immune-related adverse effects from anti-CTLA-4 (NCI CTCAE Grade 3 or 4)

21. Treatment with systemic immunostimulatory agents (including, but not limited to, interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to initiation of study treatment
    - Prior cancer vaccines and cellular immunotherapy are permitted

22. Specifically for patients <u>without</u> autoimmune disease: treatment with systemic corticosteroids or other systemic immunosuppressive medications (including, but not limited to, prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to study treatment initiation or anticipated requirement for systemic immunosuppressive medications during the study treatment period
    - For patients with CNS metastases, use of prednisone at a dose (or dose equivalent) of ≤ 20 mg/day is acceptable
    - Chronic use of prednisone or equivalent should be discussed with the Medical Monitor
    - The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency and topical steroids for cutaneous diseases are allowed.

    Note: For patients with autoimmune disease, immunosuppressive medications are permitted if the patient has controlled autoimmune disease and stable treatment (i.e., same treatment, same dose) for the previous 12 weeks.

End of Study

The end of study will occur when all patients enrolled have either died, withdrawn consent, are lost to follow up, or have been followed for 48 months since the last study patient is enrolled, whichever occurs first.

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 6 years.

Investigational Medicinal Product

The investigational medicinal product (IMP) for this study is atezolizumab.

Statistical 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 (CI) 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 (Q1 and Q3) when applicable, and minimum and maximum.

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

All analyses will be performed in SAS, version 9.3.

Primary Analysis

The primary endpoint of the study is the incidence of treatment-emergent AEs. Verbatim descriptions of AEs will be mapped to MedDRA thesaurus terms and graded according to the National Cancer Institute Common Terminology Criteria version 4.0. Multiple occurrences of the same event will be counted once at the maximum severity.

Other safety variables will include:

- Drug exposure (treatment duration, number of doses, dose intensity and dose modifications/discontinuations, with reasons)
- All AEs
- SAEs
- AEs (grade 3–5)
- AEs of special interest
- 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 confidence intervals (CIs) will be presented, as applicable. Time to first incidence of selected event types will also be estimated and presented graphically using the Kaplan-Meier method.

Treatment exposure, discontinuation rate, and cause of death will be analyzed by frequency tables. When appropriate, median time on treatment will be estimated by the Kaplan-Meier approach or 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 and newly occurring Grade 3 and 4 laboratory values during treatment will be summarized by frequency tables.

Concomitant medications recorded during the study will be summarized by frequency tables.

Determination of Sample Size

This is a single-arm safety study. There is no formal statistical hypothesis and all analyses will be descriptive. The results for the primary safety variables will be presented via percentages and corresponding 95% Clopper-Pearson CIs.

A sample size of approximately 1000 patients is planned for this study. The precision of rare AE incidence estimates presented by two-sided exact 95% Clopper-Pearson CIs are shown in the Synopsis Table.

Synopsis Table. Two-Sided Clopper-Pearson 95% Confidence Intervals for Adverse Event Rate Estimates

Number of Patients with at Least One Event (Expected) N=1000	Expected Event Rate (%)	Lower limit of CI (%)	Upper limit of CI (%)
12	1.2	0.62	2.09
10	1.0	0.48	1.83
8	0.8	0.35	1.57
6	0.6	0.22	1.3
5	0.5	0.16	1.16
4	0.4	0.11	1.02
3	0.3	0.06	0.87
2	0.2	0.02	0.72
1	0.1	0.00	0.56

CI = confidence interval.

Therefore, for a sample size of 1000 patients and an expected AE incidence of 0.5%, based on the half-width of the Clopper-Pearson 95% confidence interval, the true AE rate can be estimated with a precision of: ±(1.16% – 0.16%)/2 % = ±0.5 %.

Interim Analyses

An Independent Data Monitoring Committee (iDMC) will conduct interim reviews of accumulated safety data. The first review will be performed three months after enrollment of the first patient. The iDMC will then decide on the basis of the initial reviewed data when to meet the following time, but at minimum, the iDMC will perform another overall safety review after 500 patients have been followed up for 3 months. Ad hoc iDMC review meetings may occur as needed at any time during the study period. In case of important safety findings, the iDMC may also request to review efficacy data for an overall assessment of the risk-benefit profile to the patients.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACCI	Age-adjusted Charlson comorbidity index
AE	adverse event
ADA	anti-drug antibody
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CarboGem	carboplatin and gemcitabine
CBC	complete blood count
CI	confidence interval
ClinRO	clinician-reported outcome
COPD	chronic obstructive pulmonary disease
COVID-19	*Coronavirus disease 2019*
CR	complete response
CRO	contract research organization
CT	*computed tomography*
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
DCR	disease control rate
DoR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for the Research and Treatment of Cancer
Fc	crystallizable fragment
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GC	gemcitabine and cisplatin
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life

Abbreviation	Definition
IC	tumor-infiltrating immune cells
ICH	International Conference on Harmonisation
iDMC	Independent Data Monitoring Committee
IFN	interferon
IgG1	immunoglobulin G, subclass 1
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INR	International Normalised Ratio
IRB	Institutional Review Board
IRF	independent review facility
ITT	intent-to-treat
IV	intravenous
LDH	lactate dehydrogenase
LHL	hemophagocytic lymphohistiocytosis
MAS	macrophage activation syndrome
M-CAVI	methotrexate, carboplatin, and vincristine
MRI	*magnetic resonance imaging*
MVAC	methotrexate, vinblastine, doxorubicin, and cisplatin
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
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen
Q1 & Q3	first and third quartiles
q3w	every 3 weeks
QLQ-30	Quality-of-Life Questionnaire Core 30
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
RBR	Research Biosample Repository

Abbreviation	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
SAE	serious adverse event
SARS-CoV-2	*severe acute respiratory syndrome coronavirus 2*
SITC	*Society for Immunotherapy for Cancer*
SCC	squamous cell carcinoma
SUSAR	suspected unexpected serious adverse reaction
TC	tumor cells
TSH	thyroid stimulation hormone
UC	urothelial carcinoma of the urinary tract
ULN	upper limit of normal
WBC	white blood cell

1. BACKGROUND

Bladder cancer is the ninth most common cancer in the world (World Cancer Research Fund International 2016). In 2012, an estimated 14.1 million people worldwide had bladder cancer, of whom 330,380 were newly diagnosed; in the same year, 123,051 deaths were attributable to the disease (International Agency for Research on Cancer 2016; World Cancer Research Fund International 2016). In the United States, estimates are that 76,960 new cases of bladder cancer will be diagnosed in 2016 (about 58,950 in men and 18,010 in women), and 16,390 deaths will occur due to the disease (American Cancer Society 2016a).

1.1 UROTHELIAL CARCINOMA OF THE URINARY TRACT

Urothelial carcinoma of the urinary tract (UC), also termed transitional cell carcinoma, is the most common cancer of the urinary system, responsible for more than 90% of diagnosed cases in the industrialized world. The bladder is the predominant location for UC, but tumors can also originate in the renal pelvis, urethra, or ureter, which are also lined by urothelial cells. The 5-year relative survival rate in patients with metastatic UC is approximately 15%, compared to approximately 77% in a population comprising all stages of UC (American Cancer Society 2016b). Prognostic factors for poor survival in patients with metastatic UC include advanced stage of disease at the time of initial diagnosis, Karnofsky Performance Status < 80%, and visceral metastasis (i.e., lung, liver, or bone; (Bajorin et al. 1999)). The presence of any of these unfavorable features was associated with a median survival of 4 months, compared with 18 months in patients without these features (Loehrer et al. 1992).

Patients with previously untreated UC typically receive platinum-based chemotherapy. The first evidence that chemotherapy produced a significant benefit in patients with advanced UC came in the mid-1980s with the publication of two studies showing that the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) produced overall response rates greater than 70%, with approximately 35% of patients achieving a complete response (CR) (Sternberg et al. 1985; Sternberg et al. 1989). Subsequently, two prospective randomized Phase III trials demonstrated the superiority of MVAC with regard to overall survival (OS) in patients with advanced disease (Logothetis et al. 1990; Loehrer et al. 1992).

In an effort to develop a less toxic regimen, the combination of gemcitabine and cisplatin (GC) was tested against MVAC in the Phase III setting following the demonstration of activity in earlier phase trials. In the Phase III trial, patients allocated to GC had a similar OS to those randomized to MVAC (14.0 months for GC vs. 15.2 months for MVAC; hazard ratio [HR] = 1.09; 95% confidence interval (CI): 0.88, 1.34, p=0.66), with less Grade 3 or 4 toxicity (including neutropenia, neutropenic sepsis, and mucositis) (von der Maase et al. 2005). As a result, GC has largely displaced MVAC as the standard of care.

Despite the efficacy of first-line regimens for patients with advanced UC, nearly all patients experience disease progression and require second-line therapy. There are currently no approved second-line therapies for UC in the United States and only one approved agent, vinflunine, in the European Union.

While several chemotherapeutic agents have been studied in the second-line setting over the last two decades, the overall response rates are low (see Table 1) and associated with considerable toxicity. No survival benefit has been demonstrated with second-line chemotherapy. Consequently, the National Comprehensive Cancer Network guidelines recommend participation in a clinical trial of new agents. If no trials are available, treatment with a single-agent taxane is preferred for palliation. Additional recommended palliative options include single-agent cisplatin, carboplatin, doxorubicin, ifosfamide, pemetrexed, methotrexate, and vinblastine. European Society of Medical Oncology and European Association of Urology clinical practice guidelines recommend vinflunine, but also highlight that other agents used in this space may have similar benefit and recommend clinical trials of other treatments (Bellmunt et al. 2009; Stenzl et al. 2011).

The registrational Phase III study of vinflunine as a second-line agent compared vinflunine versus best supportive care alone in 370 patients progressing after a platinum-containing therapy. The intent-to-treat (ITT) analysis showed an improvement in response rate (8.6% vs. 0%), but did not show a statistically significant OS benefit for vinflunine compared with placebo (6.9 vs. 4.6 months, HR=0.88; 95% CI: 0.69, 1.12; p=0.287). Key toxicities included Grade 3 or 4 neutropenia (50%), febrile neutropenia (6%), anemia (19%), fatigue (19%), and constipation (16%).

A summary of single-agent Phase II trials of second-line therapy is provided in Table 1.

Table 1 Phase II Single-Agent Trials in Previously Treated Patients

Second-Line Therapy Regimen	RR (%)	PFS (months)	OS (months)
Weekly paclitaxel (n=31)	10	2.2	7.2
Nab-paclitaxel (n=47)	28	6.0	10.8
Irinotecan (n=40)	5	2.1	5.4
Ixabepilone (n=42)	11.9	2.7	8.0
Bortezomib (n=25)	0	1.4	5.7
Pemetrexed (n=47)	27.7	2.9	9.6
Oxaliplatin (n=18)	6	1.5	7.0
Ifosfamide (n=56)	20	2.4	5.5
Lapatinib (n=59)	3	2	4.5
Pemetrexed (n=12)	8	–	–
Docetaxel (n=30)	13	–	9.0
Gemcitabine (n=35)	11	4.9	8.7
Gemcitabine (n=44)	22.5	–	5.0
Topotecan (n=44)	9.1	1.5	6.3
Ifosfamide+ gemcitabine (n=34)	21	4.0	9.0
Carboplatin + paclitaxel (n=44)	16	4.0	6.0
Vinflunine (n=51)	18	3.0	6.6
Vinflunine (n=253)	8.6	3.0	6.9
Gefitinib (n=31)	3	–	3.0
Sorafenib (n=27)	0	–	6.8
Sunitinib (n=45)	7	2.4	6.9
Pazopanib (n=41)	17.1	2.6	4.7

OS = overall survival; PFS = progression-free survival; RR = response rate.
Note: Adapted from (Sonpavde et al. 2010).

1.2 NON-UROTHELIAL CANCER OF THE URINARY TRACT

Several non-urothelial subtypes of bladder cancer are also observed in the clinic, including squamous cell carcinoma (SCC) (1%–2% of all cases), adenocarcinoma (1% of all cases), small cell carcinoma (< 1% of all cases), and other rarer forms (American Cancer Society 2016a). Non-urothelial bladder cancer is more common in non-Western areas of the world (Chalasani et al. 2009). The prognosis for most forms of advanced non-urothelial bladder cancer is poor, but few clinical trials have specifically focused on treatment of these specific populations (Sternberg and Swanson 1997; Abol-Enein et al. 2007).

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) of the urinary tract has a poor prognosis, with most patients dying within 1 to 3 years of diagnosis (Abol-Enein et al. 2007; Chalasani et al. 2009). The overall 5-year survival rate is estimated to be approximately 16%, with only 8% of patients developing metastatic disease.

Reported results on the effectiveness of external irradiation have been uniformly poor (Bessette et al. 1974; Rundle et al. 1982), but surgical treatment appears to provide better outcomes (Richie et al. 1976; Swanson et al. 1990; Stenzl et al. 2001; Nishiyama et al. 2004). The role of neoadjuvant or adjuvant chemotherapy in the treatment of patients with pure SCC of the urinary tract is uncertain (Abol-Enein et al. 2007). Data from clinical trials on the effectiveness of chemotherapy in advanced SCC of the urinary tract, particularly following its recurrence after doublet chemotherapy or MVAC, is limited.

Adenocarcinoma

Primary adenocarcinoma of the urinary tract has a poor prognosis, regardless of the modalities used for treatment (Abol-Enein et al. 2007; Chalasani et al. 2009). The 5-year survival rates range from 0% to 31%. In a retrospective series of 48 patients treated for primary adenocarcinoma of the bladder, stage was the only factor that was highly predictive of outcome.

Adenocarcinoma is not a radioresponsive disease: reported 5-year survival is <20% in patients treated with external irradiation alone (Abol-Enein et al. 2007). Radical cystectomy with or without adjuvant therapy has been examined by several authors. Most published reports are based on few patients and involve short-term follow-up. Reported 5-year disease-free survival rates range from 0% to 80% (Abol-Enein et al. 2007).

Experience in the use of chemotherapy for the treatment of patients with adenocarcinoma of the urinary tract is limited. From results observed with gastrointestinal adenocarcinoma, combination chemotherapy based on 5-fluorouracil and cisplatin has been attempted by several investigators. Most published series involve small numbers, and the response is universally unsatisfactory (Nevin et al. 1974; Nocks et al. 1983; Logothetis et al. 1985).

Small Cell Carcinoma

The small number of reports on patients with small cell carcinoma of the urinary tract suggests that it behaves similarly to small cell carcinoma of the lung (Abol-Enein et al. 2007). Overall, local treatment yields poor survival rates, and systemic therapy provides improvement. In general, however, treatment of small cell carcinoma of the urinary tract has received relatively limited examination in clinical trials.

1.3 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, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

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

1.3.1 PD-L1 Expression as a Biomarker

In an increasing number of studies, expression of PD-L1 has been associated with poor prognosis in UC:

- Nakanishi et al. found that PD-L1 expression was significantly associated with a high frequency of disease recurrence and poor survival rate in UC (Nakanishi et al. 2007). Multivariate analysis also showed PD-L1 expression to be a more significant prognostic factor than tumor grade
- Zhang et al. observed PD-L1 expression in 43% of primary bladder cancers and demonstrated that immunohistochemistry (IHC) positivity and intensity was associated with tumor grade and staging (Zhang et al. 2013)
- Faraj et al. showed high intratumoral CD8+ T cell density to be associated with better OS and disease-specific survival in advanced bladder cancer (Faraj et al. 2015)
- Bellmunt et al. reported that PD-L1 is widely expressed on tumor cells and tumor-infiltrating mononuclear cells in urothelial cancers (Bellmunt et al. 2015). PD-L1 expression on tumor cells was not predictive of overall OS, but PD-L1 expression on tumor-infiltrating mononuclear cells did associate with longer survival in patients who developed metastases

The SP142 PD-L1 immunohistochemistry (IHC) assay (Investigational Use Only; Ventana Companion Diagnostics Pharma Services, Tucson, AZ) is one assay that is used to assess PD-L1 expression in tumors. This specific and sensitive assay has been designed to quantify PD-L1 expression on tumor cells (TC) and tumor-infiltrating immune cells (IC) in human formalin-fixed, paraffin-embedded (FFPE) tumor-tissue samples, utilizing the SP142 rabbit monoclonal antibody as primary antibody in the staining reaction (Herbst et al. 2014). Additional anti-PD-L1 antibodies, including but not limited to SP263, are under investigation for PD-L1 assessment.

As the expression level of PD-L1 on urothelial TC has not been correlated with OS (see, e.g., (Bellmunt et al. 2015)) the SP142 PD-L1 IHC assay is currently used in UC patients solely to quantitate PD-L1 positivity on IC. The IHC-based scoring criteria for PD-L1 expression are presented in Table 2.

Table 2 Example Criteria for PD-L1 Expression Assessment on IC

Description of IHC Scoring Criteria	PD-L1 Expression Level
Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in ICs covering < 1% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC0
Presence of discernible PD-L1 staining of any intensity in ICs covering between ≥ 1% and < 5% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC1
Presence of discernible PD-L1 staining of any intensity in ICs covering between ≥ 5% and < 10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC2
Presence of discernible PD-L1 staining of any intensity in ICs covering ≥ 10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC3

IC = tumor-infiltrating immune cell; IHC = immunohistochemistry; PD-L1 = programmed death-ligand 1.
Note: Cutoffs for PD-L1 positivity are being evaluated in ongoing trials.

The relationship between PD-L1 expression on IC and atezolizumab efficacy in patients with UC is presented below (Section 1.3.3).

1.3.2 Clinical Development Program

Four ongoing studies are currently examining the efficacy and safety of atezolizumab in advanced UC, either as monotherapy or in combination with other agents.

Phase Ia Study PCD4989g

Ongoing Study PCD4989g is a multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent by intravenous (IV) infusion every 3 weeks (q3w) to patients with locally-advanced or metastatic solid malignancies or hematologic malignancies. Ongoing expansion cohorts are studying the efficacy in patients with pancreatic cancer, bladder cancer, breast cancer, esophageal cancer, prostate cancer, small cell lung cancer, malignant lymphoma, multiple myeloma, and other less common tumor types.

As of 2 December 2014, efficacy analyses were performed on 87 patients with locally advanced or metastatic UC who were followed up for a minimum of 12 weeks. Responses were observed in all PD-L1 subgroups (ranging from 13.3% to 66.7%), with higher objective response rates (ORRs) associated with higher PD-L1 expression on IC.

Phase II Study GO29293 (IMvigor 210)

Ongoing Study GO29293 (IMvigor 210) is a single-arm, open label, Phase II study to assess the clinical benefit of atezolizumab as a single agent in patients with locally advanced or metastatic UC. The co-primary endpoints were independent review facility (IRF)-assessed ORR according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) and investigator-assessed ORR according to modified RECIST criteria. Approximately 400 patients have been enrolled into two separate cohorts: approximately 100 with advanced disease who are treatment-naive but cisplatin ineligible (Cohort 1); and 311 who progressed on prior platinum-based chemotherapy (Cohort 2). Results from Cohort 2 were recently published (Rosenberg et al. 2016) and will be described in detail below (Section 1.3.3).

Phase III Study GO29294 (IMvigor 211)

Ongoing Study GO29294 (IMvigor 211) is a two-arm, open label, randomized, Phase III study to assess the efficacy and safety of atezolizumab compared with chemotherapy (vinflunine, paclitaxel, or docetaxel) in patients with locally advanced or metastatic UC who have progressed after previous platinum-based chemotherapy. The primary endpoint of the study is investigator-assessed OS, defined as the time between the date of randomization and death due to any cause.

Phase III Study WO30070

Ongoing Study WO30070 is a Phase III, multicenter, randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of atezolizumab/gemcitabine/ carboplatin versus placebo/gemcitabine/carboplatin in patients with locally advanced or metastatic UC who have not received prior systemic therapy and who are ineligible to receive cisplatin-based therapy. The co-primary endpoints of the study are PFS and OS.

Please refer to the Atezolizumab Investigator's Brochure for more details regarding atezolizumab clinical studies.

1.3.3 Efficacy

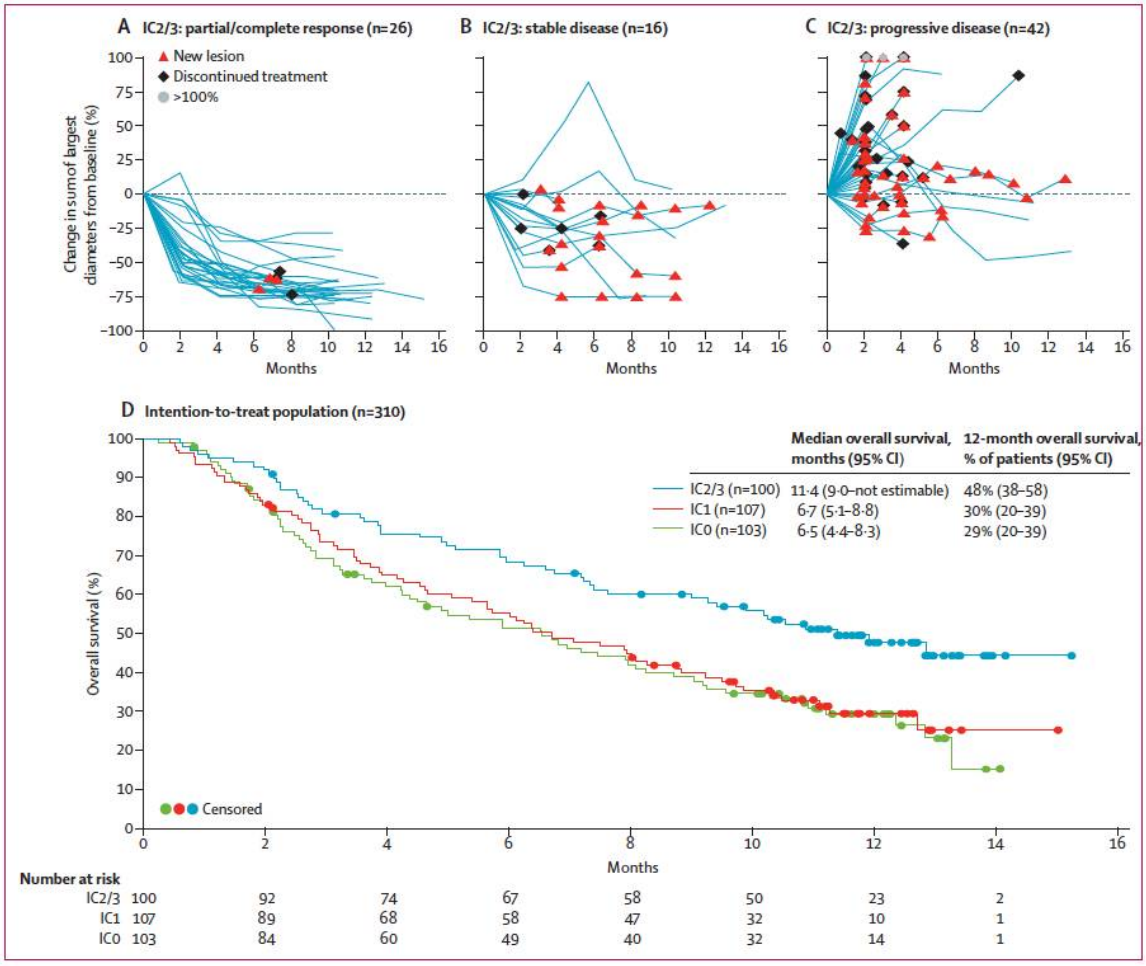
IMvigor 210 (Study GO29293) is a single-arm, open-label, Phase II study to assess the clinical benefit of atezolizumab as a single agent in patients with locally advanced or metastatic UC. The co-primary endpoints of the study were IRF-assessed ORR according to RECIST v1.1 and investigator-assessed ORR according to modified RECIST criteria. Results from Cohort 2, which contained patients whose disease had progressed after previous platinum-based chemotherapy (see Section 1.3.2), were recently published (Rosenberg et al. 2016).

Between 13 May 2014, and 19 Nov 2014, 486 patients were screened and 316 patients were enrolled into IMvigor 210. Of these, 311 patients received atezolizumab treatment (five enrolled patients later did not meet eligibility criteria and were not dosed with study drug).

The primary analysis (data cutoff 05 May 2015) showed that treatment with atezolizumab resulted in significantly improved ORR for each pre-specified immune cell group when compared with a historical control ORR of 10% (IC2/3: 27% [95% CI 19–37%], $p<0.0001$; IC1/2/3: 18% [13–24%], $p=0.0004$). The same was true for the entire population of patients (15% [11–20], $p=0.0058$). With longer follow-up by independent review (data cutoff 14 September 2015), ORRs were 26% (95% CI 18–36%) in the IC2/3 group, 18% (13–24%) in the IC1/2/3 group, and 15% (11–19%) overall in all 310 patients. Ongoing responses were recorded in 38 (84%) of 45 responders after a median follow-up of 11.7 months (95% CI 11.4–12.2 months).

Further details of the response to atezolizumab in IMvigor 210 are presented in Figure 1.

Figure 1. Change in Sum of the Diameters Over Time by Best Response in the PD-L1 IC2/3 group and Overall Survival in PD-L1 Immune Cell Groups



IC = immune cell

Note: The above figure presents the percentage change in the sum of longest diameters by IRF-assessed RECIST v1.1 in the IC2/3 group by (A) responders, (B) patients with stable disease, and (C) patients with progressive disease. Patients without a measurable baseline tumor assessment or without post-baseline tumor measurements were not included. (D) Kaplan-Meier overall survival curves for the IC0, IC1, and IC2/3 groups.

1.3.4 Safety

Safety information for atezolizumab has been gleaned from studies across the entire development program, including those where atezolizumab is investigated in combination with other unapproved agents. As of May 2016, atezolizumab has been administered to approximately 6050 patients with solid tumors and hematologic malignancies.

Study PCD4989g, in which atezolizumab is being used as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies, provides the

majority of data (with 558 safety evaluable patients as of the data extraction date of 11 May 2015) for the safety profile of atezolizumab as monotherapy. Currently, no maximum tolerated dose, no dose-limiting toxicities and no clear dose-related trends in the incidence of adverse events (AEs) have been determined. Fatigue, decreased appetite, nausea and cough were commonly reported adverse events in single and combination therapy. The overall immune-mediated adverse events reported for atezolizumab were considered mild to moderate in severity, and the majority of patients were able to continue on atezolizumab therapy.

Adverse Events

In PCD4989g of the 558 safety evaluable treated patients 376 patients (67.4%) reported at least one treatment-related adverse event, Grade 3–4 AEs were reported in 239 patients (42.8%) of which 66 (11.8%) were considered related. Grade 3 and 4 AEs considered related by the investigator included dyspnea, pneumonitis, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased gamma-glutamyl transferase (GGT), lymphocyte count decreased, cardiac tamponade, asthenia, autoimmune hepatitis, pneumonia, influenza, and hypoxia. More detailed information is provided in the latest version of the IB.

Immune-mediated Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated adverse events have been closely monitored during the atezolizumab clinical program. These include potential dermatologic, hepatic, endocrine and respiratory events. Events of immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, meningoencephalitis and infusion-related reactions are considered potential adverse drug reactions associated with atezolizumab.

IMvigor 210 (Cohort 2)

The median duration of treatment in IMvigor 210 was 12 weeks (range 0–66 weeks) at the study's cutoff date (14 September 2015). All-cause, any grade AEs were reported in 300 (97%) of 310 patients, with 170 (55%) patients experiencing a grade 3–4 AE. Two-hundred fifteen (69%) patients had a treatment-related AE of any grade, and 50 (16%) had a grade 3–4 treatment-related AE (Table 3).

Table 3 Treatment-Related Adverse Events in 310 Patients who Received Atezolizumab in IMvigor 210 (14 September 2015 Data Cut)

	Any grade n (%)	Grade 3–4 n (%)
Any adverse event	215 (69%)	50 (16%)
Fatigue	93 (30%)	5 (2%)
Nausea	42 (14%)	0
Decreased appetite	36 (12%)	2 (1%)
Pruritis	31 (10%)	1 (<1%)
Pyrexia	28 (9%)	1 (<1%)
Diarrhea	24 (8%)	1 (<1%)
Rash	23 (7%)	1 (<1%)
Arthralgia	21 (7%)	2 (1%)
Vomiting	18 (6%)	1 (<1%)
Dyspnea	10 (3%)	2 (1%)
Anaemia	9 (3%)	3 (1%)
Aspartate aminotransferase increased	10 (3%)	2 (1%)
Pneumonitis	7 (2%)	2 (1%)
Hypotension	5 (2%)	2 (1%)
Hypertension	3 (1%)	3 (1%)
Colitis	3 (1%)	2 (1%)

Adverse events reported up until data cutoff on 14 September 2015

Ninety-three (30%) patients had an AE leading to dose interruption, and 11 (4%) had an AE that led to treatment withdrawal. Treatment-related serious adverse events (SAEs) were reported in 34 (11%) of 310 patients. No cases of febrile neutropenia were reported, and no treatment-related deaths occurred during the study.

Twenty (6%) patients had an immune-mediated AE of any grade, with pneumonitis (n=5 [2%]), dyspnea (n=3 [1%]) and increased aspartate aminotransferase (n=3 [1%]) being the most common. Thirteen (4%) patients had a grade 3–4 immune-mediated AE of any cause, including colitis, autoimmune hepatitis, hepatitis, cytokine release syndrome, pericardial effusion, and paraplegia (n=1 for each). No immune-mediated renal toxicity was observed. Sixty-nine (22%) of 310 patients had an AE that necessitated systemic steroid use.

Please refer to the Atezolizumab Investigator's Brochure for more information on the safety of atezolizumab across the clinical development program, including the occurrence of serious, related and unexpected events.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

In clinical trials, treatment with atezolizumab has produced positive clinical responses in multiple cancer types (see Atezolizumab Investigator's Brochure).

In the case of UC, the benefit-risk profile of atezolizumab treatment compared to historical controls has been favorable in patients with advanced stage UC who had progressed during or following treatment with a platinum-based chemotherapy regimen or were cisplatin-ineligible. Thus, in the IMvigor 210 study, treatment of 310 previously-treated, advanced UC patients with atezolizumab resulted in statistically significant improvements in RECIST v1.1 ORR compared to historical controls in two pre-specified immune cell groups (IC2/3 and IC1/2/3), as well as in the entire study population (Rosenberg et al. 2016). Moreover, the safety profile of atezolizumab was manageable. Thus, most treatment-related AEs were mild to moderate in nature, with fatigue, nausea, decreased appetite, pruritus, pyrexia, diarrhea, rash, and arthralgia among the most common any-grade AEs. Twenty (6%) patients had an immune-mediated AE of any grade, no cases of febrile neutropenia were reported, and no renal toxicity was observed. The preceding results indicate that atezolizumab will likely provide an important new treatment modality for advanced UC in the future, a prospect that is under active investigation in ongoing clinical trials.

Appropriate to their early stage in the clinical development plan, prior atezolizumab UC studies have had stringent enrollment criteria. In part this was done to ensure optimal safety conditions for the participants, i.e., to screen out participants with greater morbidity who might have been less tolerant of atezolizumab or more susceptible to AEs arising during the course of the study. For example:

- Participants were typically required to have an ECOG performance status of 0 or 1, meaning their disease at baseline imparted relatively limited impact on daily living abilities (ECOG performance statuses of 2 were allowed in some cohorts of earlier studies)
- Participants were prohibited from having an autoimmune disease. Treatment of autoimmune diseases typically requires immunosuppressive therapies, the effects of which remain uncharacterized, vis-à-vis, atezolizumab immunotherapy. It is also imperfectly understood how checkpoint inhibition with atezolizumab may impact symptoms and progression of autoimmune diseases. For similar reasons, participants in prior studies were required to have disease that did not require treatment with systemic corticosteroids and/or other systemic immunosuppressive medications
- Participants were not allowed to have severely reduced kidney function (i.e., glomerular filtration rate ≤ 30 mL/min), a condition associated with poor health in general and a potentially increased risk of immune-mediated renal toxicity
- Participants were not allowed to be positive for HIV

Because cancer of the urinary tract is a heterogeneous disease (Kaufman et al. 2009), earlier atezolizumab studies were also restricted to relatively specific classes of patients, thereby limiting the number of additional factors that could complicate the final analyses. For example:

- Participants were only enrolled with advanced urothelial carcinoma. This restriction was easily tenable based on the fact that > 90% of bladder cancer cases have a urothelial histology (American Cancer Society 2016a), ensuring that the majority of clinical cases were being addressed in the trials
- Participants were required to have advanced on platinum-doublet therapy prior to entering the studies. This again made sense since platinum-doublet is standard first-line treatment of advanced UC (Bellmunt et al. 2014) and, thus, the majority of clinical cases should have been eligible for the study
- Finally, participants were prohibited from enrolling with CNS metastases, except in some highly defined situations if the metastases were asymptomatic. Although rare, CNS metastases in bladder cancer appear to be increasing in incidence and are associated with significant health burden and poor outcomes (Dhote et al. 1998; Protzel et al. 2002; Boyle et al. 2013; Chung et al. 2013). From both a safety perspective and a scientific perspective (e.g., the role of the blood-brain barrier in antibody drug delivery), inclusion of this class of patients in earlier atezolizumab trials was deemed premature

Given the high unmet need for new therapies for advanced bladder cancer, it is of considerable interest to evaluate atezolizumab in a population of bladder cancer patients that mimics more closely a standard clinical population. As a first step in this process, the primary objective of Study MO29983 will be to analyze the safety of atezolizumab in a population of bladder cancer patients that includes patients who would have been screened out of many of the previous studies. The large majority of eligibility criteria in Study MO29983 remain unchanged from earlier trials and the safety of participants remains the highest priority. However, a small number of criteria have been broadened:

- Patients with a baseline ECOG performance status of 2 will now be eligible for enrollment, in addition to patients with ECOG performance statuses of 0 and 1
- CNS metastases will be allowed at baseline, if stable
- Patients with a renal clearance of ≥ 15 mL/min (rather than ≥ 30 mL/min) and/or a history of renal failure will be allowed in the study
- Prior treatment with non-platinum regimens will be allowed
- Patients with CNS metastases will be allowed to receive steroid treatments if the dose of prednisone is ≤ 20 mg/day (or equivalent)
- Patients with underlying controlled and stable autoimmune diseases will be allowed
- Patients with non-urothelial carcinoma of the urinary tract will be permitted to enroll in the trial

- Patients with HIV will be eligible, based on evidence suggesting that the PD-L1/PD-1 pathway may be operative in HIV infection and that PD-L1/PD-1 inhibition may have a role in reducing viral load

In addition to assessing safety, the current study will have secondary objectives to assess response and patient-reported outcomes, which will further advance the understanding of atezolizumab therapy in patients with cancer of the urinary tract. Finally, in exploratory analyses, the study will assess PD-L1 prevalence in tumor tissue using an IHC assay and will correlate a panel of biomarkers with efficacy and safety outcomes. These studies will continue to expand our understanding of atezolizumab and lay the groundwork for future clinical trials.

For additional rationale statements explaining the current study design, please refer to Section 3.3.

Several steps will be taken to ensure the safety of participants in MO29983. First, administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies (Section 4.3.1). Second, identified and potential risks associated with atezolizumab treatment will continue to be closely monitored throughout this study (Section 5.1.1). Third, the study will have an independent data monitoring committee (iDMC) to assess safety signals on an ongoing basis. Finally, the study contains protocol-specified drug interruption criteria designed to ensure safety (Section 5.1.2).

Overall, the efficacy and safety data in ongoing studies have shown a favorable benefit/risk ratio for atezolizumab treatment in patients with bladder cancer. With the above safety precautions in place, the estimated benefits of atezolizumab treatment outweigh the risks in this study, especially given the potential of atezolizumab—and the dearth of effective therapeutic agents currently available—in patients who have advanced urothelial and non-urothelial carcinoma of the urinary tract.

COVID-19 *Benefit–Risk Assessment*

In the setting of the *coronavirus disease 2019* (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 *severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection*. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of *SARS-CoV-2 infection*.

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 *SARS-CoV-2 infection* is altered by cancer immunotherapy.

Severe *SARS-CoV-2 infection* appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-γ *(IFN)-*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 *SARS-CoV-2 infection*.

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 *SARS-CoV-2 infection* related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy of Cancer [SITC] 2020).

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab treatment to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When

administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4.1).

2. OBJECTIVES AND ENDPOINTS

This study is being conducted to evaluate the safety of atezolizumab as second-line treatment for locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract. The study will also evaluate treatment efficacy and explore potential tumor biomarkers related to atezolizumab. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the safety of atezolizumab based on the following endpoints:

- Nature, severity, duration, frequency and timing of adverse events (AEs)
- Changes in vital signs, physical findings, and clinical laboratory results during and following atezolizumab administration

2.2 SECONDARY OBJECTIVES

The secondary objectives of the study include evaluation of the efficacy of atezolizumab based on the following disease response endpoints:

- Overall survival (OS), defined as the time from initiation of study treatment to death from any cause
- Progression-free survival (PFS), defined as the time from initiation of study treatment to the first occurrence of disease progression or death from any cause, whichever occurs first. PFS will be calculated based on disease status evaluated by the investigator according to RECIST v1.1, and also by disease status evaluated by the investigator according to modified RECIST
- Overall response rate (ORR), defined as the proportion of patients with a best overall response of either complete response (CR) or partial response (PR). ORR will be calculated based on disease status evaluated by the investigator according to RECIST v1.1, and also by disease status evaluated by the investigator according to modified RECIST
- Disease control rate (DCR), defined as the sum of the CR, PR and stable disease (SD) rates. DCR will be calculated based on disease status evaluated by the investigator according to RECIST v1.1, and also by disease status evaluated by the investigator according to modified RECIST
- Duration of response (DoR), defined as the time from first occurrence of a documented response to disease progression or death from any cause, whichever occurs first. Duration of response will be calculated based on disease status evaluated by the investigator according to RECIST v1.1, and also by disease status evaluated by the investigator according to modified RECIST

Additional secondary study objectives include the evaluation of efficacy of atezolizumab according to the following patient-reported outcomes (PROs; Appendix 4):

- Change from baseline in health-related quality of life (HRQoL), as assessed using the EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30)
- EuroQol EQ-5D-5L-assessed utility

2.3 EXPLORATORY OBJECTIVES

Exploratory study objectives may include evaluations of atezolizumab efficacy according to additional efficacy endpoints.

2.4 BIOMARKER OBJECTIVES

The biomarker objectives of the study are as follows:

- To evaluate PD-L1 prevalence based on retrospective evaluation of PD-L1 expression in tumor tissue measured by IHC. PD-L1 testing may be conducted on a subset of samples at local laboratories for inter-laboratory concordance evaluation
- To examine centrally assessed biomarkers and biomarker profiles in tumor tissue, and to correlate these with safety and/or efficacy outcomes. Biomarkers and biomarker profiles may be assessed using various methodologies including, but not limited to, IHC (single and multiplex, e.g., PD-L1 expression and immune cell infiltration analyses), RNA and DNA analysis (e.g., mutation and expression analyses)

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study MO29983 is an open label, single-arm, multicenter study of the safety of atezolizumab as second-line treatment for patients with locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract. The study includes evaluation of the efficacy of atezolizumab and potential tumor biomarkers associated with atezolizumab. An overview of study design is shown in Figure 2.

Study screening will take place within 28 days prior to initiation of study treatment. Eligible patients will be enrolled and begin treatment with 1200 mg atezolizumab IV every 3 weeks. The single agent study treatment will continue until investigator-assessed loss of clinical benefit, unacceptable toxicity, investigator or patient decision to withdraw from therapy, or death (whichever occurs first).

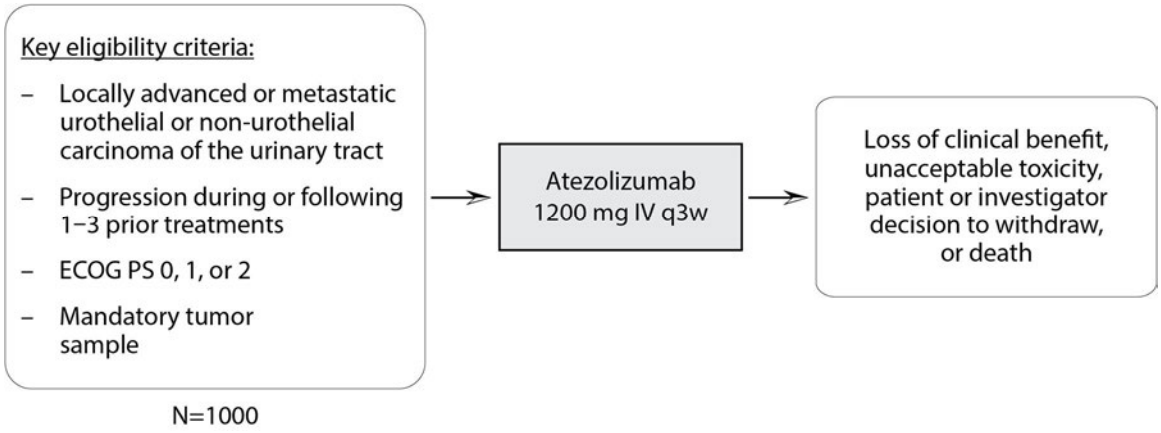
During the study treatment period, patients will be followed for safety based on AE assessments including vital signs, physical findings and clinical laboratory test results. Efficacy will be evaluated by the investigator according to both RECIST v1.1 (Appendix 3) and modified RECIST (Appendix 2). Exploratory biomarker analyses will be conducted based on primary tumor tissue or biopsied metastatic tumor tissue

collected at baseline and an optional tumor sample collected at the second study treatment cycle.

Following discontinuation of study treatment, safety assessments will be conducted 30 days after the last study drug administration or until initiation of other anti-cancer therapy (whichever occurs first). Thereafter, patients will be followed for disease progression (unless this has already occurred), SAEs, AEs of special interest, anti-cancer therapy and survival. Follow-up will continue for up to four years after the last patient is enrolled in the study.

An iDMC established for the study will review all AEs, SAEs and AEs of special interest and cumulative safety data.

Figure 2 Study Schema



ECOG PS, Eastern Cooperative Oncology Group performance status; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; GC, gemcitabine and cisplatin.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of study will occur when all patients enrolled have either died, withdrawn consent, are lost to follow up, or have been followed for 48 months since the last study patient is enrolled, whichever occurs first.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 6 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population and Analysis Groups

Please refer to Section 1.3, Study Rationale and Benefit Risk Assessment.

3.3.2 Rationale for an Open-Label Single-Arm Design

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

3.3.3 Rationale for Atezolizumab Dose and Schedule

The fixed dose of 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g as described below.

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

The atezolizumab dose is also informed by available clinical activity, safety, PK, and immunogenicity data. Anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg. The maximum tolerated dose of atezolizumab was not reached, and no dose-limiting toxicities have been observed at any dose in Study PCD4989g. Available preliminary PK data (0.03–20 mg/kg) from Study PCD4989g suggest that for doses ≥ 1 mg/kg, overall atezolizumab exhibits pharmacokinetics that are both linear and consistent with typical IgG1 antibodies.

Detectable anti-drug antibodies (ADAs) were observed in patients at all dose levels but were associated with changes in pharmacokinetics for some patients in only the lower dose cohorts (0.3, 1, and 3 mg/kg). It is unclear from currently available data in these lower dose cohorts if administration of higher doses to patients with both detectable ADAs and reduced exposure would necessarily restore exposure to expected levels. No clear relationship between the development of measurable ADAs and safety or efficacy has been observed. Available data suggest that the development of detectable ADAs does not appear to have a significant impact on the pharmacokinetics for doses from 10 to 20 mg/kg in most patients. Correspondingly, patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained target trough levels of drug despite the detection of ADAs.

Currently available PK and ADA data suggest that the 15-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent) for Phase II and Phase III studies would be sufficient to both maintain C_{trough} ≥ 6 µg/mL and further safeguard against both interpatient variability and the potential effect of ADAs that could lead to subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent). From inspection of available observed C_{trough} data, moving further to the 20-

mg/kg atezolizumabq3w regimen does not appear to be warranted to maintain targeted C_{trough} levels relative to the proposed 15-mg/kg atezolizumab q3w level.

Simulations do not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight. On the basis of this analysis, a fixed dose of 1200 mg has been selected (equivalent to an average body weight-based dose of 15 mg/kg).

Selection of an every-21-day dosing interval is supported by this preliminary PK evaluation and allows for a convenient integration with common chemotherapeutic regimens.

3.3.4 Rationale for Biomarker Assessments in Tumor Samples

Cancer of the urinary tract is a heterogeneous disease (Kaufman et al. 2009), and PD-L1 expression has been shown to vary among patients (Rosenberg et al. 2016). Published results have demonstrated that response to atezolizumab correlated with expression levels of PD-L1 in UC tumors (Rosenberg et al. 2016).

Further defining the relationship between atezolizumab treatment outcomes in bladder cancer and PD-L1 expression is important for at least two reasons: first, it will advance the understanding of how best to use PD-L1 expression levels as a potentially predictive marker of atezolizumab treatment success; and second, it will add to the understanding of the basic biology underlying immune checkpoints and their role in cancer.

Therefore, to address these issues, a maximum of three FFPE tumor specimens will be collected from each patient at the following timepoints:

1. A mandatory representative formalin-fixed paraffin-embedded (FFPE) tumor tissue block (e.g., archival primary tumor or metastatic lesion) must be submitted. If a tumor block is not available, tumor FFPE tissue obtained by biopsy during screening will be submitted
2. Only in patients who are eligible for the study and who submit archival tissue, an optional tumor biopsy may be collected during screening, as well
3. In patients who had a screening biopsy, an optional tumor sample may be collected ideally from the same lesion at Cycle 2, Day 1 (± 1 week), if feasible

Only tissue from core needle (with ≥ 3 cores), will be accepted. Cytological samples (such as, for example, from fine-needle aspirations) and bone tissue are not acceptable.

The archival and screening tissue sample will be used, for example, to correlate baseline levels of PD-L1 with subsequent safety and efficacy outcomes (the screening sample may also be used for other exploratory analyses). The optional samples at Cycle 2 will be used to investigate changes in the tumor microenvironment induced by atezolizumab treatment.

In addition to PD-L1, other biomarkers may be examined in this study on an exploratory basis. This may be accomplished by IHC and/or by a variety of DNA- and RNA-based profiling methodologies. These analyses are of significant interest for their potential of revealing molecular mechanisms involved in advanced bladder cancer carcinogenesis and susceptibility to atezolizumab treatment.

3.3.5 Rationale for Patient-Reported Outcome Assessments

PROs provide an understanding of a treatment's impact from the patient's perspective, an important consideration in many of today's quality initiatives (Institute of Medicine (U.S.). Committee on Quality of Health Care in America. 2001). Currently, there are no fully validated PRO instruments to measure symptoms and HRQoL specifically for patients with advanced/metastatic urothelial or non-urothelial carcinoma of the urinary tract. This study will therefore use two general instruments that have been widely used in assessing self-reported outcomes in patients with cancer (Appendix 4):

- EORTC QLQ-C30: The EORTC QLQ-C30 was developed to assess quality of life in cancer patients (European Organisation for Research and Treatment of Cancer 2016). The instrument incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale (Aaronson et al. 1993). Several single-item symptom measures are also included
- EQ-5D-5L: The EQ-5D-5L is a self-report health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis (EuroQol 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EuroQol EQ-5D: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale that measures health state. Published weighting systems allow for creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The EQ-5D will be utilized in this study for economic modeling

3.3.6 Rationale for Testing Atezolizumab in Patients with UC Who Have Failed Prior Therapy

Despite recent improvements in treatment, the prognosis for patients with advanced UC remains dismal, with median OS of approximately 15 months (Garcia and Dreicer 2006). Patients who receive second-line treatment for their disease have an even worse prognosis, with median survival duration of approximately 7–9 months (Sonpavde et al. 2010). Approved therapies are associated with significant toxicities (e.g., neuropathy, febrile neutropenia, myelosuppression, and alopecia) that negatively impact quality of life. Therefore, there is a continuing need for more efficacious, better-tolerated treatments for patients with advanced UC who have failed prior platinum therapy.

3.3.7 Rationale for the Use of Modified Response Criteria (Immune Based)

Cancer immunotherapies may result in early apparent radiographic progression (pseudoprogression/tumor immune infiltration), including the appearance of new lesions, followed by delayed response (Wolchok et al. 2009). Additionally, responding tumors may appear to increase in size because of the influx of immune cells (Hoos et al. 2010; Pennock et al. 2012). Unconventional response patterns have been described in patients treated with anti−cytotoxic T lymphocyte−associated antigen 4 (Wolchok et al. 2009) and have been observed in the preliminary experience with atezolizumab in Study PCD4989g. Therefore, modified RECIST will be used in this study to accommodate the possible appearance of new lesions and to allow the apparent increase in tumor burden to be confirmed at a subsequent assessment prior to designation of progressive disease.

3.3.8 Rationale for Allowing Patients to Continue Atezolizumab Treatment Beyond Initial Progression

Anti-tumor immune responses such as those associated with atezolizumab may result in objective responses that are delayed and that can be preceded by initial apparent radiological progression. This initial apparent progression may occur as a result of either delayed anti-tumor activity and/or robust tumor immune cell infiltration with a concomitant increase in tumor size (pseudo-progression). In addition, lesions that might otherwise be undetectable with conventional imaging may increase in size as a result of these processes and be recorded as new lesions (Hales et al. 2010).

For example, in IMvigor 210, 121 of the 311 enrolled patients with advanced UC were treated beyond progression for a median of 7.8 weeks (range 0–51 weeks), of whom 20 (17%) subsequently experienced target lesion reduction of at least 30% from their baseline scans (Rosenberg et al. 2016). Likewise, in Study PCD4989g, several patients with NSCLC who progressed by RECIST v1.1 criteria continued on atezolizumab treatment and demonstrated durable anti-tumor activity. In some responding patients, the growth of known lesions or the appearance of new radiographic lesions were shown to contain immune cells and no viable cancer cells on biopsy.

Because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure, conventional response criteria may not adequately assess the activity of immunotherapeutic agents. This study will therefore allow patients to remain on atezolizumab after apparent radiographic progression, provided the benefit-risk ratio is judged to be favorable. Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status (see Section 4.6.2).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 1000 patients with locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract who progressed on one to three prior lines of systemic therapy for inoperable, locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract will be enrolled in this study. Patients who discontinue the study prior to study treatment initiation will not be replaced.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed informed consent form
2. Age≥ 18 years
3. Is, according to the investigator's judgment, able to comply with the study protocol
4. Histologically documented locally advanced (T4b, any N; or any T, N 2−3) or metastatic (M1, Stage IV) urothelial or non-urothelial carcinoma of the urinary tract
   - Urinary tract carcinoma includes carcinoma of the bladder, ureter, urethra, and renal pelvis
   - Primary non-urothelial carcinoma includes all sub-types listed in the WHO classification (see Appendix 8)

     Bellini collecting duct tumors are allowed if independently reviewed by two expert pathologists from different sites

   - Lymphoma, sarcoma, and renal cell carcinoma are excluded
5. Patients with measurable and/or non-measurable disease according to RECIST v1.1 are allowed
6. Must have progressed during or following treatment with at least one (and not more than 3) prior treatments for inoperable, locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract
   - Patients who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment will be considered as having a first line of treatment for metastatic disease
   - Patients who were intolerant to prior systemic treatment are allowed as long as they had received at least 2 treatment cycles
   - Platinum- or non-platinum-based chemotherapy regimens are allowed
   - Low-dose chemotherapy given as radiosensitizer for curative treatment of localized disease does not count as a line of systemic chemotherapy
7. Representative formalin-fixed paraffin-embedded (FFPE) tumor specimen block available for submission.

- Only tissue from core needle (with ≥ 3 cores), punch, incisional, excisional, or forceps biopsies will be accepted. Fine-needle aspiration, brushing, bone tissue, and lavage samples are not acceptable
- If an appropriate tumor specimen is not available, a sample will be collected by biopsy during the study screening period
- ONLY at sites where local laws and regulations prohibit the sending of tumor specimen blocks to an outside central laboratory, specimen slides are acceptable. A minimum of 15 unstained serially-cut sections must be prepared and sent per tumor sample. For details, please refer to the Sample Handling Manual

8. Eastern Cooperative Oncology Group (ECOG) Performance Status 0, 1 or 2
9. Life expectancy ≥ 12 weeks
10. Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 2 weeks prior to the first study treatment:
    - Absolute neutrophil count ≥ 1500 cells/μL (without granulocyte colony-stimulating factor support within 2 weeks prior to the first study treatment)
    - White blood cell count > 2500/μL
    - Lymphocyte count ≥ 500/μL
    - Platelet count ≥ 100,000/μL (without transfusion within 2 weeks prior to the first study treatment)
    - Hemoglobin ≥ 9.0 g/dL (patients may be transfused or receive erythropoietic treatment to meet this criterion)
    - Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase ≤ 2.5 times the upper limit of normal (ULN), with the following exceptions:

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

      Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 × ULN

    - Serum bilirubin ≤ 1.5 ×ULN. Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled
    - Calculated creatinine clearance ≥ 15 mL/min (Cockcroft-Gault formula)
    - International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤1.5 ×ULN. This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation must be on a stable dose
11. Patients with treated, asymptomatic central nervous system (CNS) metastases are eligible, provided they meet all of the following criteria:
    - Evaluable disease outside the CNS

- No history of intracranial or spinal cord hemorrhage
- No evidence of significant vasogenic edema
- No stereotactic radiation within 7 days or whole-brain radiation or neurosurgical resection within 2 weeks before the start of study treatment
- Have had a screening CNS radiography≥ 2 weeks since completion of radiotherapy or surgical resection
- Radiographic demonstration of interim stability (i.e. no progression) between the completion of CNS-directed therapy and the screening radiographic study

Note: Patients on stable doses of anticonvulsants or on prednisone doses (or dose equivalents) of ≤ 20 mg/day are allowed

12. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab
    - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus)
    - Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception

4.1.2 Exclusion Criteria

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

1. Treatment with more than three prior lines of systemic therapy for inoperable, locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract
2. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 4 weeks prior to study treatment initiation
    - Patients who were in another clinical trial with therapeutic intent within 4 weeks of study treatment initiation but were not on active drug in that prior trial are eligible
    - Patients who were in another clinical trial with therapeutic intent within 4 weeks of study treatment initiation but were in the follow-up phase of that prior trial and had stopped receiving active drug 4 or more weeks before study treatment initiation are eligible

3. Treatment with chemotherapy within 2 weeks prior to study treatment initiation
4. Treatment with radiotherapy ongoing at the time of study entry (for CNS-directed radiotherapy, please refer to Inclusion Criterion 11)
5. Pregnant or lactating, or intending to become pregnant during the study
   - Women who are not postmenopausal (postmenopausal defined as ≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 2 weeks prior to initiation of study drug
6. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)
7. Malignancies other than the one studied in this protocol within 5 years prior to Cycle 1, Day 1
   - Patients with localized low risk prostate cancer (defined as Stage ≤ pT2b, Gleason score ≤ 7, and prostate-specific antigen [PSA] at prostate cancer diagnosis ≤ 20 ng/mL) treated with curative intent and without PSA recurrence are eligible
   - Patients with pre-existing low risk prostate cancer (defined as Stage T1/T2a, Gleason score ≤ 6, and PSA ≤ 10 ng/mL) who are treatment-naive and undergoing active surveillance are eligible
   - Patients with malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death < 5% at 5 years) are eligible provided they meet all of the following criteria:

     Malignancy treated with expected curative intent (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent)

     No evidence of recurrence or metastasis by follow-up imaging and any disease-specific tumor markers
8. Significant cardiovascular disease, such as New York Heart Association cardiac disease ≥ Class III, myocardial infarction within 3 months, unstable arrhythmias, or unstable angina
   - Patients with known coronary artery disease or left ventricular ejection fraction < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate
9. Significant renal disorder indicating a need for renal transplant
10. Signs or symptoms of severe infection within 2 weeks prior to initiation of study treatment, including but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia

11. Major surgical procedure within 4 weeks prior to study treatment initiation or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis
12. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
13. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
14. History of autoimmune disease (Appendix 5) are allowed if controlled and on stable treatment (i.e., same treatment, same dose) for the last 12 weeks, with the exception of:
    - Patients taking concurrent abatacept or belatacept treatment, unless therapy has been withdrawn for > 8 weeks
    - Patients with a history of serious or life threatening immune-related events
    - No more than 1 concomitant autoimmune disease at the time of study entry is allowed unless one of them is:

      Autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone

      Controlled Type I diabetes mellitus on a stable dose of insulin regimen

      A medical history of such entities as atopic disease or childhood arthralgias, where the clinical suspicion of autoimmune disease is low. 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)

      Vitiligo

15. Prior allogeneic stem cell or solid organ transplantation
16. History of idiopathic pulmonary fibrosis (including pneumonitis, drug-induced pneumonitis, organizing pneumonia (i.e. bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan
    - History of radiation pneumonitis in the radiation field (fibrosis) is permitted
17. Patients with active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C
    - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible
    - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA
18. Active tuberculosis

19. Administration of a live, attenuated vaccine within 4 weeks prior to study treatment initiation
    - Influenza vaccination should be given during influenza season only (e.g., approximately October to March in the Northern Hemisphere and April through September in the Southern Hemisphere) and must not be a live, attenuated vaccine
    - Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to study treatment initiation or at any time during the study treatment, and so until 5 months thereafter

20. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti−CTLA-4, anti−PD-1, and anti−PD-L1 therapeutic antibodies
    - Patients who have received prior treatment with anti-CTLA-4 may be enrolled provided at least 5 half-lives (approximately 75 days) have elapsed from the last dose of anti−CTLA-4 to the first dose of atezolizumab and there was no history of severe immune-related adverse effects from anti-CTLA-4 (NCI CTCAE Grade 3 or 4)

21. Treatment with systemic immunostimulatory agents (including, but not limited to, interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to initiation of study treatment
    - Prior cancer vaccines and cellular immunotherapy are permitted

22. Specifically for patients without autoimmune disease: treatment with systemic corticosteroids or other systemic immunosuppressive medications (including, but not limited to, prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to study treatment initiation or anticipated requirement for systemic immunosuppressive medications during the study treatment period
    - For patients with CNS metastases, use of prednisone at a dose (or dose equivalent) of ≤ 20 mg/day is acceptable
    - Chronic use of prednisone or equivalent should be discussed with the Medical Monitor
    - The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency and topical steroids for cutaneous diseases are allowed.

    Note: For patients with autoimmune disease, immunosuppressive medications are permitted if the patient has controlled autoimmune disease and stable treatment (i.e., same treatment, same dose) for the previous 12 weeks.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label (unblinded) study in which all subjects will be assigned to receive the same treatment, i.e., atezolizumab.

4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is atezolizumab.

4.3.1 Formulation, Packaging, and Handling

The atezolizumab drug product will be provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20.0 mL (1200 mg) of atezolizumab solution, but may contain more than the stated volume to enable delivery of the entire 20.0 mL volume. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

Atezolizumab must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

For further details, see the Atezolizumab Pharmacy Manual and Investigator's Brochure.

4.3.2 Dosage, Administration, and Compliance

The dose of atezolizumab in this study will be 1200 mg administered by intravenous infusion every 3 weeks (21 [± 3] days). No other dilution of the vial contents is required out of the infusion bag dilution.

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

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

The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated AEs, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion if clinically indicated, and within 30 (± 10) minutes after the infusion.

Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. The management of infusion-related reactions will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) infusion-related event, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should continue to deliver the infusion at the reduced rate for 30 minutes (± 10) minutes. If tolerated, the infusion rate may then be increased to the original rate
- In the event that a patient experiences a moderate infusion-related event (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the patient should have his or her infusion immediately interrupted and should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the infusion-related event
- For severe or life-threatening infusion-related events (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening infusion-related events will not receive further infusion and will be further managed as clinically indicated until the event resolves

For anaphylaxis precautions, see Appendix 6.

Guidelines for dosage modification, treatment interruption or discontinuation, and the management of specific adverse events are provided in Section 5.1.2.

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

Please refer to the Pharmacy Manual for detailed instructions on drug preparation, storage and administration.

4.3.3 Investigational Medicinal Product Accountability

The Investigational medicinal product (IMP) required for completion of this study (atezolizumab) will be provided by the Sponsor.

The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling

reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMP supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

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

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

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

4.3.4 Post-Trial Access to Atezolizumab

The Sponsor will offer *continued* access to *Roche IMP (*atezolizumab*) free of charge* to *eligible* patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product*, as outlined below.*

A patient will be eligible to receive Roche IMP (atezolizumab) after completing the study if all of the following conditions are met:

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

A patient will not be eligible to receive Roche IMP (atezolizumab) after completing the study if any of the following conditions are met:

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

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

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

Patients may be eligible to receive atezolizumab as part of an extension study, if no other option in the country is possible.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine and/or famotidine or another H2 receptor antagonist, as per standard practice (equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists; see Appendix 6).

Systemic corticosteroids and tumor necrosis factor−α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab, but may be administered at the discretion of the treating physician after consultation with the Medical Monitor (see Exclusion Criterion 21 [Section 4.1.2]). If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for cycles ≥ 2 at the discretion of the treating physician after consultation with the Medical Monitor. The use of inhaled corticosteroids for COPD and mineralocorticoids (e.g., fludrocortisone) and low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency is

allowed. Megestrol administered as an appetite stimulant is acceptable while the patient is enrolled in the study.

Colony-stimulating factors, such as granulocyte colony-stimulating factor and erythropoietin, should only be used according to manufacturers' labels and the ASCO and ASCO/ASH guidelines (Smith et al. 2006; Rizzo et al. 2010).

Inactivated vaccinations (such as influenza*, COVID-19) are permitted.* Live, attenuated vaccines *are not permitted (see Section 4.4.2).*

Patients *experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue* study treatment *at the investigator's discretion. The Medical Monitor is available to advise as needed. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.*

Patients who use hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer, oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy (see Section 4.1.2) should continue their use.

All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

4.4.2 Prohibited Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, is prohibited. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, or investigational agents (except for maintenance therapies outlined in Section 4.1.1 and 4.1.2)
  - After completion of Cycle 1, certain forms of radiotherapy may be considered for palliation if patients are deriving benefit (e.g., treatment of known bone metastases or symptomatic hematuria)
- Traditional herbal medicines are not recommended because the ingredients of many herbal medicines are not fully studied, and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity
- Patients who are receiving a receptor activator of nuclear factor kappa B ligand inhibitor (denosumab) prior to enrollment must be willing and eligible to receive a bisphosphonate instead while on study; denosumab could potentially alter the activity and the safety of atezolizumab
- Patients should not receive abatacept or belatacept treatment (those who were receiving it must stop it > 8 weeks before study entry)

Live, attenuated *vaccines* (e.g., FluMist®) *are prohibited within 4 weeks prior to initiation of study treatment,* during atezolizumab *treatment,* and for 5 months after the discontinuation of atezolizumab.

Patients are not allowed to receive immunostimulatory agents, including but not limited to interferon (IFN)-α, IFN-γ, or IL-2, during the entire study. These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.

With the exception of autoimmune disease patients, patients should not receive immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of atezolizumab.

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

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy.

Patients with CNS metastases are allowed to receive anticonvulsants and steroid treatments if the dose of prednisone is ≤ 20 mg / day (or equivalent).

In addition, all patients (including those who discontinue the study early) should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab.

The above list of medications is not necessarily comprehensive. The investigator should consult the prescribing information for any concomitant medication and contact the Medical Monitor if questions arise regarding medications not listed above.

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

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

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases (including autoimmune diseases), surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and 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 the screening visit. A history of pleural or pericardial effusion or of ascites requiring intervention should be entered in the medical history.

Cancer history will include an assessment of prior treatment with bacillus Clamette-Guerin (BCG).

To further evaluate medical history, Investigators should determine an age-adjusted Charlson comorbidity index for each subject during screening (Koppie et al. 2008). Refer to Appendix 9 for the AACI worksheet.

Demographic data will include age, ECOG performance status, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

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

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

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature.

For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) must be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion, during the infusion if clinically indicated, and within 30 (± 10) minutes after the infusion.

4.5.5 Tumor and Response Evaluations

Screening assessments must include CT scans (with oral/IV contrast unless contraindicated) or MRI of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained, but is not a requirement.

A CT (with contrast if not contraindicated) or MRI scan of the brain is required for patients with known CNS metastases, or to confirm or refute a diagnosis of CNS metastases at baseline in the event of symptoms or suspicion of CNS metastases. Patients with active CNS metastases are eligible for this study if non-symptomatic, treated and stable (please refer to Inclusion Criterion 11). 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.

Bone scans (Technetium-99m [TC-99m]) or sodium fluoride PET (NaF-PET) should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans, or if clinically indicated, TC-99m or NaF-PET bone scans should be repeated when complete response is identified in target disease or when progression in bone is suspected.

CT scans of the neck or extremities should also be performed if clinically indicated and followed throughout the study if there is evidence of disease at screening. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

Results of standard of care tests or examinations performed prior to obtaining Informed Consent and ≤ 28 days prior to study entry may be used for the purposes of Screening rather than repeating such tests.

For subsequent tumor assessments, procedures for tumor assessment should be performed as clinically indicated. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation. Response will be assessed by the investigator using RECIST v1.1 and modified RECIST (see Appendix 2 and Appendix 3). The same evaluator should perform assessments if possible to ensure internal consistency across visits.

At the investigator's discretion, CT scans should be repeated at any time if progressive disease is suspected.

Patients who continue treatment beyond radiographic disease progression will be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 9 weeks. If the scan frequency is every 12 weeks (see Appendix 1), the follow-up scan must be performed at 9 weeks (± 2 weeks) as an unscheduled tumor assessment or earlier if clinically indicated.

4.5.6 Ongoing Tumor Assessments

Patients who discontinue study treatment early during the initial treatment stage for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments (See Appendix 1) until the patient dies, experiences confirmed disease progression, withdraws consent, until study termination, or until the study closes, whichever occurs first.

Patients who start a new anti-cancer therapy in the absence of disease progression should continue to be followed for progression according to the protocol schedule of response assessments, unless consent is withdrawn or the patient experiences disease progression or death or until study termination or withdrawal from study, whichever occurs first.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistries (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin)
- Coagulation panel (aPTT and INR)
- Serum pregnancy test (for women of childbearing potential, including premenopausal women who have had a tubal ligation)
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)
- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4)
- Hepatitis B virus (HBV) serology (HBsAg, antibodies against HBsAg)
- Hepatitis C virus (HCV) serology (anti-HCV) – prior to inclusion only. Patients positive for HCV antibody must be tested for HCV using RNA polymerase chain reaction

- All patients will be tested for human immunodeficiency virus (HIV) prior to inclusion into the study (in accordance with national and/or institutional guidelines), but HIV-positive patients will not be excluded from the clinical trial

Samples for exploratory biomarker analyses will be sent to one or several central laboratories for analysis:

- Central laboratories will coordinate the collection of archival, fresh and leftover tumor tissue for biomarker assessments (e.g., but not limited to, PD-L1 expression and biomarkers/profiles). Leftover material derivatives thereof will be transferred to the Research Biosample Repository, if the subject provides consent.

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

Exploratory biomarker research may include, but will not be limited to, the following analyses:

- PD-L1 IHC assessment
- Tumor DNA isolation for tumor mutation detection
- Tumor RNA isolation for expression profiling

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.10.5), biological samples will be destroyed 5 years after the final Clinical Study Report has been completed, with the following exception:

- Archival leftover tumor tissue that remains after 15 slides have been collected will be returned to the study site, if requested

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

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

4.5.8 Electrocardiograms

A 12-lead ECG will be obtained at specified timepoints, as outlined in the Schedule of Assessments (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

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

4.5.9 Patient-Reported Outcomes

PRO data will be collected via questionnaires to document the treatment benefit and more fully characterize the safety profile of atezolizumab. The questionnaires, translated into the local language as required, will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered or interviewer-administered (as appropriate) before the patient or clinician receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

Two PRO questionnaires will be used in this study:

- The EORTC QLQ-C30, which was developed to assess quality of life of cancer patients (European Organisation for Research and Treatment of Cancer 2016). The EORTC QLQ-C30 incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale (Aaronson et al. 1993). Several single-item symptom measures are also included.
- In addition, subjects in this study will complete the EuroQol 5-Dimension Questionnaire (EQ-5D-5L). The EQ-5D-5L is a self-report health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis (EuroQol 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EuroQol EQ-5D: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale (VAS) that measures health state. Published weighting systems allow for creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The EQ-5D will be utilized in this study for economic modeling.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

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

RBR specimens will be used to achieve the following objectives:

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

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

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

4.5.10.3 Sample Collection

The following optional samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to atezolizumab and locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract:

- Leftover FFPE tissue freshly collected during screening and at Cycle 2, Day 1 (with the exception of archival FFPE blocks, which can be returned to sites upon request) after study-related tests have been performed

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

The above samples may be sent to one or more laboratories for DNA and RNA extraction to enable analysis of tumor mutations via next-generation sequencing (NGS), or other genetic analysis methods, as well as for gene expression or protein analyses.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger

dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

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

4.5.10.4 Confidentiality

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

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

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

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

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

4.5.10.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason.

However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her *RBR samples during the study,* the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent*/Withdrawal eCRF. If a* patient *wishes* to withdraw consent *to the testing of his or her RBR samples* after *closure of* the *site,* the *investigator must inform* the *Sponsor by emailing the study number and patient number to the following email address:*

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.10.7 Monitoring and Oversight

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

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient’s safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance

Every effort should be made to obtain *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.* Subjects who discontinue will be asked to provide consent allowing the Study Investigator and/or F. Hoffman-La Roche Ltd to collect follow up information regarding disease progression and survival. Patients who withdraw from the study will not be replaced.

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

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment (but will continue to receive tumor assessments) if they experience any of the following:

- Intolerable toxicity related to study treatment
- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment
- Use of another systemic anti-cancer therapy (see Section 4.4.2)
- Pregnancy
- Radiographic disease progression per RECIST v1.1

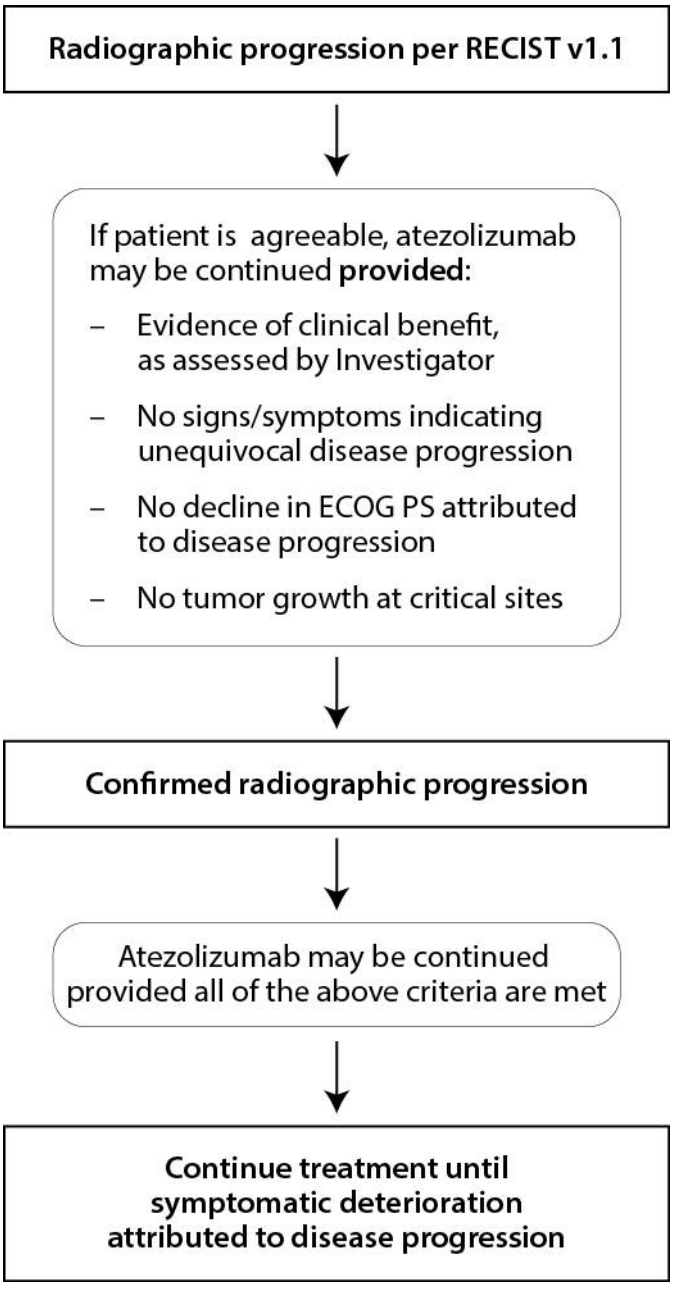
  Exception: Patients will be permitted to continue atezolizumab after RECIST v1.1 criteria for progressive disease are met if they meet all of the following criteria (see Figure 3 for schematic representation):

  - Evidence of clinical benefit (defined as the stabilization or improvement of disease-related symptoms) as assessed by the investigator
  - Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
  - No decline in ECOG performance status that can be attributed to disease progression
  - Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing

  Patients who demonstrate confirmed radiographic disease progression may be considered for continued study treatment at the discretion of the investigator, provided they continue to meet all the criteria above

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Figure 3 Conditions for Continuing Atezolizumab in the Presence of Increased Radiographic Tumor Size



ECOG PS, Eastern Cooperative Oncology Group performance status; ICF, Informed Consent Form; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, Version 1.1.

4.6.3 Study and Site Discontinuation

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

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

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

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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

Measures will be taken to ensure the safety of patients participating in this study, including the use of carefully chosen inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new anti-cancer therapy, whichever occurs first. SAEs and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new anti-cancer therapy, whichever occurs first.

Guidelines for managing anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below (Section 5.1.2), in Appendix 11, and in Section 6 of latest version of the Atezolizumab Investigator's Brochure. Refer to Protocol Sections 5.2–5.6 for details on safety reporting during the study.

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 *SARS-CoV-2 infection* 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*SARS-CoV-2 infection*, 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 *SARS-CoV-2 infection* 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, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab.

Refer to Appendix 11 and Section 6 of the latest version of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab, including the occurrence of serious, related and unexpected events.

Guidelines for managing patients who experience anticipated adverse events are provided in Appendix 11.

5.1.2 Management of Patients Who Experience Specific Adverse Events

Dose Modifications

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

Treatment Interruption

Atezolizumab may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If atezolizumab is withheld for > 12 weeks, the patient will be discontinued from study drug. *Atezolizumab can be resumed after being withheld for >12 weeks if* the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk* and *documented by the investigator.* The Medical Monitor is *available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures).*If a patient must be tapered off steroids

that have been used to treat adverse events, then atezolizumab may be withheld for more than 12 weeks from the last dose until the steroids are discontinued or reduced to a prednisone dose (or dose equivalent) of ≤ 10 mg/day. For patients with CNS metastases or autoimmune disease who require chronic steroid therapy, who have been receiving additional steroids to treat adverse events, and who now require a reduction in steroid dosage, atezolizumab may be withheld for more than 12 weeks from the last dose until the steroid dosage has returned to its baseline value. The investigator will determine the acceptable length of treatment interruption. The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator 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.*

For the management of atezolizumab related adverse events please refer to Appendix 11 and Section 6 of the latest version of the Investigator's Brochure.

For patients developing a new autoimmune disease not listed in Appendix 11 and Section 6 of the latest version of the Atezolizumab Investigator's Brochure, or for patients 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

Severe Cutaneous Adverse Events

Severe cutaneous adverse reactions (SCARs) are a heterogeneous group of immunologically mediated drug eruptions. Although rare, these events are potentially fatal, and mainly constituted by erythema multiforme, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS).

- For suspected SCARs, patients should be referred to a dermatologist for further diagnosis and management
- Atezolizumab should be withheld for patients with suspected SJS or TEN
- Atezolizumab should be permanently withdrawn for any grade confirmed SJS or TEN
- Caution should be used when considering the use of atezolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents

Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab.

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

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

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

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq 181 \times 10^9$/L (181,000/μL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14 in appendix 11.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)

- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

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

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal Insufficiency, hypothyroidism/hyperthyroidism and hypophysitis
- Hepatitis
- Transaminitis Grade ≥ 2 (AST or ALT >3x ULN and bilirubin >2x ULN) OR AST/ALT >10x ULN
- Systemic lupus erythematosus
- Neurological: Guillian-Barre Syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Vasculitis

- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH, and MAS
- 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 (seeSection 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

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

- Cardiac toxicities of Grade ≥ 2 (e.g., atrial fibrillation, myocarditis, pericarditis)
- Autoimmune flare of Grade ≥ 3

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 Electronic Case Report Form (eCRF) and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4– 5.6.

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study drug and 90 days for serious adverse events or adverse events of special interest.

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 National Cancer Institute Common Terminology for Adverse Events, Version 4.0 (NCI CTCAE v4.0) will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no"

accordingly. The following guidance should be taken into consideration (see also Table 5):

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

Table 5 Causal Attribution Guidance

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

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. Use NCI CTCAE (v4.0) terminology each time it is possible.

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

5.3.5.1 Infusion-Related Reactions and Cytokine-Release Syndrome

There may be significant overlap in signs and symptoms of IRRs and cytokine-release syndrome (CRS). While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions,

sepsis or infections, HLH, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

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 on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction" or "cytokine-release syndrome"). Avoid ambiguous terms such as "systemic reaction." Cases of late-onset CRS should be reported as "cytokine-release syndrome" on the Adverse Event eCRF. Associated signs and symptoms of an IRR should be recorded on the dedicated Infusion-Related Reaction eCRF.

If a patient experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with associated signs and symptoms of an IRR also recorded separately on the dedicated Infusion-Related Reaction eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 11.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events, 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 not be recorded as a separate event on the Adverse Event eCRF, but the “intermittent” box should be ticked.

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

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 x ULN) in combination with either an elevated total bilirubin (>2 x 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 x ULN in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST >3 x ULN 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 and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event (see Section 5.2.2) or a non-serious adverse event of special interest (see Section 5.2.3).

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 locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An iDMC will monitor the frequency of deaths from all causes.

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Locally Advanced or Metastatic Urothelial or Non-Urothelial Carcinoma of the Urinary Tract

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

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

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

  The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer

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

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

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

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be

recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, 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).

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. *Sites are not expected to review the PRO data for adverse events.*

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

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

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide

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

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until *90* days after the *final* dose of study drug *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 electronic data capture (EDC) system.

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

Instructions for reporting serious adverse events that occur > *90* days after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to

investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

5.4.3.2 Abortions

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

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.

5.4.3.3 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to

follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

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

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

5.5.2 Sponsor Follow-Up

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

5.6 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 90 days after the final dose of study drug 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 that is believed to be related to prior study drug treatment, the event should be reported through use of the Adverse Event eCRF.

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the *reference safety information contained in the* Atezolizumab Investigator's Brochure*, which serves* as *the* reference document *for this study:*

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

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is an open-label, single-arm safety study.

Analysis populations

This study will include the following analysis populations:

- Safety population: The primary analysis population for this study will include all enrolled patients who have received at least one dose of atezolizumab. The safety population will be used for all baseline and safety analyses, unless otherwise stated
- Intent-to-treat population: The intent-to-treat (ITT) population will include all enrolled patients. The ITT population will be used for all efficacy analyses, unless otherwise stated. In case the difference between the ITT and safety populations is 5 or fewer patients, all efficacy analyses will be based only on the safety population

A per-protocol population will not be defined for this study. However all major deviations (at study entry and on study) will be summarized and reported.

General Analyses 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 (CI) 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.

All analyses will be performed in SAS version 9.3.

Timing of the Analyses

The primary analysis will occur 6 months after the last patient has been enrolled.

The final analysis will occur at the end of the study, i.e., approximately 4 years after enrollment of the last study patient.

In addition, iDMC interim safety reviews will occur at minimum 3 months after the first patient was enrolled and 3 months after 500 patients have been enrolled and followed up for safety. Additional analyses might also be conducted if recommended or required by the iDMC or Steering Committee.

6.1 DETERMINATION OF SAMPLE SIZE

This is a single-arm safety study. There is no formal statistical hypothesis and all analyses will be descriptive. The results for the primary safety variables will be presented via percentages and corresponding 95% Clopper-Pearson CIs.

A sample size of approximately 1000 patients is planned for this study. The precision of rare AE incidence estimates presented by two-sided exact 95% Clopper-Pearson CIs are shown in Table 6.

Table 6 Two-Sided Clopper-Pearson 95% Confidence Intervals for Adverse Event Rate Estimates

Number of Patients with at Least One Event (Expected) N=1000	Expected Event Rate (%)	Lower limit of CI (%)	Upper limit of CI (%)
12	1.2	0.62	2.09
10	1.0	0.48	1.83
8	0.8	0.35	1.57
6	0.6	0.22	1.3
5	0.5	0.16	1.16
4	0.4	0.11	1.02
3	0.3	0.06	0.87
2	0.2	0.02	0.72
1	0.1	0.00	0.56

CI = confidence interval.

Therefore, for a sample size of 1000 patients and an expected AE incidence of 0.5%, based on the half-width of the Clopper-Pearson 95% confidence interval, the true AE rate can be estimated with precision of: ±(1.16% – 0.16%)/2 %= ±0.5 %.

6.2 ANALYSIS OF THE CONDUCT OF THE STUDY

Enrollment (by country, by site), screening failures, study treatment administration, and discontinuation (including reasons) from the study will be summarized using descriptive statistics.

6.3 SUMMARIES OF TREATMENT GROUP

Demographic and other baseline characteristics (at patient and disease level), medical history, prior treatments (study and non-study condition related) will be presented descriptively using the overall safety population. These may also be presented using the ITT population if the difference is more than 5 patients compared with the number of patients in the safety population.

6.4 PRIMARY SAFETY ANALYSIS

The primary endpoint of the study is the incidence of treatment-emergent AEs. Verbatim descriptions of AEs will be mapped to MedDRA thesaurus terms and graded according to the National Cancer Institute Common Terminology Criteria version 4.0. Multiple occurrences of the same event will be counted once at the maximum severity.

Other safety variables will include:

- Drug exposure (e.g., treatment duration, number of doses, dose intensity and dose modifications/discontinuations, with reasons)
- All AEs
- SAEs
- AEs (grade 3–5)
- AEs of special interest
- 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 confidence intervals (CIs) will be presented, as applicable. Time to first incidence of selected event types will also be estimated and presented graphically using the Kaplan-Meier method.

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

Concomitant medications recorded during the study will be summarized by frequency tables.

6.5 EFFICACY ANALYSES

Efficacy variables assessed in the study will include:

- OS (defined in Section 2.1)
- HRQoL, as assessed by QLQ-C30 questionnaire
- PFS (defined in Section 2.1)
- ORR (defined in Section 2.1)
- DCR (defined in Section 2.1)
- DoR (defined in Section 2.1)
- Utilities collected using the EQ-5D-5L for pharmacoeconomic models

Further exploratory efficacy endpoints might also be considered, as applicable.

The intent-to-treat (ITT) population will be the main population for the efficacy variables. If the difference between the ITT and safety populations is 5 or fewer patients, all analyses will be based only on the safety population.

Estimates for the survival function for PFS, OS, and DoR will be obtained by the Kaplan-Meier approach.

The analysis of ORR will be assessed by best overall response (BOR), defined as a complete or partial response determined on two consecutive investigator assessments ≥ 4 weeks apart in patients with measurable disease at baseline. BOR rate will be defined as the percentage of patients who have a complete or partial response as their BOR. Patients without a post-baseline tumor assessment will be considered non-responders. The number and proportion of responders and non-responders will be presented with the corresponding Clopper-Pearson 95% CI.

DCR will be defined as the percentage of patients with a BOR of CR, PR, or SD and will be presented along with the 95% Clopper-Pearson CI.

Analyses on the PRO instruments will include summary statistics and change (absolute and percentage) from baseline, in addition to the time to event, such as time to deterioration, analysis.

6.6 SUBGROUP ANALYSES

Key safety and/or efficacy parameters will also be analyzed by the following subgroups:

- ECOG Performance status: 0–1 vs. 2
- Presence of CNS metastases at baseline: yes vs. no
- Renal impairment at study entry: yes vs. no
- Patient requiring dialysis: yes vs. no
- HIV status: negative vs. positive
- History of autoimmune disease: yes vs. no
- Progression on, or within 12 months of, prior platinum-based treatment: yes vs. no
- Concomitant steroid treatment ongoing at baseline: yes vs. no
- History of non-urothelial urinary tract carcinoma histology: yes vs. no
- Previous lines of cancer therapy (1 vs. 2 vs. 3)
- Age-adjusted Charlson comorbidity index (AACI): ≤ 11 vs. > 11
- PD-L1 expression: low vs. high (cut-offs to be defined)
- Region (grouping countries into regions will be specified in the Statistical Analysis Plan)

All subgroup analyses will be based on the same methods as overall analyses of the primary and secondary variables. In addition, graphical displays such as forest plots will be used to descriptively visualize the homogeneity of key safety and efficacy parameters (proportions and 95% CI, or KM medians and corresponding 95% CI, as applicable will be displayed) across different levels of the pre-specified subgroup variables.

6.7 BIOMARKER ANALYSES

The biomarker objectives of this trial include correlating clinical benefit (e.g., OS, PFS, ORR, DCR, and DoR) with baseline expression levels of various biomarkers and profiles including, but not limited to, tumor PD-L1 as assessed by IHC. Biomarkers and biomarker profiles may be assessed using various methodologies including, but not limited to, IHC (single and multiplex e.g., PD-L1 expression and immune cell infiltration analyses), RNA and DNA analysis (e.g., mutation and expression analyses).

Different statistical methods will be used for the exploratory biomarker analyses, for example (but not limited to): frequencies and proportions (including 95% CI) of binary variables like response rates in different biomarker profile groups, and exact binomial tests to evaluate the associations of biomarkers and biomarker profiles with binary endpoints like objective response rates. Estimations of time-to-event outcomes in different biomarker subgroups (including duration of response, progression-free survival, and overall survival) might be analyzed by Kaplan-Meier methods; medians and corresponding 95% CI will be reported by biomarker subgroups. For continuous

biomarkers, such as tumor mutation burden, sliding window analyses might be used to determine the ideal cut-off.

6.8 INTERIM ANALYSES

The iDMC will conduct interim reviews of accumulated safety data. The first review will be performed three months after enrollment of the first patient. The iDMC will then decide on the basis of the initial reviewed data when to meet the following time, but at a minimum, the iDMC will perform another overall safety review after 500 patients have been followed up for 3 months. Ad hoc iDMC review meetings may occur as needed at any time during the study period. In case of important safety findings, the iDMC may also request to review efficacy data for an overall assessment of the risk-benefit profile to the patients.

Given the descriptive nature of this single-arm safety study, with the primary endpoint based on safety variables and the objective of the interim iDMC being to review safety, no adjustment for multiplicity is considered necessary.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for the 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 Sponsor will perform oversight of the data management of this study. The CRO will produce eCRF Specifications for the study based on Sponsor's templates including quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

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 CRO.

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and Institutional Review board (IRB)/Ethics Committee (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, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

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 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 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.

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a patient's willingness to continue in the study, the patient or a legally authorized representative must re-*consent by signing* the most current version of the Consent Forms *or the* addendum, in accordance with applicable laws and IRB/EC policy.

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 the analyses, data derived from exploratory biomarker specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.6).

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, which may include imaging 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 9.6).

8.5 FINANCIAL DISCLOSURE

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

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 MANAGEMENT OF STUDY QUALITY

The Sponsor *has* implement*ed* a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor identifi*ed* potential risks associated with critical trial processes and data and implement*ed* plans for evaluating and controlling these risks. Risk evaluation and control include*d* the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits *are* provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' 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.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. and was designed in collaboration with outside guidance from a Steering Committee. The Sponsor will provide clinical operations management, data management, and medical monitoring. An iDMC will review SAEs and accumulating safety data.

Approximately 200 sites in approximately 30 countries across Europe, North America, Latin America, North Africa, the Asia Pacific region, and the Middle East will participate to enroll approximately 1000 patients.

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

9.6 *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, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. *Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request*. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

10. REFERENCES

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Appendix 1
Schedule of Assessments

	Screening Period [a]		Treatment Period	Treatment Discontinuation	Follow-Up Period
	Day –28 to Day –1	Day -14 to -1	Day 1 (±3 days) of each 3 week treatment cycle	30 (±7) days from last treatment or at initiation of other anti-cancer therapy (whichever occurs first)	
Informed Consent [a]	x				
Review of eligibility criteria	x				
Medical history and demographics [b]	x				
Age-adjusted Charlson comorbidity index	x				
12-lead ECG [c]	x		as clinically indicated		
Tumor sample	x (mandatory)[d]		Cycle 2, Day 1 (optional) [e]		
Weight	x		x	x	
Height	x				
Complete physical examination [f]	x			x	
Limited physical examination [f]			x [g]		
ECOG Performance Status	x		x [g]	x	
Vital signs [h]	x		x	x	
HIV, HBV, HCV serology [i]	x		as clinically indicated		
Hematology [j]		x	x [g]	x	
Coagulation (aPTT, INR)		x		x	
TSH, free T3, free T4			Every other cycle		
Serum chemistry [k]		x	x [g]	x	

Appendix 1
Schedule of Assessments (cont.)

	Screening Period [a]		Treatment Period	Treatment Discontinuation	Follow-Up Period
	Day –28 to Day –1	Day -14 to -1	Day 1 (±3 days) of each 3 week treatment cycle	30 (±7) days from last treatment or at initiation of other anti-cancer therapy (whichever occurs first)	
Urinalysis [l]		x	x [g]	x	
Pregnancy test [m]		x	x		
Tumor assessment [n]	x		Every 9 weeks ± 3 business days for 54 weeks from study treatment start; thereafter every 12 weeks ± 6 business days until confirmed PD or until study discontinuation (for patients who continue to receive atezolizumab following disease "pseudo-progression")		
EORTC QLQ-C30			Day 1 of first 3 cycles then with tumor assessments	x	
EQ-5D-5L			Day 1 of first 3 cycles then with tumor assessments	x	
Concomitant medications [o]	x		x	x	
Adverse events [p]	x		x	x	x
Study drug infusion			x		
Survival and anti-cancer therapy [q]				x	x

Appendix 1
Schedule of Assessments (cont.)

Abbreviations: aPTT: activated partial thromboplastin time; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EORTC: European Organisation for Research and Treatment of Cancer; INR: international normalized ratio; PD: progressive disease.

Note: Unless otherwise indicated, assessments scheduled on the study treatment days should be performed prior to initiation of study treatment infusion.

a. Written informed consent is required for performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry (except where otherwise specified) may be used for screening assessments rather than repeating such tests.
b. Medical history includes surgical and cancer histories. Cancer history includes stage, date of diagnosis, and prior anti-cancer treatment. Reproductive status and smoking history should also be captured. Demographic information includes age, sex, and self-reported race/ethnicity.
c. ECG recordings will be obtained during screening and when clinically indicated. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.
d. A representative formalin-fixed paraffin-embedded (FFPE) archival tumor block must be submitted. If an archival tumor block is not available, a tumor FFPE block obtained by biopsy during screening must be submitted. Only tissue from core needle (with ≥ 3 cores), will be accepted.

Appendix 1
Schedule of Assessments (cont.)

Cytological samples (such as, for example, from fine-needle aspirations) and bone tissue are not acceptable. ONLY at sites where local laws and regulations prohibit the sending of tumor specimen blocks to an outside central laboratory, slides (≥15) are acceptable.
Only for patients eligible for the study and who submitted archival tissue, an optional tumor biopsy may be taken during screening.

e. For patients who underwent screening biopsy, an optional tumor sample ideally from the same lesion may be taken at Cycle 2, Day 1 (± 1 week), if feasible.

f. A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

g. ECOG Performance Status, limited physical examination, and local laboratory assessments may be obtained ≤ 96 hours before Day 1 of each cycle. It is not necessary to repeat these assessments again prior to Cycle 1 if they have been conducted for screening within this time period.

h. Vital signs include respiratory rate, heart rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Treatment cycle Day 1 vital sign assessments will be done prior to study treatment.

i. HIV testing will be performed in accordance with national and/or institutional guidelines. HBV serology includes HBsAg testing. HCV serology includes anti-HCV antibody testing and, if indicated due to anti-HCV antibody positivity, PCR testing for HCV RNA. See Section 4.5.7.

j. Hematology consists of CBC (including RBC count), hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. A manual differential may be done if clinically indicated.

k. Serum chemistry includes glucose, BUN or urea, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.

l. Urinalysis includes specific gravity, pH, glucose, protein, ketones, and blood.

m. A serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Day 1. On-study pregnancy tests performed every treatment cycle can be conducted with serum or urine.

n. The same radiographic procedure should be used throughout the study for each patient. A CT (with contrast) or MRI of the head must be included in screening tumor assessments for patients with known or suspected CNS disease. Results must be reviewed by the investigator before dosing at the next cycle. Patients who continue treatment beyond radiographic disease progression assessed per RECIST v1.1 should be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 9 weeks. If the scan frequency is every 12 weeks, a follow-up scan is recommended at 9 weeks (± 2 weeks) as an unscheduled tumor assessment or earlier if clinically indicated. Investigators may perform additional scans or more frequent assessments if clinically indicated.

o. Concomitant medications include any prescription medications, over-the-counter medications, or herbal remedies. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

Appendix 1
Schedule of Assessments (cont.)

p. After informed consent has been obtained, but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all SAEs and AEs of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other AEs, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After this period, the investigator should report any SAEs or AEs of special interest 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.

q. Survival and new anti-cancer therapy follow-up information will be collected via telephone contact, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, end of study, patient withdrawal or study termination by the Sponsor, whichever occurs first.

Appendix 2
Modified Response Evaluation Criteria in Solid Tumors

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions. Therefore, modified response criteria have been developed that account for the possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment.

Modified Response Evaluation Criteria in Solid Tumors (RECIST) is derived from RECIST, Version 1.1 (RECIST v1.1) conventions[1] and immune-related response criteria[2] (irRC). When not otherwise specified, RECIST v1.1 conventions will apply.

Modified RECIST and RECIST, Version 1.1: Summary of Changes

	RECIST v1.1	Modified RECIST
New lesions after baseline	Define progression.	New measurable lesions are added into the total tumor burden and followed.
Nontarget lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of ≥20% increase in the sum of diameters or unequivocal progression in nontarget disease	Determined only on the basis of measurable disease; may be confirmed by a consecutive assessment ≥4 weeks from the date first documented

RECIST = Response Evaluation Criteria in Solid Tumors.

DEFINITIONS OF MEASURABLE/NONMEASURABLE LESIONS

All measurable and nonmeasurable lesions should be assessed at screening and at the protocol-specified tumor assessment timepoints. Additional assessments may be

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

2 Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012;366:2443–54.
Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res 2009;15:7412–20.

performed, as clinically indicated for suspicion of progression. The investigator will evaluate response to treatment with use of modified RECIST.

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 no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

NONMEASURABLE LESIONS

Nonmeasurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm), as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable 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

Bone scan, positron emission tomography (PET) scan, or 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 as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are nonmeasurable.

CYSTIC LESIONS

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

LESIONS WITH PRIOR LOCAL TREATMENT

Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TUMOR RESPONSE EVALUATION

DEFINITIONS OF TARGET/NONTARGET LESIONS

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 recorded as nonmeasurable lesions (even if the size is $>$ 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but 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. Nodal 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 nontarget lesions. Nodes that have a short axis of $<$ 10 mm are considered non-pathological and should not be recorded or followed.

Lesions irradiated within 3 weeks prior to Cycle 1, Day 1 may not be counted as target lesions.

Nontarget Lesions

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required.

It is possible to record multiple nontarget lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

After baseline, changes in nontarget lesions will contribute only in the assessment of complete response (i.e., a complete response is attained only with the complete disappearance of all tumor lesions, including nontarget lesions) and will not be used to assess progressive disease.

New Lesions

During the study, all new lesions identified and recorded after baseline must be assessed at all tumor assessment timepoints. New lesions will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST v1.1 (e.g., non–lymph node lesions must be $\geq$ 10mm; see note for new lymph node lesions below). Up to a maximum of five new lesions total (and a maximum of two lesions per organ), all with measurements at all timepoints, can be included in the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST v1.1 cannot be included in the tumor response evaluation.

Appendix 2
Modified Response Evaluation Criteria in Solid Tumors (cont.)

CALCULATION OF SUM OF THE DIAMETERS

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as a measure of tumor burden.

The sum of the diameters is calculated at baseline and at each tumor assessment for the purpose of classification of tumor responses.

Sum of the Diameters at Baseline: The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

Sum of the Diameters at Tumor Assessment: For every on-study tumor assessment collected per protocol or as clinically indicated, the sum of the diameters at tumor assessment will be calculated using tumor imaging scans. All target lesions selected at baseline and all—up to five—new measurable lesions (with a maximum of two new lesions per site) that have emerged after baseline will contribute to the sum of the diameters at tumor assessment. Hence, each net percentage change in tumor burden per assessment with use of modified RECIST accounts for the size and growth kinetics of both old and new lesions as they appear.

Note: In the case of new lymph nodes, RECIST v1.1 for measurability (equivalent to baseline target lesion selection) will be followed. That is, if at first appearance the short axis of a new lymph node lesion is ≥ 15 mm, it will be considered a measurable new lesion and will be tracked and included in the sum of diameters. Thereafter, the lymph node lesion will be measured at subsequent timepoints and measurements will be included in the sum of diameters, even if the short axis diameter decreases to < 15 mm (or even < 10 mm). However, if it subsequently decreases to < 10 mm and all other lesions (including nontarget lesions) are no longer detectable (or have also decreased to a short axis diameter of < 10 mm if lymph nodes) then a response assessment of CR may be assigned.

If at first appearance the short axis of a new lymph node is ≥ 10 mm and < 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion. It will not be included in the sum of diameters unless it subsequently becomes measurable (short axis diameter ≥ 15 mm).

The appearance of new lymph nodes with a diameter of < 10 mm should not be considered pathological and not be considered a new lesion.

Appendix 2
Modified Response Evaluation Criteria in Solid Tumors (cont.)

RESPONSE CRITERIA

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Lymph nodes that shrink to <10 mm short axis are considered normal.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.

Note: The appearance of new measurable lesions is factored into the overall tumor burden but does not automatically qualify as progressive disease until the sum of the diameters increases by $\geq 20\%$ when compared with the sum of the diameters at nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the diameters while on study.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and all new measurable lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Impact of New Lesions on Modified RECIST

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall modified RECIST tumor response.

EVALUATION OF BEST OVERALL RESPONSE USING MODIFIED RECIST

TIMEPOINT RESPONSE

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

MISSING ASSESSMENTS AND INEVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point 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 at follow-up 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.

% Change in Sum of the Diameters (Including Measurable New Lesions When Present)	Nontarget Lesion Response	Overall Modified RECIST Timepoint Response
−100% [a]	CR	CR
−100% [a]	Non-CR or not all evaluated	PR
≤−30%	Any	PR
>−30% to <+20%	Any	SD
Not all evaluated	Any	NE
≥+20%	Any	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met since a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm in order to meet the definition of CR.

BEST OVERALL RESPONSE: ALL TIMEPOINTS

The best overall response is determined once all the data for the patient are known.

The best overall response according to modified RECIST is interpreted as below:

- **CR**: Complete disappearance of all tumor lesions (target and nontarget) and no new measurable or unmeasurable lesions, confirmed by a consecutive assessment ≥ 4 weeks from the date first documented. All lymph nodes short axes must be < 10 mm.
- **PR**: Decrease in the sum of the diameters of all target and all new measurable lesions ≥ 30% relative to baseline, in the absence of CR, confirmed by a consecutive assessment ≥ 4 weeks from the date first documented.
- **SD**: Criteria for CR, PR, and PD are not met.

- **PD**: Increase in the sum of the diameters of all target and all new measurable lesions ≥20% relative to the nadir, which may be confirmed by a consecutive assessment ≥4 weeks from the date first documented as follows:

  The confirmatory assessment shows an additional measurable increase in tumor burden as measured by the sum of the diameters of all target and all new measurable lesions.

This protocol allows patients to continue to receive study treatment even after confirmed radiographic PD per modified RECIST, and patients may achieve a best overall response of PR or CR based on tumor regression achieved at any time prior to study treatment discontinuation.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1: Excerpt from Original Publication

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

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

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

Measurable Tumor Lesions

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

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

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

Nonmeasurable Tumor Lesions

Nonmeasurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal

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

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

masses/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:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of Lesions

All measurements should be recorded in metric notation, with use of 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.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Excerpt from Original Publication (cont.)

Method of Assessment

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

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

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

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

Ultrasound. Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Excerpt from Original Publication (cont.)

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF TARGET AND NONTARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as nonmeasurable lesions (even if the size is >10 mm by CT scan).

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

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

Appendix 3
Response Evaluation Criteria in Solid Tumors: Excerpt from Original Publication (cont.)

but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- **Complete response (CR)**: disappearance of all target lesions

  Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.

- **Partial response (PR)**: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- **Progressive disease (PD)**: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

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

  The appearance of one or more new lesions is also considered progression.

- **Stable disease (SD)**: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Appendix 3
Response Evaluation Criteria in Solid Tumors: Excerpt from Original Publication (cont.)

Special Notes on the Assessment of Target Lesions

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

Target Lesions That Become Too Small to Measure. While on study, all lesions (nodal and non-nodal) 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 the CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the eCRF as follows:

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

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

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. Whereas some nontarget lesions may actually be

Appendix 3
Response Evaluation Criteria in Solid Tumors: Excerpt from Original Publication (cont.)

measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- **CR**: disappearance of all nontarget lesions and (if applicable) normalization of tumor marker level

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

- **Non-CR/Non-PD**: persistence of one or more nontarget lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits

- **PD**: unequivocal progression of existing nontarget lesions

  The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Nontarget Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Nonmeasurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. Whereas it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Excerpt from Original Publication (cont.)

When the patient has bone lesions at baseline. When a bone scan is the sole indicator of progression, progression in bone will be defined as when at least two or more new lesions are seen on bone scan compared with screening. In situations where the scan findings are suggestive of a flare reaction, or apparent new lesion(s) which may represent trauma, these results must be confirmed with other imaging modalities such as MRI or fine-cut CT to constitute progression. Only a single new bone lesion on bone scan is required for progression if the lesion can be correlated on CT, MRI or plain film.

New Lesions

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

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

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

New osteoblastic bone lesions identified on plain films, CT, or MRI will not be considered progression in an otherwise stable or responding subject, if, in the opinion of the physician, the osteoblastic lesion appears to be healing or a response to therapy.

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have nonmeasurable (therefore nontarget) disease only, Table 2 is to be used.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Excerpt from Original Publication (cont.)

Table 1 Timepoint Response: Patients with Target Lesions (with or without Nontarget Lesions)

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

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

Table 2 Timepoint Response: Patients with Nontarget Lesions Only

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

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

[a] "Non-CR/non-PD" is preferred over "stable disease" for nontarget disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing

lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more nontarget lesions are not assessed, the response for nontarget lesions should be “unable to assess” except where there is clear progression. Overall response would be “unable to assess” if either the target response or the nontarget response is “unable to assess,” except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Excerpt from Original Publication (cont.)

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

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

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

NOTE: In this study, stable disease must persist for at least 4 weeks (minimum duration) to be considered a bona fide SD.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Excerpt from Original Publication (cont.)

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and nontarget disease as shown in Table 1, Table 2, and Table 3.

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

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or nontarget lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or nontarget lesion.

Appendix 4
Patient-Reported Outcomes Instruments

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

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

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

Please go on to the next page

Appendix 4
Patient-Reported Outcomes Instruments (Cont.)

ENGLISH

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 4
Patient-Reported Outcomes Instruments (Cont.)

Health Questionnaire

English version for the UK

Appendix 4
Patient-Reported Outcomes Instruments (Cont.)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

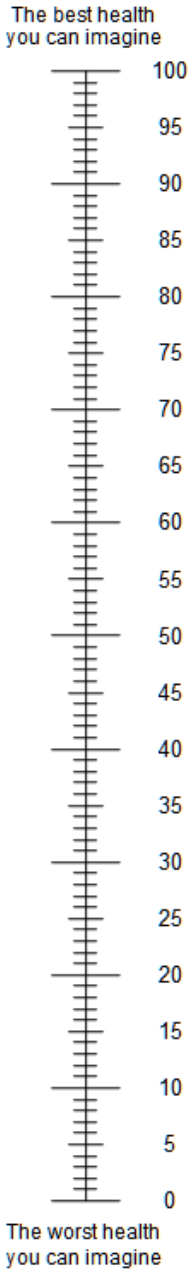
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Appendix 4
Patient-Reported Outcomes Instruments (Cont.)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 5
Preexisting Autoimmune (Chronic Inflammatory) Diseases

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with a history of immune deficiencies or autoimmune disease (see Table below) are allowed in the study.

Patients with a history of more than one immune deficiency or autoimmune disease are excluded from participating in the study unless one of them is:

- Autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone
- Controlled Type I diabetes mellitus on a stable dose of insulin regimen
- A medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. 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).
- Vitiligo

The Medical Monitor *is available to advise on* any uncertainty over autoimmune exclusions.

Acute disseminated encephalomyelitis	Epidermolysis bullosa acquista	Ord's thyroiditis
Addison's disease	Gestational pemphigoid	Pemphigus
ANKA positive vasculitis	Giant cell arteritis	Pernicious anemia
Ankylosing spondylitis	Glomerulonephritis	Polyarteritis nodusa
Antiphospholipid antibody syndrome	Goodpasture's syndrome	Polyarthritis
Aplastic anemia	Graves' disease	Polychondritis
Autoimmune hemolytic anemia	Guillain-Barré syndrome	Polyglandular autoimmune syndrome
Autoimmune hepatitis	Hashimoto's disease	Polymyositis
Autoimmune hypoparathyroidism	IgA nephropathy	Primary biliary *cholangitis*
Autoimmune hypophysitis	Inflammatory bowel disease	Psoriasis
Autoimmune myocarditis	Interstitial cystitis	Pyoderma gangrenosum
Autoimmune oophoritis	Kawasaki's disease	Reactive arthritis
Autoimmune orchitis	Lambert-Eaton myasthenia syndrome	Rheumatoid arthritis
Autoimmune thrombocytopenic purpura	Lupus erythematosus	Sarcoidosis
Behcet's disease	Lyme disease – chronic	Scleroderma

Appendx 5
Preexisting Autoimmune (Chronic Inflammatory) Disease (Cont.)

Bullous pemphigold	Mixed connective tissue disease	Sjögren's syndrome
Celiac disease	Mooren's ulcer	Stiff-Person syndrome
Chronic fatigue syndrome	Morphea	Takayasu's arteritis
Chronic inflammatory demyelinating polyneuropathy	Multiple sclerosis	Ulcerative colitis
Chung-Strauss syndrome	Myasthenia gravis	Vitiligo
Crohn's disease	Neuromyotonia	Vogt-Kovanagi-Harada disease
Dermatomyositis	Opsoclonus myoclonus syndrome	Wegener's granulomatosis
Dysautonomia	Optic neuritis	

Appendix 6
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

EQUIPMENT *AND MEDICATION* NEEDED

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- *Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer*
- Oxygen
- Epinephrine for *intramuscular (preferred route),* subcutaneous, intravenous, and/or endotracheal use in accordance with *institutional guidelines*
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

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

1. Stop the study drug infusion.
2. *Call for additional medical assistance.*
3. Maintain an adequate airway.
4. *Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.*
5. Administer antihistamines, epinephrine, or other medications *and IV fluids* as required by patient status and directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 7
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 8
Non-Urothelial Tumors of the Urinary Tract That are Eligible for This Study

Squamous neoplasms

- Squamous cell carcinoma
- Verrucous carcinoma
- Squamous cell papilloma

Glandular neoplasms

- Adenocarcinoma
  - Enteric
  - Mucinous
  - Signet-ring cell
  - Clear cell
- Villous adenoma

Neuroendocrine tumors

- Small cell carcinoma
- Carcinoid
- Paraganglioma

NOTE: Bellini collecting duct tumors are non-urothelial tumors of the urinary tract.

Based on: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs: World Health organization Classification of Tumours. Available at https://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb7/BB7.pdf.

Appendix 9
Age-Adjusted Charlson Comorbidity Index Worksheet

The purpose of this worksheet is to assist you in calculating the score of the age-adjusted Charlson Comorbidity Index (ACCI). The form should be completed by the Principle Investigator or designated person.

Patient Number:	**Patient Age:**

Condition	**Weight**	**Calculate Score**	**Notes**
1. Myocardial infarction	1		
2. Congestive heart failure	1		
3. Peripheral vascular disease or bypass	1		
4. Cerebrovascular disease or transient ischemic disease	1		CVA only
5. Hemiplegia	2		If hemiplegia, do not count CVA separately
6. Pulmonary disease/ asthma	1		
7. Diabetes	1		Diabetes only
7a. Diabetes with end organ damage	2		If end organ damage, do not count Diabetes separately
8. Renal disease	2		
9. Mild liver disease	2		
9a. Severe liver disease	3		
10. Gastric or peptic ulcer	1		
11. Cancer (lymphoma, leukemia, solid tumor)	2		• Non-metastatic cancer only • A patient with non-metastatic cancer only should be assigned a score of 2 on question 11 and a score of 0 on 11a • Points are additive by cancer type, i.e., if the patient has 2 types of non-metastatic cancer, his or her score will be 4 • Includes the urothelial or non-urothelial cancer assessed in this study

Appendix 9
Age-Adjusted Charlson Comorbidity Index Worksheet (Cont.)

11a. Metastatic solid tumor	6		• A patient with metastases from a single type of solid tumor should be assigned a score of 0 on question 11 and a score of 6 on 11a • Points are additive by cancer type, i.e., if the patient has metastases from 2 types of solid tumors, his or her score will be 12 • Includes the urothelial or non-urothelial cancer assessed in this study
12. Dementia or Alzheimer's	1		
13. Rheumatic or connective tissue disease	1		
14. HIV or AIDS	6		
15. Hypertension	1		
16. Skin ulcers/ cellulitis	2		
17. Depression	1		
18. Warfarin	1		

1 point for each decade over age 40 age 40 – 49 years = 0 age 50 – 59 years = 1 age 60 – 69 years = 2 age 70 – 79 years = 3 age 80 – 89 years = 4 age 90 – 99 years = 5		

TOTAL Score	

1. Has the patient had a myocardial infarction?	**Yes ☐ No ☐**
Criteria: Myocardial infarction includes patients with one or more definite or probable myocardial infarction. These patients should have been hospitalized for chest pain or an equivalent clinical event and have had electrocardiographic and/ or enzyme changes. Patients with electrocardiographic changes alone who have no clinical history are not designated as having had an infarction	

2. Has the patient been hospitalized or treated for heart failure?	**Yes ☐ No ☐**
Criteria: Congestive heart failure includes patients who have had exertional or paroxysmal nocturnal dyspnea and who have responded symptomatically (or on physical examination) to digitalis, diuretics, or afterload reducing agents. It does not include patients who are on one of those medications but who have had no response and no evidence of improvement of physical signs with treatment.	

3. Does the patient have peripheral vascular disease?	**Yes ☐ No ☐**
Criteria: Peripheral vascular includes patients with intermittent claudication or those who had a bypass for arterial insufficiency, those with gangrene or acute arterial insufficiency, and those with a treated or untreated thoracic or abdominal aneurysm (6 cm or more).	

Appendix 9
Age-Adjusted Charlson Comorbidity Index Worksheet (Cont.)

4. Has the patient had a CVA or transient ischemic disease?	**Yes ☐ No ☐**
Criteria: Cerebrovascular disease includes patients with a history of a cerebrovascular accident with minor or no residua, and patients who have had transient ischemic attacks. If the CVA resulted in hemiplegia, code only hemiplegia	

5. Does the patient have hemiplegia?	**Yes ☐ No ☐**
Criteria: This includes patients with a hemiplegia or paraplegia, whether it occurred as a result of a cerebrovascular accident or other condition	

6. Does the patient have asthma, chronic lung disease, chronic bronchitis or emphysema?	**Yes ☐ No ☐**
Criteria: Pulmonary disease includes patients with asthma, chronic bronchitis, emphysema, and other chronic lung disease who have ongoing symptoms such as dyspnea or cough, with mild or moderate activity. This includes patients who are dyspneic with slight activity, with or without treatment and those who are dyspneic with moderate activity despite treatment, as well as patients who are dyspneic at rest, despite treatment, those who require constant oxygen, those with CO2 retention and those with a baseline PO2 below 50 torr.	

7. Does the patient have diabetes that requires treatment?	**Yes ☐ No ☐**
Criteria: Diabetes includes all patients with diabetes treated with insulin or oral hypoglycemic, but not diet alone. Diabetes during pregnancy alone is not counted.	

7a. Does the patient have end organ damage from diabetes?	**Yes ☐ No ☐**
Criteria: This includes patients with retinopathy, neuropathy, or nephropathy attributable to diabetes.	

8. Does the patient have moderate or severe renal disease?	**Yes ☐ No ☐**
Criteria: Moderate renal insufficiency includes patients with a serum creatinine >3 mg/dl. Severe renal disease includes patients on dialysis, those who had a transplant, and those with uremia.	

9. Does the patient have a chronic liver disease?	**Yes ☐ No ☐**
Criteria: Mild liver disease consists of chronic hepatitis (B or C) or cirrhosis without portal hypertension.	

9a. Does the patient have moderate to severe liver disease?	**Yes ☐ No ☐**
Criteria: Moderate liver disease consists of cirrhosis with portal hypertension, but without bleeding. Severe liver disease consists of patients with ascites, chronic jaundice, portal hypertension or a history of variceal bleeding or those who have had liver transplant.	

10. Has the patient had gastric or peptic ulcers?	**Yes ☐ No ☐**
Criteria: Peptic ulcer disease includes patients who have required treatment for ulcer disease, including those who have bled from ulcers.	

Appendix 9
Age-Adjusted Charlson Comorbidity Index Worksheet (Cont.)

11. Has the patient had cancer?	**Yes ☐ No ☐** **If yes, which:** **☐ Lymphoma?** **☐ Leukemia?** **☐ Melanoma?** **☐ Prostate cancer?** **☐ Solid tumor (which?)** _____
Criteria: Lymphoma includes patients with Hodgkins, lymphosarcoma, Waldenstrom's macroglobulinemia, myeloma, and other lymphomas. Leukemia includes patients with acute and chronic myelogenous leukemia, acute and chronic lymphocytic leukemia, and polycythemia vera. Solid tumor consists of patients with solid tumors without documented metastases, including breast, colon, lung, prostate, and a variety of other tumors.	

11a. Does the patient have (or has he or she had) a metastatic solid tumor?	**☐ Breast** **☐ Colon** **☐ Prostate** **☐ Lung** **☐ Melanoma** **☐ Urothelial and/or non-urothelial cancer?** **☐ Other**
Criteria: Metastatic cancer includes patients with metastatic solid tumors, including breast, lung, colon and other tumors	

12. Does the patient have Alzheimer's, dementia from any etiology or any serious cognitive impairment?	**Yes ☐ No ☐**
Criteria: Dementia includes patients with moderate to severe chronic cognitive deficit resulting in impaired function from any cause.	

13. Does the patient have any rheumatic or connective tissue disease?	**Yes ☐ No ☐**
Criteria: Rheumatologic disease includes patients with systemic lupus erythematous, polymyositis, mixed connective tissue disease, rheumatoid arthritis, polymyositis, polymyalgia rheumatica, vasculitis, sarcoidosis, Sjogrens syndrome or any other systemicvasculitis	

14. Does the patient have HIV or AIDS?	**Yes ☐ No ☐**
Criteria: Acquired immune deficiency syndrome includes patients with definite or probable AIDS, i.e. AIDS related complex, and those who are HIV positive and asymptomatic.	

15. Does the patient have hypertension?	**Yes ☐ No ☐**
Criteria: Hypertension includes patients who have systolic pressures >140 mm Hg and/ or diastolic pressures >90 mm Hg if without diabetes or renal disease, as well as controlled hypertensives; or patients with diabetes or renal disease who have systolic pressures >140 mm Hg or diastolic pressures >80 mm Hg.	

16. Has the patient had decubitus ulcers, peripheral skin ulcers or repeated episodes of cellulitis?	**Yes ☐ No ☐**

Appendix 9
Age-Adjusted Charlson Comorbidity Index Worksheet (Cont.)

Criteria: Partial thickness loss of skin over legs or back with open ulcers or two or more episodes of cellulitis requiring treatment with antibiotics, regardless of etiology.

17. Does the patient have depression?	**Yes ☐ No ☐**
Criteria: Patients who are currently receiving treatment for depression, whether pharmacologic or psychotherapy, or cognitive behavioral therapy, or notes indicating that the patient has probable or definite depression.	

18. Is the patient on warfarin or coumadin?	**Yes ☐ No ☐**

CONDITIONS THAT ARE NOT ASSIGNED WEIGHTS:

- Angina includes patients with chronic exertional angina, those who had coronary artery bypass graft, and those initially admitted with unstable angina
- Arrhythmia includes patients with chronic atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias requiring chronic treatment.
- Valvular disease includes patients with hemodynamically significant aortic stenosis and/or insufficiency, those with significant mitral stenosis and/or insufficiency, and those with prosthetic aortic or mitral valves, asymmetric septal hypertrophy requiring treatment, or tricuspid insufficiency
- Other neurologic conditions includes patients with Parkinson's disease, uncontrolled seizures, or syncope without an identified cause or treatment
- Other endocrine includes patients with hypopituitarism, adrenal insufficiency, and recurrent acidosis
- Inflammatory bowel disease includes patients with ulcerative colitis or regional enteritis
- Gastrointestinal bleeding includes those who have had bleeding requiring transfusions from causes other than ulcer disease
- Coagulopathy includes patients with a circulating anticoagulant, or other coagulopathy

Appendix 10
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 11
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. *The decision to* re-*challenge patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator. The Medical Monitor *is available to advise as needed*.

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for >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 patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed*. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator 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.*

MANAGEMENT GUIDELINES

PULMONARY EVENTS

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

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • *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. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events *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 *IV methylprednisolone* or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 *the equivalent of* ≤10 mg/day oral prednisone before atezolizumab can be resumed.

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

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

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

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

Table 2 Management Guidelines for Hepatic Events

Event	Management
Guidelines for patients without hepatocellular carcinoma	
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 corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

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

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Guidelines for patients without hepatocellular carcinoma (cont.)	
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 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.
Guidelines for patients with hepatocellular carcinoma	
AST/ALT is within normal limits at baseline and increases to > 3 × ULN to ≤ 10 × ULN **or** AST/ALT is > ULN to ≤ 3 × ULN at baseline and increases to > 5 × ULN to ≤ 10 × ULN **or** AST/ALT is > 3 × ULN to ≤ 5 × ULN at baseline and increases to > 8 × ULN to ≤ 10 × ULN	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Monitor LFTs more frequently until return to baseline values. • For events of > 5 days' duration, consider initiating treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to baseline or to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to baseline or to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

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

Table 2 Management Guidelines for Hepatic Events (cont.)

Guidelines for patients with hepatocellular carcinoma (cont.)	
Event	Management
AST or ALT increases to >10×ULN or total bilirubin increases to >3×ULN	• 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 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 baseline, taper corticosteroids over ≥1 month.

LFT=liver function test; ULN=upper limit of normal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

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

GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 3.

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

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 *the equivalent of* ≤10 mg/day oral prednisone before atezolizumab can be resumed.

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

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 *the equivalent of* ≤10 mg/day oral prednisone before atezolizumab can be resumed.

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

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • *Consider patient referral to endocrinologist* **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism. • *Consider patient referral to endocrinologist*
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone The acceptable length of the extended period of time *must be based on an assessment of benefit–risk* by the investigator 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 *the equivalent of* ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

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

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 *the equivalent of* ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

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

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 *the equivalent* of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-*challenge* patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). 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 5.

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] [a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator 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 *the equivalent of* ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

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

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. *Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly.* Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

Table 6 Management Guidelines for Immune-mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 1	• Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myocarditis, Grade 2-4	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. [a] • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

[a] 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 documented by *should be based on investigator's assessment of benefit–risk* and the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

INFUSION-RELATED REACTIONS AND CYTOKINE RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, anti-pyretics, 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 1.

Severe *SARS-CoV-2 infection* 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 *SARS-Co V-2 infection*, 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 *SARS-CoV-2 infection* is confirmed, the disease should be managed as per local or institutional guidelines.

Table 1 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

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

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

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

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

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

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

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

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

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

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. *The decision to* re-*challenge patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after *assessing* the benefit–risk ratio.

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

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

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

Table 8 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-related mediated, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

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

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • *If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.*
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]

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced *to the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 *the equivalent of* ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

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

Table 9 Management Guidelines for Dermatologic Events (cont.)

Event	Management
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.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* $\leq$10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 *the equivalent of* $\leq$10 mg/day oral prednisone before atezolizumab can be resumed.

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

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology *and refer patient to neurologist*. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • *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.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 *the equivalent of* ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

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

IMMUNE-MEDIATED MENINGOENCEPHALITIS

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

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for Immune-mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Refer patient to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

RENAL EVENTS

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine *and urine protein*, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

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

IMMUNE-MEDIATED MYOSITIS

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

Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13 Management Guidelines for Immune-Mediated Myositis

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

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

Table 13 Management Guidelines for Immune-Mediated Myositis (cont.)

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

Table 13 Management Guidelines for Immune-Mediated Myositis (cont.)

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to *the equivalent of* ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator 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 the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-*challenge patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate. 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), which are considered to be potential risks for atezolizumab.

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

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

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

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq 181 \times 10^9$/L (181,000/μL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

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

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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