PROTOCOL

TITLE:	**A PHASE Ib/II, OPEN-LABEL STUDY OF THE SAFETY AND PHARMACOLOGY OF ATEZOLIZUMAB ADMINISTERED WITH OR WITHOUT BACILLE CALMETTE-GUÉRIN IN PATIENTS WITH HIGH-RISK NON–MUSCLE-INVASIVE BLADDER CANCER**
PROTOCOL NUMBER:	WO29635
VERSION NUMBER:	6
EUDRACT NUMBER:	Not applicable
IND NUMBER:	120827
NCT NUMBER:	NCT02792192
TEST PRODUCT:	Atezolizumab (MPDL3280A) Bacille Calmette-Guérin
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 7 May 2015
DATES AMENDED:	Version 2: 21 December 2015 Version 3: 27 September 2016 Version 4: 11 January 2018 Version 5: 18 October 2018 Version 6: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
10-Feb-2020 18:55:18	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 6:
RATIONALE

Protocol WO29635 has been amended to align the protocol with the most recent Atezolizumab Investigator's Brochure (Version 15). Changes to the protocol, along with a rationale for each change, are summarized below:

- Background information on atezolizumab has been updated to account for additional approved indications (Section 1.3).
- Language has been added to clarify that, after withdrawal of consent for participation in the Roche Clinical Repository (RCR), remaining RCR samples will be destroyed or will no longer be linked to the patient (Section 4.5.12.6).
- The list of atezolizumab risks has been updated to include myositis for consistency with the list of identified risks in the Atezolizumab Investigator's Brochure (Section 5.1.1).
- To align with the Atezolizumab Investigator's Brochure, Version 15, "immune-related" has been changed to "immune-mediated" when describing events associated with atezolizumab (Section 5.1.1 and Appendix 12).
- To address a request by the [redacted] systemic immune activation has been replaced by hemophagocytic lymphohistiocytosis and macrophage activation syndrome in the list of potential risks for atezolizumab (Section 5.1.1) and the management guidelines for systemic immune activation have been replaced with management guidelines for hemophagocytic lymphohistiocytosis and macrophage activation syndrome (Section 5.1.1 and Appendix 12). In addition, systemic immune activation has been removed from the list of adverse events of special interest (Section 5.2.3).
- Language has been added to indicate that the study will comply with applicable local, regional, and national laws (Section 8.1).
- A new section has been added to describe the implementation of a system to manage the quality of the study (Section 9.3).
- Language has been revised to clarify that redacted Clinical Study Reports and other summary reports will be made available upon request (Section 9.5).
- The Appendix 8 (Anaphylaxis Precautions) has been modified to remove the requirement for use of a tourniquet. The application of a tourniquet is no longer recommended due to the limited therapeutic benefit and risk of losing time for more important measures (Ring J, Beyer K, Biedermann T, et al. Allergo J Int. 2014;238:96–112).
- To address a request by the [redacted], the atezolizumab adverse event management guidelines have been revised to add laboratory (e.g., B-type natriuretic peptide) and cardiac imaging abnormalities as signs or symptoms that are suggestive of myocarditis (Appendix 12).

- Guidelines for managing patients who experience atezolizumab-associated adverse events have been revised to include myositis (Appendix 12).
- The management guidelines for infusion-related reactions associated with atezolizumab have been updated to include guidelines for cytokine-release syndrome (CRS) to align with the definition, grading, and management of CRS reflected in a recent publication (Lee et al. 2019) (Appendix 12).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy to the contact provided to the investigator at study start.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE Ib/II OPEN-LABEL STUDY OF THE SAFETY AND PHARMACOLOGY OF ATEZOLIZUMAB ADMINISTERED WITH OR WITHOUT BACILLE CALMETTE-GUÉRIN IN PATIENTS WITH HIGH-RISK NON–MUSCLE-INVASIVE BLADDER CANCER**
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IND NUMBER:	120827
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TEST PRODUCT:	Atezolizumab (MPDL3280A) Bacille Calmette-Guérin
PHASE:	Ib/II
INDICATION:	Non–muscle-invasive bladder cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

This study will evaluate the safety, pharmacokinetics, immunogenicity, patient-reported outcomes (PROs), and preliminary anti-tumor activity of atezolizumab administered as a single agent and in combination with bacille Calmette-Guérin (BCG) in patients with BCG-unresponsive non–muscle-invasive bladder cancer (NMIBC), and in combination with BCG in patients with BCG-relapsing, and VHR, BCG-naive NMIBC.

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab administered as a single agent and in combination with BCG
- To identify the dose-limiting toxicities (DLTs) and to determine the maximum tolerated dose (MTD) or tolerability at the maximum administered dose (MAD) of BCG when administered in combination with atezolizumab

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is as follows:

- To characterize the pharmacokinetics of atezolizumab administered as a single agent and in combination with BCG

Immunogenicity Objective

The immunogenicity objective for this study is as follows:

- To evaluate the immune response to atezolizumab, as measured by the incidence of anti-therapeutic antibodies (ATAs)

Efficacy Objective

The efficacy objective for this study is as follows:

- To make a preliminary assessment of the anti-tumor activity of atezolizumab administered as a single agent and in combination with BCG, as measured by the primary endpoint of 6-month complete response (CR) rate. Secondary endpoints include 3-month CR rate, duration of CR, RFS rate, bladder-intact DFS, PFS, cystectomy-free survival (CFS), and overall survival.

Patient-Reported Outcome Objective

The PRO objective for this study is as follows:

- To make a preliminarily assessment of patient-reported symptoms, function, and health-related quality of life (HRQoL) associated with atezolizumab administered as a single agent and in combination with BCG, as measured by the European Organisation for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) and the EORTC QLQ-Non Muscle Invasive Bladder Cancer 24 (NMIBC24)

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To make a preliminary assessment of biomarkers that might act as indicators of anti-tumor activity of atezolizumab administered as a single agent and in combination with BCG
- To make a preliminary assessment of biomarkers that might act as indicators of the immunomodulatory effect of atezolizumab administered as a single agent and in combination with BCG
- To explore the potential relationship between immunogenic response and pharmacokinetics, safety, and efficacy

Study Design

Description of Study

This is a Phase Ib/II, open-label, multicenter study designed to assess the safety, tolerability, pharmacokinetics, immunogenicity, PROs, and preliminary anti-tumor activity of atezolizumab administered by intravenous (IV) infusion as a single agent and in combination with intravesical BCG in patients with high-risk NMIBC.

Atezolizumab will be evaluated in the following patient cohorts:

- Cohort 1: Patients with BCG-unresponsive NMIBC
  - Cohort 1A: Atezolizumab as a single agent
  - Cohort 1B: Atezolizumab in combination with BCG
- Cohort 2: Atezolizumab in combination with BCG in patients with BCG-relapsing NMIBC
- Cohort 3: Atezolizumab in combination with BCG in patients with very high-risk (VHR) BCG-naive NMIBC

The study will be conducted at approximately 10 to 20 sites in the United States and will enroll up to approximately 70 patients across all cohorts. All patients will be required to have histologically confirmed non-muscle invasive urothelial carcinoma of the bladder with carcinoma in situ (CIS).

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (q3w) for a maximum of 96 weeks. BCG will be administered to evaluate DLTs, MTD, or MAD. De-escalation will be allowed for up to three dose levels of BCG (full dose [50 mg], 66% of a full dose, and 33% of a full dose [Cohort 1B only]).

The study will be conducted as follows:

- Cohort 1A

  Cohort 1A will commence enrollment first. Cohort 1A will evaluate the safety and tolerability of atezolizumab as a single agent in patients with BCG-unresponsive NMIBC. Up to approximately 12 safety- and efficacy-evaluable patients will be enrolled into Cohort 1A.

- Cohort 1B

  Cohort 1B will commence enrollment once 3 patients in Cohort 1A have completed one cycle (21 days) of study therapy. Cohort 1B will evaluate the safety and tolerability, DLTs, and MTD or MAD of the combination of atezolizumab and BCG in patients with BCG-unresponsive NMIBC. Data from Cohort 1B will be used to inform on the safety and tolerability of combination treatment in NMIBC, as determined at the MTD or MAD, as well as the recommended starting BCG dose in Cohorts 2 (BCG-relapsing NMIBC) and 3 (VHR BCG-naive NMIBC). Approximately 8–18 patients will be enrolled into Cohort 1B. If fewer than 8 patients are required to establish MTD or MAD in this cohort, additional patients will be enrolled for a minimum of 8 patients in this cohort.

- Cohort 1 Expansion

  An expansion cohort will allow enrollment of up to approximately 10 additional patients from Cohorts 1A or 1B. The purpose of this expansion cohort is to provide additional safety and efficacy data on these patients, depending on the safety profile observed in Cohort 1B. If few or no DLTs are observed with the combination of atezolizumab and BCG, additional Cohort 1B patients will be enrolled to better characterize the safety clinical activity of combination therapy. Alternatively, if the combination of atezolizumab and BCG is deemed intolerable in the Cohort 1B population, additional Cohort 1A patients will be enrolled to provide additional safety and efficacy data for atezolizumab monotherapy in the BCG-unresponsive patients.

Enrollment into Cohorts 2 and 3 will not begin until safety and preliminary anti-tumor activity results from approximately 20 patients across Cohort 1 (1A and 1B) are obtained and the preliminary benefit/risk has been evaluated.

- Cohort 2

  Cohort 2 will commence once the preliminary risk/benefit assessment from Cohorts 1A and 1B has demonstrated an acceptable safety and efficacy profile. Cohort 2 will evaluate the safety, tolerability and preliminary efficacy of the combination of atezolizumab and BCG (dosed at the MAD or MTD defined by Cohort 1B) in patients with BCG-relapsing NMIBC. Approximately 10 patients will be enrolled into Cohort 2.

- Cohort 3

  Cohort 3 will commence simultaneously with Cohort 2. Cohort 3 will evaluate the safety, tolerability, and preliminary efficacy of the combination of atezolizumab and BCG (dosed at the MAD or MTD defined by Cohort 1B) in patients with VHR BCG-naive NMIBC. Approximately 10 patients will be enrolled in Cohort 3.

- Cohorts 2 and 3 Expansion

  An expansion cohort will allow enrollment of up to approximately 10 patients in total from Cohorts 2 and/or 3. The purpose of this expansion cohort is to provide additional safety and efficacy data for these populations.

Cohort 1A

Enrollment in Cohort 1A will begin first. The treatment regimen for Cohort 1A patients is atezolizumab 1200 mg IV q3w monotherapy. Patients may be treated for a maximum of 32 q3w cycles of atezolizumab (or for a maximum treatment duration of 96 weeks, whichever comes first). Dosing of the second and third patients will be staggered by a minimum of 1 week relative to the first patient.

Cohort 1B

Enrollment of patients into Cohort 1B will begin once 3 patients in Cohort 1A have completed one cycle (21 days) of therapy. Cohort 1B will follow a "3 + 3" BCG dose de-escalation scheme evaluating up to three dose levels of BCG until the BCG MTD (or MAD) for the two-drug combination in BCG-unresponsive NMIBC is defined. The dose of atezolizumab will be fixed; dose de-escalation will occur only for BCG. The three BCG dose levels to be evaluated in Cohort 1B will be the full BCG dose (with a starting dose of 50 mg), followed by 66% of a full BCG dose (33 mg), followed by 33% of a full BCG dose (16.5 mg) [Cohort 1B only]. In the first course, patients will receive concurrent atezolizumab + BCG at the assigned dose. The MTD or MAD will be determined on the basis of DLTs observed during the DLT assessment window (defined as Days 1–21 of BCG Induction Course). After the MTD or MAD is determined for Cohort 1B, this dose will be used for all subsequent patients enrolled into Cohorts 1B, 2, and 3, unless the MTD is determined to be 33% of a full BCG dose. If MTD is determined to be 33% of a full BCG dose, then, no patients will be enrolled into Cohorts 2 and 3 until an assessment of the safety and activity of the combination of atezolizumab plus 33% of a full BCG dose is completed. Atezolizumab plus 33% of a full dose will not be carried into Cohorts 2 and 3 unless a favorable risk-benefit profile is demonstrated. If MTD or MAD is reached before 8 patients have been enrolled in Cohort 1B, additional patients will be enrolled up to a minimum of 8 total patients. These additional patients will be treated at the established MTD or MAD. See the protocol for a description of the BCG dose de-escalation scheme and for the definition of DLT.

A minimum of 3 patients will be enrolled into each BCG dose level evaluated. However, for the starting dose level in Cohort 1B, dosing of the second and third patients will be staggered by a minimum of 1 week relative to the first patient. If the first patient does not experience unacceptable toxicity during the first week of combination treatment, the second and third patients at the first dose level may start combination treatment without delay. Dosing for subsequent dose levels will not be staggered.

The treatment regimen for Cohort 1B patients is as follows:

BCG

- BCG Induction Course (12 weeks): BCG induction will begin on study Day 1. BCG will be administered at the assigned dose (see protocol) weekly for a total of six doses (BCG induction).
- BCG Maintenance Course 1 (12 weeks): BCG will be administered at the assigned dose weekly for a total of three doses (BCG maintenance).
- BCG Maintenance Courses 2–5 (every 24 weeks, beginning 12 weeks after initiation of Maintenance Course 1): BCG maintenance Courses 2–5 are optional for patients in Cohort 1B. BCG maintenance Courses 2–5 may be administered if, at the investigator's discretion, there is felt to be ongoing clinical benefit of BCG. The Medical Monitor will review and approve this on a case-by-case basis. These patients will receive BCG administered at the assigned dose weekly for a total of three doses per maintenance course.

Atezolizumab

- Atezolizumab therapy will begin on study Day 1. All patients will continue to receive atezolizumab 1200 mg IV q3w for a maximum of 32 q3w cycles or 96 weeks, whichever comes first.

Cohort 2

Patients in Cohort 2 will be treated with atezolizumab 1200mg IV q3w in combination with BCG dosed at the MAD or MTD determined by Cohort 1B (provided MAD or MTD is determined to be either full dose or 66% of a full BCG dose).

The treatment regimen for Cohort 2 patients is as follows:

BCG

- BCG Induction Course (12 weeks): BCG induction will begin on study Day 1. BCG will be administered at the assigned dose weekly for a total of six doses (BCG induction).
- BCG Maintenance Course 1 (12 weeks): BCG will be administered at the assigned dose weekly for a total of three doses.
- BCG Maintenance Course 2–5 (every 24 weeks, beginning 12 weeks after initiation of Maintenance Course 1): BCG will be administered at the assigned dose weekly for a total of three doses per course.

Atezolizumab

- Atezolizumab therapy will begin on study Day 1. Patients will receive atezolizumab 1200 mg IV q3w for a maximum of 32 q3w cycles or 96 weeks, whichever comes first.

Cohort 3

Patients in Cohort 3 will be treated with atezolizumab 1200mg IV q3w in combination with BCG dosed at the MAD or MTD determined by Cohort 1B.

The treatment regimen for Cohort 3 patients is as follows:

BCG

- BCG Induction Course (12 weeks): BCG induction will begin on study Day 1. BCG will be administered at the assigned dose weekly for a total of six doses (BCG induction).
- BCG Maintenance Course 1 (12 weeks): BCG will be administered at the assigned dose weekly for a total of three doses.
- BCG Maintenance Course 2–5 (every 24 weeks, beginning 12 weeks after initiation of Maintenance Course 1): BCG will be administered at the assigned dose weekly for a total of three doses per course.

Atezolizumab

- Atezolizumab therapy will begin on study Day 1. Patients will receive atezolizumab 1200 mg IV q3w for a maximum of 32 q3w cycles or 96 weeks, whichever comes first.

Number of Patients

The total planned enrollment for this study is up to approximately 70 patients: up to approximately 12 patients in Cohort 1A, approximately 8–18 patients in Cohort 1B, up to approximately 10 patients in the Cohort 1 expansion, approximately 10 patients in Cohort 2, approximately 10 patients in Cohort 3, and approximately 10 patients in the Cohort 2 and 3 expansion.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Ability to comply with protocol
- Age $\geq$ 18 years

- Histologically confirmed non–muscle-invasive TCC of the bladder with CIS

  Patients with mixed histologies, where the dominant (>50% tumor volume) histology is TCC, may be considered on a case-by-case basis upon approval by the Medical Monitor.

  Patients may have Ta/T1 lesions, provided they have been completely resected.

- High-risk NMIBC defined by the following:

  BCG-unresponsive NMIBC (Cohorts 1A and 1B):

  Persistence of high-grade CIS at 6 months following an adequate course of BCG; OR

  Stage/grade progression at 3 months after induction BCG; OR

  Recurrence of high-grade CIS after achieving a disease-free state (i.e., CR) following an adequate course of BCG that occurs < 6 months after the last exposure to BCG

  BCG-relapsing NMIBC (Cohort 2):

  Recurrence of high-grade CIS after achieving a disease-free state following an adequate course of BCG that occurs ≥ 6 months after the last exposure to BCG

  VHR BCG-naive NMIBC (Cohort 3):

  VHR NMIBC, defined as having at least one of the following:

  Multiple and/or large (> 3 cm) T1, (HG/G3) tumors

  T1, (HG/G3) tumor with concurrent CIS

  T1, G3 with CIS in prostatic urethra

  Micropapillary variant of non-muscle invasive urothelial carcinoma

- For BCG-unresponsive and BCG-relapsing NMIBC, patients must have received an adequate course of BCG. An adequate course of BCG is defined as at least one course of induction (minimum of five weekly instillations) and one course of maintenance (minimum of two weekly instillations) with the following exceptions:

  Patients with grade/stage progression after induction BCG (minimum of five weekly instillations) are eligible.

  Patients with persistent or recurrence of high-grade disease after two BCG induction courses (minimum of five weekly instillations, each) are eligible.

  Patients who did not receive an adequate course of BCG as a result of the worldwide BCG shortage may be eligible following discussion with the Medical Monitor.

- Resection of all pTa/pT1 papillary disease

  Prior to enrollment, patients must have undergone repeat transurethral resection of bladder tumor (TURBT) to ensure no evidence of residual papillary disease.

- No prior radiation to bladder or pelvic region
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2
- Life expectancy ≥ 12 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment:

  ANC ≥ 1500/μL (without granulocyte colony-stimulating factor support within 2 weeks prior to the first dose of study treatment)

  WBC counts > 2500/μL and < 15,000/μL

  Lymphocyte count ≥ 300/μL

  Platelet count ≥ 100,000/μL (without transfusion within 2 weeks prior to the first dose of study treatment)

  Hemoglobin ≥ 9.0 g/dL

  Patients may be transfused or receive erythropoietic treatment to meet this criterion.

AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ upper limit of normal (ULN)

Serum bilirubin $\leq 1.5 \times$ ULN

Patients with known Gilbert disease who have serum bilirubin level $\leq 3 \times$ ULN may be enrolled.

INR and aPTT $\leq 1.5 \times$ ULN

This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.

Creatinine clearance $\geq$ 30 mL/min (calculated using the Cockcroft-Gault formula)

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

  Women must remain abstinent 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 study drug. Women must refrain from donating eggs during this same period.

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

  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 study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men receiving BCG: agreement to remain abstinent (refrain from sexual intercourse) or use a condom to prevent transmission of BCG to sexual partners:

  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.

- Tumor tissue biopsy

  A sample of tumor tissue is required within 60 days prior to study entry. Fresh tissue biopsy is preferred; however, an archival specimen may be submitted in lieu of fresh tissue if a tissue biopsy is contraindicated owing to patient safety or tumor tissue accessibility and the archival specimen was obtained within 60 days of study screening. The specimen may consist of a formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred) or at least 10 unstained, serial sections. Patients with cystoscopy results indicating pTa/pT1 papillary disease must undergo a TURBT procedure for removal of residual papillary disease prior to study entry.

- Willingness to complete all study-related procedures including patient-reported questionnaires

Additional Cohort 3–Specific Inclusion Criteria

- No prior treatment with intravesical BCG

Exclusion Criteria

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

Cancer-Specific Exclusions

- Evidence of locally advanced or metastatic bladder cancer (including but not limited to disease involving renal pelvis, ureter, or prostatic urethra)
- Evidence of muscle-invasive bladder cancer

- Evidence of extravesical bladder cancer
- Any malignancy within 5 years prior to Cycle 1, Day 1, except adequately resected basal cell and squamous cell skin cancer or adequately treated carcinoma in situ of the cervix. Patients with malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death $< 5\%$ at 5 years) may be allowed after discussion with the Medical Monitor.

  Patients with prostate cancer who are at low risk and are undergoing active surveillance (Stage T1/T2a, Gleason score ≤ 7 and PSA ≤ 10 ng/mL) are eligible.
- Treatment with any approved anti-cancer therapy, including chemotherapy (systemic or intravesical), radiation therapy (to the bladder or pelvic region), or hormonal therapy within 3 weeks prior to the first dose of study treatment

  Use of hormone-replacement therapy and oral contraceptives is permitted.
- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to the first dose of study treatment

General Medical Exclusions

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

  Women who are not postmenopausal ($\geq$ 12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to the first dose of study treatment.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells
- Allergy or hypersensitivity to components of the atezolizumab formulation
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

  Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study after discussion with and approval by the Medical Monitor.

  Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study after discussion with and approval by the Medical Monitor.
- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Serum albumin < 2.5 g/dL
- Positive test for HIV
- Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening)

  Patients with past or resolved hepatitis B (HBV) infection (defined as having a negative HBsAg test and a positive anti-hepatitis B core antigen [anti-HBc] antibody test) are eligible. HBV DNA must be obtained in these patients prior to the first dose of study treatment.
- Active hepatitis C

  Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction assay is negative for HCV RNA.
- Active tuberculosis

- Severe infections within 28 days prior to the first dose of study treatment, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of infection within 14 days prior to the first dose of study treatment
- Treatment with therapeutic oral or IV antibiotics within 14 days prior to the first dose of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible.
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within the previous 3 months, unstable arrhythmias, or unstable angina
- Major surgical procedure other than for diagnosis within 28 days prior to the first dose of study treatment, or anticipation of need for a major surgical procedure during the course of the study
- Administration of a live/attenuated vaccine within 28 days prior to the first dose of study treatment, within 5 months following the administration of the last dose of study drug, or anticipation that such a live/attenuated vaccine will be required during the study

  Influenza vaccination should be given during influenza season only (approximately October to May in the Northern Hemisphere and from April through September in the Southern Hemisphere). Patients must agree not to receive live/attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to first dose of study treatment, during treatment or within 5 months following the last dose of atezolizumab.
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications.

Exclusion Criteria Related to BCG

- History of prior significant toxicity or intolerance to BCG requiring discontinuation of treatment
- History of prior systemic BCG infection

  Note: This is applicable to patients receiving combination BCG and atezolizumab therapy (Cohorts 1B or 2). Patients in Cohort 1A may be eligible, pending that they have received an adequate course of BCG and meet all other eligibility criteria.
- History of immunosuppression, or conditions associated with congenital or acquired immune deficiency, whether because of concurrent disease (e.g., AIDS, leukemia, lymphoma), cancer therapy (e.g., cytotoxic drugs, radiation), or immunosuppressive therapy (e.g., corticosteroids)
- Concurrent febrile illness, urinary tract infection, or gross hematuria

Exclusion Criteria Related to Medications

- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–cytotoxic T lymphocyte–associated antigen 4, anti–PD-1, and anti–programmed death–ligand 1 (PD-L1) therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including but not limited to interferons and interleukin 2 [IL-2]) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to the first dose of study treatment

- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor alpha [TNF-α] agents) within 2 weeks prior to the first dose of study treatment, or anticipated requirement for systemic immunosuppressive medications during the study.

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.

  The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed. Use of physiologic doses of corticosteroids for adrenal insufficiency is allowed.

End of Study

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur approximately 120 weeks after the last patient is enrolled in the study.

Length of Study

The study is expected to last approximately 3.5 years after the first patient is enrolled.

Outcome Measures

Safety Outcome Measures

The safety and tolerability of atezolizumab and BCG will be assessed using the following outcome measures:

- Incidence, nature, and severity of adverse events, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0)
- Changes in selected vital signs and clinical laboratory results during and following administration of atezolizumab alone and in combination with BCG

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Serum atezolizumab maximum serum concentration (C_{max}) after the first infusion of atezolizumab
- Serum atezolizumab minimum serum concentration (C_{min}) prior to the infusion at specified timepoints

Immunogenicity Outcome Measure

The immunogenicity outcome measure for this study is as follows:

- Incidence of ATA response to atezolizumab and potential correlation with PK, pharmacodynamic, safety, and efficacy parameters

Efficacy Outcome Measures

The primary efficacy outcome measure for this study is as follows:

- CR at the 6-month evaluations after the start of study treatment. Patients must be evaluated for CR by both cystoscopy and cytology and bladder biopsies will be required for the 6-month CR disease assessment.

The secondary efficacy outcome measures for this study are as follows:

- CR at the 3-month disease assessment, evaluated by both cystoscopy and cytology.
- Duration of CR, defined as time from first occurrence of a documented CR until the time of recurrence of NMIBC or death from any cause
- RFS rate at 6, 12, and 18 months, defined as the proportion of patients who are alive and free of persistent/recurrent high-risk NMIBC

- Bladder-intact DFS, defined as time from first study treatment to earliest evidence of progression to muscle-invasive disease in the bladder, regional pelvic progression, distant metastasis, bladder cancer–related death, or cystectomy or death from any cause
- PFS, defined as the time from first study treatment to the first occurrence of progression to muscle-invasive disease or death from any cause
- CFS, defined as the time from first study treatment to cystectomy or death from any cause
- Overall survival, defined as the time from first study treatment to death from any cause

Patient-Reported Outcome Measure

The exploratory PRO outcome measure for this study is as follows:

- Change from baseline in patient-reported symptoms, function, and HRQoL, as measured by the EORTC QLQ-C30 and EORTC QLQ-NMIBC24

Exploratory Biomarker Outcome Measures

The following biomarker endpoints will be assessed when appropriate:

- PD-L1 status by immunohistochemistry (IHC) in archival tissues and/or fresh biopsies
- Status of other exploratory biomarkers related to PD-L1 or immune cell biology (including but not limited to CD8 or programmed death–1 [PD-1]) and tumor biology

The following exploratory biomarker outcome measures will be assessed when appropriate:

- Changes in immune-related markers (including but not limited to CD8, granzyme B, and other exploratory markers) in archival and/or fresh tumor tissue prior to and during atezolizumab and BCG treatment

Investigational Medicinal Products

Atezolizumab and BCG (OncoTICE®) are both considered an investigational medicinal product (IMP) in this study.

Test Product (Investigational Drug)

Atezolizumab

The dose level of atezolizumab in this study is 1200 mg administered by IV infusion q3w. There will be no dose reduction of atezolizumab.

Cohort 1A: Patients receive atezolizumab 1200 mg IV q3w, for a maximum of 32 doses over 96 weeks.

Cohort 1B: During BCG Induction Course (12 weeks), patients receive atezolizumab 1200 mg IV q3w for a total of four doses. During BCG Maintenance Course 1 (12 weeks), patients will receive atezolizumab 1200 mg IV q3w for a total of four doses. Additional BCG maintenance courses are not required for patients in Cohort 1B but may be allowed on a case-by-case basis after discussion with the Medical Monitor. BCG Maintenance Courses 2–5 (each 24 weeks), patients receive atezolizumab 1200 mg IV q3w for a total of eight doses per course. The maximum treatment duration of atezolizumab is 96 weeks.

Cohorts 2 and 3: During BCG Induction Course (12 weeks), patients receive atezolizumab 1200 mg IV q3w for a total of four doses. During BCG Maintenance Course 1 (12 weeks), patients will receive atezolizumab 1200 mg IV q3w for a total of four doses. During BCG Maintenance Courses 2–5 (each 24 weeks), patients receive atezolizumab 1200 mg IV q3w for a total of eight doses per course. The maximum treatment duration of atezolizumab is 96 weeks.

BCG

BCG will not be administered in Cohort 1A.

Cohort 1B: The three BCG dose levels to be evaluated in Cohort 1B will be full dose (starting dose of 50 mg), followed by 2/3 of a full BCG dose, followed by 1/3 of a full dose.

During BCG Induction Course (12 weeks), patients will receive BCG at the assigned dose weekly for a total of six doses. During BCG Maintenance Course 1 (12 weeks), patients receive

BCG at the assigned dose weekly for a total of three doses. During BCG Maintenance Courses 2–5 (each 24 weeks), patients receive BCG at the assigned dose weekly for a total of three doses per course.

Cohorts 2 and 3: During BCG Induction Course (12 weeks), patients will receive BCG at the MTD/MAD (established in Cohort 1B) weekly for a total of six doses. During BCG Maintenance Course 1 (12 weeks), patients receive BCG at the MTD/MAD weekly for a total of three doses. During BCG Maintenance Courses 2–5 (each 24 weeks), patients receive BCG at the MDT/MAD weekly for a total of three doses per course.

Statistical Methods

Primary Analysis

All analyses will be performed by cohort. Selected analyses may also be performed for all cohorts combined as specified below.

All patients treated with any amount of study drug (atezolizumab or BCG) will be included in all analyses unless specified otherwise.

Analyses of DLTs will be performed on an ongoing basis. Analyses of endpoints related to anti-tumor activity will be performed periodically among patients with sufficient follow up. Final analyses will be performed after the LPLV has occurred.

Continuous variables will be summarized using means, SDs, medians, and ranges. Categorical variables will be summarized by proportions. The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

Determination of Sample Size

The sample sizes for Cohorts 1A, 2, and 3 were based on clinical and operational considerations. The sample size for Cohort 1B was based on a 3 + 3 dose de-escalation design appropriate for assessing DLTs and MTD or MAD of BCG in combination with atezolizumab.

An evaluation of results from Cohorts 1A and 1B will be performed prior to initiation of enrollment in Cohorts 2 and 3. The protocol shows the 95% CI for selected observed CR rates for a range of sample sizes for Cohorts 1A and 1B pooled.

Planned Interim Analyses

A preliminary assessment of anti-tumor activity and safety will be performed on Cohorts 1A and 1B prior to initiation of enrollment into Cohorts 2 and 3.

Given the nature of this study, the Sponsor may choose to perform additional periodic analyses of safety or efficacy on any cohort.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AC	all comers
anti-HBc	anti-hepatitis B core antigen
ATA	anti-therapeutic antibody
AUA	American Urological Association
BCG	bacille Calmette-Guérin
BOR	best overall response
C1D1	Cycle 1, Day 1
CCOD	clinical cutoff date
CFS	cystectomy-free survival
CIS	carcinoma in situ
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
DFS	disease-free survival
DLT	dose-limiting toxicity
DOR	duration of response
EAU	European Association of Urology
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
FACS	fluorescence-activated cell sorting
FFPE	formalin-fixed paraffin-embedded
FDA	U.S. Food and Drug Administration
GM-CSF	granulocyte macrophage colony-stimulating factor
GU	genitourinary
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation	Definition
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
HRQoL	health-related quality of life
IC	PD-L1 tumor-infiltrating immune cell
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IUO	investigator use only
IV	intravenous
IxRS	interactive Web/voice response system
LFT	liver function test
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next generation sequencing
NMIBC	non–muscle-invasive bladder cancer
NMIBC24	QLQ-Non–Muscle-Invasive Bladder Cancer 24
ORR	overall response rate
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
PD-L	programmed death–ligand
PD-L1	programmed death–ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PPD	purified protein derivative
PRO	patient-reported outcome
pT1	invasive papillary carcinoma that has invaded in the sub-epithelial connective tissue of the bladder
pTa	non-invasive papillary carcinoma that has not invaded in the sub-epithelial connective tissue of the bladder

Abbreviation	Definition
PUNLMP	papillary urothelial neoplasm of low malignant potential
PVC	polyvinyl chloride
q3w	every 3 weeks
QLQ-C30	Quality-of-Life Questionnaire Core 30
OS	overall survival
RCR	Roche Clinical Repository
RDA	recommended daily allowance
RFS	recurrence-free survival
SOC	standard-of-care
SWOG	Southwest Oncology Group
TCC	transitional cell carcinoma
TIMC	tumor-infiltrating mononuclear cell
Tis	carcinoma in-situ
TNF-α	tumor necrosis factor-α
TSH	thyroid-stimulating hormone
TURBT	transurethral resection of bladder tumor
UC	urothelial carcinoma
ULN	upper limit of normal
VHR	very high-risk (BCG-naive NMIBC)

1. BACKGROUND

1.1 NON–MUSCLE-INVASIVE BLADDER CANCER

Urothelial carcinoma (also termed transitional cell carcinoma [TCC]) is the most common cancer of the urinary system worldwide, with urothelial carcinoma (UC) of the bladder being the predominant histologic type and location. It is estimated that in 2015, there will be 74,690 new cases of bladder cancer and 15,580 deaths (about 11,510 in men and 4490 in women in the United States; American Cancer Society 2015). Worldwide data estimated 429,793 new cases of bladder cancer, with 165,084 deaths, in 2012 (GLOBOCAN 2012). Between 75% and 85% of new cases of UC will present at first diagnosis as non–muscle-invasive bladder cancer (NMIBC). By rough estimates, in 2015, there will be 60,000 new cases of NMIBC in the United States alone and approximately 340,000 new cases of NMIBC worldwide (Lightfoot et al. 2011).

The primary management of NMIBC is surgical via cystoscopy and transurethral resection of bladder tumor (TURBT), which may be curative in rare cases (Brausi et al. 2002). Unfortunately, the overall prognosis for many patients with NMIBC can be considered poor and this disease carries a high unmet medical need.

The natural history of NMIBC is characterized by multiple recurrences in up to 90% of patients (over a 5-year period), leading to frequent diagnostic and therapeutic interventions including cystoscopy and TURBT, impacting patient-reported health-related quality of life (Yoshimura et al. 2005; Wei et al. 2013) and disease progression (with radical cystectomy and loss of bladder) in up to 45% of patients (Lightfoot et al. 2011). The morbidity and impact of bladder cancer is highest among the elderly in the NMIBC setting, as patients require life-long surveillance with cystoscopic examinations, intermittent imaging, and intravesical therapies. These procedures carry the risk of side effects, complications that can negatively impact bladder function. This burden of bladder cancer is further compounded by the indirect impact on psychological health and quality of life of patients and their families (Mossanen and Gore 2014).

For patients with NMIBC who experience treatment failure, the gold standard is radical cystectomy. This procedure includes complete removal of the bladder followed by one of several techniques to create a urinary diversion. The significant morbidity that can include urinary leakage, frequent self-catheterization, erectile dysfunction, body image dissatisfaction, infertility, and high perioperative mortality associated with radical cystectomy has been well defined over the years, with postoperative complication rates as high as 64% (Donat et al. 2009). The negative health economic impact of the high complication rate is highlighted by a recent comparison of major surgical procedures performed in hospitals, which identified cystectomy as having one of the highest associated costs (Nathan et al. 2015).

1.1.1 Classification and Risk Stratification for Non–Muscle-Invasive Bladder Cancer

Sylvester et al. (2006) conducted a meta-analysis of seven European Organization for Research and Treatment of Cancer (EORTC) studies in NMIBC. From this analysis, a simple scoring system was derived for estimating the risk of disease recurrence and disease progression, based on major pathological risk factors. This scoring system, commonly referred to as the EORTC risk calculator, is used to assess risk of recurrence or progression in NMIBC (Sylvester et al. 2006; Babjuk et al. 2011).

NMIBC comprises a heterogeneous group of tumors with varying outcomes:

- Stage Ta is non-invasive papillary carcinoma that has not invaded in the sub-epithelial connective tissue of the bladder.
- Stage T1 is papillary carcinoma that has invaded into the sub-epithelial connective tissue (lamina propria) of the bladder lining.
- Carcinoma in-situ (CIS or Tis) consists of flat, non-papillary, high-grade lesions characterized by severe cellular dysplasia and localized to the sub-epithelial surface of the bladder (Babjuk et al. 2011).

Approximately 70% of NMIBC presents as predominantly Ta disease, 20% of patients present with predominantly T1 disease, and 10% present as predominantly CIS. CIS is considered a distinct entity because of the difficulty in detection with standard cystoscopy examination and its high propensity for disease progression (Nese et al. 2009). Primary CIS occurs in approximately 3% of all UC; however, it is found concurrently with T1 disease in up to 50% of cases (Kim and Steinberg 2001). The presence of CIS is associated with a high incidence of progression to invasive disease, even after surgical and intravesical therapy. The rate of disease progression to muscle invasion with or without TURBT with CIS has been shown to be 50%–60% (Casey et al. 2015). In a single institution, where a series of 155 patients with CIS were managed with TURBT and intravesical bacille Calmette-Guérin (BCG), the 5-year cumulative incidence of progression to T1 or higher disease was 45% (95% CI: 37–55). In this study, it was observed that diffuse involvement of the mucosa with CIS was associated with a particularly aggressive disease, with disease progression in 60%–80% of such patients (Chade et al. 2010). From a therapeutic perspective, NMIBC is broadly categorized into low-risk and intermediate/high-risk, on the basis of the risk of recurrence and/or disease progression (Babjuk et al. 2011).

High-risk NMIBC is characterized by any one or more of the following:

- T1 tumor
- High-grade tumor
- CIS
- Multiple and recurrent and large (>3 cm) low-grade Ta lesions (all 3 conditions must be met for low-grade Ta lesions).

These tumors are at high-risk of recurrence and progression, with progression to muscle invasive disease being the primary concern (Sylvester et al. 2006; Babjuk et al. 2013).

The European Association of Urology (EAU) describes a group of patients with NMIBC that falls into an extremely high-risk group, hereafter referred to as "very high-risk" (VHR) NMIBC (Babjuk et al. 2013). These include patients with any of the following:

- Multiple and/or large (>3 cm) high-grade T1 tumors
- High-grade T1 tumors with concurrent CIS
- High-grade T1 tumors with CIS in the prostatic urethra
- Micropapillary variant NMIBC

Patients in the first two groups described above have a 1-year recurrence risk of 25%–40% and progression rates of 5%–17%. By year five, >60% of patients develop recurrence, and 45% exhibit progression to muscle-invasive disease (Sylvester et al. 2006; Fernandez-Gomez et al. 2009). Prostatic urethral involvement and micropapillary variant histology are two rare risk factors not well represented in the larger meta-analyses. Smaller studies demonstrate an extremely high risk of progression and death from bladder cancer for these subgroups, although exact risk estimates are challenging due to small numbers (Palou et al. 2012; Giannarini et al. 2014; Jackson et al. 2015).

1.1.2 Initial Treatment for Non–Muscle-Invasive Bladder Cancer

The backbone of therapy for patients with NMIBC is surgical resection with TURBT. This procedure is both diagnostic and therapeutic, with the goal of complete removal of malignant tumor and histologic review of resected disease to determine the risk of recurrence. One pitfall of this procedure is that it is operator-dependent. Brausi et al. (2002) demonstrated that the quality of TURBT had a major impact on recurrence rates. In a study of 83 patients with NMIBC, Grimm et al. (2003) observed that residual disease was found in 27% of Ta and 53% of T1 cases.

Divrik et al. (2010) demonstrated the benefit of repeat TURBT in a prospective, randomized study. Data from this study showed 5-year recurrence-free survival (RFS) rates of 59% with re-TURBT, compared with 32% with single TURBT alone. Similarly, the 5-year progression-free survival (PFS) rates were 93% with re-TURBT, compared with 79% for the single TURBT alone (Divrik et al. 2010). As a result, repeat or restaging TURBT is routinely recommended, especially for cases of an incomplete initial TURBT, absence of muscle layer in the resected specimen (with the exception of Ta low-grade tumors and primary CIS), all T1, and all high-grade tumors (except CIS) (Babjuk et al. 2011).

Use of radical cystectomy, a treatment option for high-risk NMIBC, can be curative but remains controversial for most patients (Skinner 2007). Data from a study by Denzinger et al. (2007), evaluating early cystectomy as a treatment option for high-risk NMIBC, revealed a 30% incidence of upstaging following cystectomy. Cancer-specific survival rates were prolonged in the early cystectomy group compared with the late cystectomy group; the presence of CIS was a major determining factor for outcome (Denzinger et al. 2007). The EAU recommends considering cystectomy as an initial treatment option for the subgroup of patients with VHR NMIBC defined in the previous section (Babjuk et al. 2013).

1.1.3 BCG Immunotherapy for High-Risk Non–Muscle-Invasive Bladder Cancer

BCG is a live attenuated form of *Mycobacterium bovis* and the most commonly used agent for intravesical therapy. Per the American Urological Association (AUA) and the EAU bladder cancer guidelines it is the standard treatment for patients with high-risk NMIBC following a restaging TURBT.

Herr and Morales (2008) were the first to report successful treatment of NMIBC with intravesical BCG in 1976. Although the mechanism of action for intravesical BCG is not fully understood, there is evidence to suggest that activity occurs through initiation of an inflammatory response with T-cell activation and release of an array of pro-inflammatory cytokines and chemokines such as interleukin (IL)−1, IL-6, IL-8, tumor necrosis factor−α (TNF-α), and granulocyte macrophage colony-stimulating factor (GM-CSF). Following T-cell activation, there is an influx of tumor-infiltrating immune cells with formation of BCG-induced granulomata in the bladder wall (Redelman-Sidi et al. 2014). Supportive evidence has shown that development of the Th-1 cytokine profile (interferon [IFN]-γ, IL-2, IL-12) is associated with the therapeutic effects of BCG. In contrast, the presence of high levels Th-2 cytokines (e.g., IL-10) is associated with BCG failure (Luo 2014).

Adverse reactions from intravesical BCG are typically local and include dysuria, cystitis, frequency, and hematuria. Less than 10% of these local effects occur with Grade $\geq$3 toxicity. Less common local effects observed include granulomatous prostatitis, epididymitis, ureteral obstruction, and contracted bladder. Systemic effects observed include fever, influenza-like symptoms, BCG-induced lung infection, hepatotoxicity, and BCG-sepsis. Skin rash, arthralgia, and arthritis have also been classified as possible allergic reactions (TICE® USPI). Results from a study by Brausi et al. (2014), showed the frequency of these adverse reactions to be unrelated to dose with the majority of these effects occurring within the first year of therapy.

Sylvester et al. (2005) performed a meta-analysis of studies comparing intravesical BCG to intravesical chemotherapy for high-risk NMIBC. In this meta-analysis, complete responses (CRs) for CIS were observed in 68.1% of patients treated with intravesical BCG compared with 51.5% with intravesical chemotherapy. Median follow-up was 3.6 years with recurrence rates of 34% and 50% for BCG and chemotherapy, respectively, with significant superiority of BCG over chemotherapy observed in studies where maintenance BCG was administered (Sylvester et al. 2005).

A summary of the studies from these analyses has been provided in Table 1.

Table 1 Randomized Studies with BCG in High-Risk Non–Muscle-Invasive Bladder Cancer

High-Risk NMIBC (Recurrent Ta/T1 or CIS)	No. of Patients	CR (%) (CIS Only)	2-year DFS (%) (Duration of Follow-Up)
BCG vs. doxorubicin BCG vs. doxorubicin vs. thiotepa BCG Schedule: 15 courses [a]	202	NA	88 vs. 40/67 (3 years)
SWOG 8216: BCG vs. Doxorubicin BCG Schedule: 6-week induction ± re-induction 3-week maintenance at 3, 6, 12, 18, 24, 30, and 36 months [b]	262	70 vs. 34	45 vs. 18 (5 years)
EORTC 30906: BCG vs. Epirubicin BCG Schedule: 6-week induction ± re-induction 3-week maintenance at 3, 6, 12, 18, 24, 30, and 36 months [c]	168	65 vs. 56	5.1 vs. 1.4 (TTR) (5.6 years)
BCG vs. MMC SWOG 8795: BCG vs. MMC BCG Schedule: 6-week induction then 6 weekly at 8 and 12 weeks, then monthly to 1 year [d]	469	55 vs. 46	57 vs. 45 (2 years)
Nijmegen Study: BCG (TICE/RIVM) vs. MMC BCG Schedule: 6-week induction ± re-induction (no maintenance) [e]	469	70/47 vs. 42	54/62 vs. 65 (2 years)
BCG (TICE/RIVM) vs. MMC BCG Schedule: 6-week induction ± re-induction (no maintenance) [f]	437	74/60 vs. 67	42/55 vs. 59 (3 years)
BCG vs. MMC BCG Schedule: 6-week induction then monthly for 1 year and every 3 months for Year 2 [g]	261	NA	42 vs. 34 (5 years)

Table 1 Randomized Studies with BCG in High-Risk Non–Muscle-Invasive Bladder Cancer (cont.)

BCG = bacille Calmette-Guérin; CIS = carcinoma in situ; CR = complete response; DFS = disease-free survival; EORTC = European Organisation for Research and Treatment of Cancer; MMC = mitomycin C; NA = not applicable; NMIBC = non–muscle-invasive bladder cancer; RIVM; SWOG = Southwest Oncology Group; TTR = time to response.

[a] Martinez-Pineiro JA, Jimenez LJ, Martinez-Pineiro L Jr, et al. Bacillus calmette-guerin versus doxorubicin versus thiotepa: a randomized prospective study in 202 patients with superficial bladder cancer. J Urol 1990;143:502–6.

[b] Lamm DL, Blumenstein BA, Crawford ED, et al. A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette–Guerin for transitional-cell carcinoma of the bladder. N Engl J Med 1991;325:1205–9.

[c] de Reijke TM, Kurth KH, Sylvester RJ, et al. Bacillus calmette-guerin versus epirubicin for primary, secondary or concurrent carcinoma in situ of the bladder: results of a european organization for the research and treatment of cancer-genitourinary group phase III trial (30906). J Urol 2005 ;173 :405–9.

[d] Lamm DL, Blumenstein BA, Crawford DE, et al. Randomized intergroup comparison of bacillus calmette-guerin immunotherapy and mitomycin C chemotherapy prophylaxis in superficial transitional cell carcinoma of the bladder a southwest oncology group study. Urol Oncol 1995;1:119–26.

[e] Witjes JA, vd Meijden AP, Witjes WP, et al. A randomised prospective study comparing Intravesical instillations of mitomycin-C, BCG-Tice, and BCG-RIVM in pTa-pT1 tumours and primary carcinoma in situ of the urinary bladder. Dutch southeast cooperative urological group. Eur J Cancer 1993;29A:1672–6.

[f] Vegt PD, Witjes JA, Witjes WP, et al. A randomized study of intravesical mitomycin C, bacillus Calmette-Guerin Tice and bacillus Calmette-Guerin RIVM treatment in pTa-pT1 papillary carcinoma and carcinoma in situ of the bladder. J Urol 1995;153:929–33.

[g] Malmstrom PU, Wijkstrom H, Lundholm C, et al. 5-year follow-up of a randomized prospective study comparing mitomycin C and bacillus calmette-guerin in patients with superficial bladder carcinoma. Swedish-Norwegian bladder cancer study group. J Urol 1999;161:1124–7.

Lamm et al. (2000) evaluated the role of adding BCG maintenance therapy in a large, randomized, Phase III study from the Southwest Oncology Group (SWOG). In this study (SWOG 8507) of high-grade pTa/T1 and/or CIS disease, patients were randomized to receive maintenance therapy with BCG versus no maintenance therapy with BCG following an induction course of intravesical and percutaneous BCG. Maintenance therapy with BCG consisted of intravesical and percutaneous BCG administered each week for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months from initiation of induction therapy. Of the 278 patients enrolled with CIS disease, 141 (50.7%) achieved a CR following their induction course. The median RFS was 76.8 months (95% CI: 64.3, 93.2) in the maintenance arm compared with 35.7 months (95% CI: 25.1, 56.8) in the no maintenance arm ($p < 0.0001$). No Grade ≥ 4 toxicities were observed in the maintenance arm; however, only 16% of 243 maintenance cases were able to receive all eight scheduled maintenance courses over the 3-year period.

A prospective randomized study by the EORTC (EORTC 30962) assessed optimal dosing and treatment schedule for intravesical BCG utilizing dosing schema of full dose versus 1/3rd dose and a schedule of 1-year maintenance versus 3-year maintenance. Results of this 1355 patient study showed no significant difference in toxicity for 1/3rd dose compared with full dose; however, the intent-to-treat analysis for disease-free interval showed the 1/3rd dose for 1 year to be suboptimal compared with the full dose for 3 years (hazard ratio [HR]: 0.75; 95% CI: 0.59–0.94; $p = 0.01$) with highest benefit observed in the high-risk group. These findings were supportive of full-dose BCG with 3-year maintenance for high-risk NMIBC (Oddens et al. 2013).

Table 2 summarizes key studies evaluating BCG maintenance dose and scheduling.

Table 2 Randomized Phase II/III Studies of BCG Maintenance Therapy

High-Risk NMIBC (Recurrent Ta/T1 or CIS)	No. of Patients	RFS (%) (months)	OS (%)
BCG: No maintenance vs. maintenance [a]	86	18.0 vs. 18.1	NA
BCG: Full dose, 1 year vs. 3 years SWOG 8507: BCG intravesical + percutaneous [b]	660	35.7 vs. 76.8	57 vs. 45 (5 years)
BCG: 1/3 dose vs. full dose, 1 year vs. 3 years EORTC-GU 30962 Study [c]	1355	5-year DFS 57 vs. 63 (1 year vs. 3 years) 5-year DFS 59 vs. 62 (1/3 dose vs. full dose)	NA

BCG = bacille Calmette-Guérin; CIS = carcinoma in situ; DFS = disease-free survival; EORTC = European Organisation for Research and Treatment of Cancer; GU = genitourinary; NA = not applicable; NMIBC = non–muscle-invasive bladder cancer; OS = overall survival; RFS = recurrence-free survival; SWOG = Southwest Oncology Group.

[a] Badalament RA, Herr HW, Wong GY, et al. A prospective randomized trial of maintenance versus non-maintenance intravesical bacillus calmette-guérin therapy of superficial bladder cancer. J Clin Oncol 1987;5:441–9.

[b] Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol 2000;163:1124–9.

[c] Oddens J, Brausi M, Sylvester R, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus calmette-guerin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol 2013;63:462–72.

On the basis of the result from SWOG8759, SWOG8216, and SWOG8507, the U.S. Food and Drug Administration (FDA) approved intravesical BCG in 1990 for the treatment of CIS of the bladder. This indication was later expanded in 1998 to include pTa/T1 disease (TICE USPI) and approved also for use in the European Union.

BCG is now indicated for treatment of primary or concurrent CIS of the urinary bladder and for the prevention of recurrence of high-grade and/or relapsing superficial papillary TCC of the urinary bladder (TICE USPI; OncoTICE® Summary of Product Characteristics [SmPC]). To date, BCG immunotherapy has emerged as the standard against which all newer therapies are compared.

BCG Shortage

From 2012 until 2015, a worldwide BCG shortage has led to some patients being treated with a less-than-the optimal course of BCG therapy (American Urological Association 2012). Although the AUA, with guidance from the FDA, does not support dilution of BCG doses ("Shortages & Price Increases in Drugs Used to Treat Urologic Conditions," www.auanet.org), there are reports that some patients did not receive the recommended dose or treatment course of BCG (Loftus 2015).

1.1.3.1 Surveillance

Per current National Comprehensive Cancer Network (NCCN), AUA, and EAU surveillance guidelines, patients with high-risk NMIBC after diagnosis and management with TURBT and BCG are followed with cystoscopy and urine cytology every 3 months for 2 years, followed by every 6 months for 3 years, then annually. Upper urinary tract imaging is recommended for baseline assessment and annually (as clinically indicated) (Babjuk et al. 2011; NCCN 2014; Hall et al. 2007).

1.1.4 BCG Failure in High-Risk Non–Muscle-Invasive Bladder Cancer

Despite the significant activity of BCG in high-risk NMIBC, most patients will experience treatment failure with BCG with 50% having disease recurrence within the first year and up to 90% within 5 years (Lightfoot et al. 2011). Broadly speaking, any persistence or recurrence of disease after an adequate course of BCG therapy can be referred to as BCG failure. Definitions to better clarify the patterns of BCG failure have been put forth in a recent consensus meeting of the Genitourinary (GU) Group of the American Society of Clinical Oncology in 2015 (Lerner et al. 2015). New terms defining BCG failure now include the following:

- BCG-unresponsive NMIBC is defined as follows:

  Persistence of high-grade (Grade 3) disease at 6 months following an adequate course of BCG; OR

  Stage/grade progression at 3 months after induction BCG; OR

  Recurrence of high-grade (Grade 3) disease after achieving a disease-free state (i.e., CR) following induction of an adequate course of BCG that occurs <6 months after the last exposure to BCG

- BCG-relapsing NMIBC is defined as follows:

  Recurrence of high-grade (Grade 3) disease after achieving a disease-free state following induction of an adequate course of BCG that occurs ≥ 6 months after the last exposure to BCG

- An adequate course of BCG (assuming an adequate BCG supply worldwide) includes one course of induction (minimum of five weekly instillations) AND one course of maintenance (minimum of two weekly instillations)

Failure to achieve a CR with induction has been associated with increased risk of disease recurrence/progression and death in patients with high-risk NMIBC (Herr and Dalbagni 2003). In a follow-up analysis of SWOG 8507 with Lerner et al. (2009), the 5-year survival probability was significantly higher in patients with a CR following BCG induction (77%) versus those with BCG failure following induction (62%). These observations have led the effort to improve the efficacy of BCG in reducing and/or preventing recurrence and disease progression (Lerner et al. 2009).

Solsona et al. (2000) reported on 3-month clinical response to intravesical therapy as a predictive factor for disease progression in high-risk NMIBC. In addition to this, the highest risk of disease recurrence is observed within the first 2 years of diagnosis (Sylvester et al. 2006).

Shirakawa et al. (2012) reported on 173 patient-case series of BCG-failures. In this series with a median follow-up period from initial BCG failure of 4.7 years, multivariate analysis showed high-grade NMIBC at BCG failure ($p = 0.014$; risk ratio 2.84) and BCG-refractory disease ($p < 0.001$; risk ratio 4.68) were independent predictors for stage progression. The 10-year PFS rates were 53.2%, 91.1%, and 93.8% in the BCG-refractory, BCG-relapsing, and BCG-intolerant groups, respectively. The stage progression rate was higher in the BCG-refractory than in the BCG-relapsing ($p < 0.001$) and BCG-intolerant ($p = 0.007$) groups. Similarly, the 10-year disease-specific survival rate in the BCG-refractory group was significantly worse than those in the other BCG failure groups ($p < 0.001$) (Shirakawa et al. 2012).

1.1.5 Treatment Options following BCG Failure in High Risk Non–Muscle-Invasive Bladder Cancer

Limited treatment options exist following BCG failure for patients who relapse or recur with high-grade NMIBC; both NCCN and EAU guidelines recommend radical cystectomy (Babjuk et al. 2011; NCCN 2014; Hall et al. 2007). A recommendation is also made for bladder-sparing approaches with immunotherapy, intravesical chemotherapy, or other modalities for patients who are unwilling or unfit to undergo cystectomy (Yates et al. 2012).

1.1.5.1 Immunotherapy

To improve BCG immunotherapy in NMIBC, several approaches have been pursued to enhance BCG induction of the Th-1 immune response, including the use of recombinant IFN-α, IL-2, IL-12, IFN-γ, TNF-α, and GM-CSF as a single agent or in combination with BCG. Data from O'Donnell et al. (2001) have suggested potential activity of BCG in combination with IFN-α2b.

There is rationale to support the use of immunotherapy combinations in BCG failure, on the basis of the potential mechanism of BCG resistance, which includes dampening of the cytokine stimulation and type 1 T-helper cell response.

BCG in Combination with Interferon

As a biological response modifier, IFN-α has shown limited single-agent activity in BCG failures with response rates under 15%. However, in contrast, significant activity has been observed with the agent when used in combination with intravesical BCG.

Joudi et al. (2006) investigated the combination BCG and IFN-α in patients with BCG-refractory and BCG-naive NMIBC. In this large, multicenter, Phase II study, 1007 evaluable BCG-naive and BCG-failure patients were treated with BCG in combination with IFN-α. Patients received 50–100 MU of IFN-α with adjusted doses of BCG (on the basis of prior exposure). At a median of 24 months of follow-up, disease-free survival (DFS) rates were 59% and 45% evaluable BCG-naive and BCG-failure populations, respectively ($p < 0.0001$) (Joudi et al. 2006).

Nepple et al. (2010) conducted a multicenter prospectively randomized study of 670 patients; evaluating BCG versus BCG in combination with IFN α–2B. Patients were further randomized to recommended daily allowance (RDA) vitamin or megadose vitamin preparation. At a median of 24 months of follow-up, the disease-free rates were similar in all groups with 63% in the BCG with RDA vitamin group, 59% in BCG with megadose vitamins, 55% in BCG in combination with IFN α–2B with RDA vitamin, and 61% in BCG with BCG in combination with IFN α–2B megadose vitamins ($p > 0.05$). The addition of IFN α–2B was associated with a more frequent incidence of fever (11% vs. 5%; $p = 0.0037$) and constitutional symptoms (18% vs. 11%; $p = 0.00183$) versus BCG alone (Nepple et al. 2010).

BCG in Combination with IL-12

To date, this combination has only been studied in a nonclinical setting in mice. Intravesical administration of the combination resulted in higher urine and serum levels IFNγ compared with either agent alone. Clinical translation is pending (O'Donnell et al. 1999; Smith et al. 2015).

1.1.5.2 Intravesical Chemotherapy

Valrubicin is a cytotoxic anthracycline antibiotic and a derivative of doxorubicin that is used a chemotherapeutic agent. It acts by inhibition of DNA and RNA synthesis via inhibition of various nucleosides and topoisomerases. Valrubicin was approved by the FDA in 1998 for use in BCG-refractory CIS on the basis of a single-arm Phase II study of 90 patients with BCG-refractory CIS with or without concurrent pTa/T1 disease. Results of the study showed an initial CR rate of 21% at the 6-month follow-up assessment with 8% of all patients enrolled having a durable response with a median follow-up of 30 months. The majority of adverse events observed were local with 66% of patients reporting frequency, 63% reporting urgency, and 60% reporting dysuria. Most of the local bladder symptoms reported were of mild to moderate severity and none was life threatening. Three of 90 patients enrolled discontinued therapy because of bladder symptoms (Steinberg et al. 2000).

In addition to valrubicin, several approved chemotherapies by intravestical administration are being tested, including gemcitabine, docetaxel, and epirubicin. In addition to this, multimodality treatments such as the hyperthermic administration of mitomycin C have been examined.

1.1.5.3 Radiation Therapy

Radiation therapy is rapidly becoming an expanding non-surgical option for BCG failures. Small patient studies have shown response rates of up to 60% (Chung et al. 2007). Harland et al. (2007) reported on one of the largest randomized studies to date in patients for radiation therapy, comparing radical radiation therapy to intravesical treatment or observation for high-grade T1 NMIBC. In this study of 210 patients with high-grade pT1 Grade 3 NMIBC, radical radiation therapy (60 Gy in 30 fractions) showed no difference between treatments in terms of PFS and overall survival for patients with unifocal disease, over best supportive care or BCG for those with multifocal disease or CIS (Harland et al. 2007). As a result, radiation therapy alone has largely remained a bladder preservation option for patients who are unwilling or unfit to undergo radical cystectomy or intravesical treatment.

There are increasing data on the utility of combined radiochemotherapy for high-risk NMIBC, particularly following TURBT. Weiss et al. (2006) reported results on a study comparing radiotherapy or radiochemotherapy (utilizing platinum-based chemotherapy) in 141 patients with pT1 NMIBC where a CR rate of 88% was achieved. Tumor progression rates at 5 and 10 years were 19% and 30% (13% and 29% for high-grade T1 tumors), respectively, and overall disease-specific survival was 82% and 73% (89% and 79% for complete responders, 80% and 71% for high-grade T1 tumors), respectively (Weiss et al. 2006).

1.1.5.4 Radical Cystectomy

For BCG-failures, in particular BCG-unresponsive NMIBC, radical cystectomy remains the recommended treatment (Babjuk et al. 2011; NCCN 2014; Hall et al. 2007). Reports from various studies including Herr and Sogani (2001) and Soloway et al. (2011) have demonstrated benefit in survival for patients with high-risk NMIBC who undergo earlier cystectomy, particularly in cases of BCG-failure.

This is in large part because of upstaging that occurs in a significant number of cases of high-risk NMIBC with BCG-failure. Although bladder-sparing approaches for BCG-unresponsive and BCG-relapsing NMIBC remain investigational, radical cystectomy provides for a definitive treatment. That said, this procedure carries a significant morbidity and mortality rate of up to 28% and 8.3%, respectively (Lightfoot et al. 2011). Complication rates for radical cystectomy vary widely from 19% to 64%, with a resulting loss of quality of life for many patients (Liedberg 2010). In addition, some patients are not candidates for surgery because of comorbid medical illness, and others refuse surgery after considering the impact to their quality of life despite recognition of the risks of disease progression. To date, there have been no

prospective randomized studies comparing cystectomy with second-line intravesical therapy for BCG-unresponsive NMIBC and BCG-relapsing NMIBC. Thus, while bladder-sparing approaches continue to be actively developed, radical cystectomy remains the standard of care for high-risk NMIBC with BCG failure.

Given the poor outcomes and undesirable therapeutic options for patients with BCG-relapsed, BCG-unresponsive, and VHR BCG-naive NMIBC, novel therapies are needed. Immunotherapy, which has demonstrated activity in this disease, holds the greatest promise for improving durable responses, preventing progression to muscle invasion, and offering an acceptable safety profile for this early disease space.

1.2 PD-L1/PD-1 PATHWAY IN NON–MUSCLE-INVASIVE BLADDER CANCER

Programmed death–ligand 1 (PD-L1) is an extracellular protein that down regulates immune responses primarily in peripheral tissues through binding to its two receptors programmed death–1 (PD-1) and B7.1. Many human tumors have been found to overexpress PD-L1, which acts to suppress anti-tumor immunity. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer (Blank et al. 2005; Keir et al. 2008). Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen-presenting cells can mediate downregulation of immune responses, including inhibition of T-cell activation and cytokine production (Butte et al. 2007; Yang et al. 2011).

In bladder cancer, expression of PD-L1 has been associated with poor prognosis. Nakanishi et al. (2007) were one of the first groups to observe an association between expression of PD-L1 (B7-H1) and outcomes in advanced urothelial cancers. In their study, PD-L1 (B7-H1) expression was significantly associated with a high frequency of disease recurrence and poor survival rate. Multivariate analysis also showed PD-L1 (B7-H1) expression to be a more significant prognostic factor than tumor grade (Nakanishi et al. 2007). Zhang et al. (2013) similarly presented data on PD-L1 expression and outcomes in urothelial carcinoma of the bladder. Results of this study showed PD-L1 expression in 43% of primary bladder cancers with an association between immunohistochemistry (IHC) positivity and intensity with tumor grade and staging (Zhang et al. 2013). Faraj et al. (2015) showed high intratumoral CD8+ T cell density to be associated with better overall survival and disease-specific survival in advanced bladder cancer. Bellmunt et al. (2015) reported on PD-L1 expression in tumor cells and tumor-infiltrating mononuclear cells (TIMCs). Results of this study showed PD-L1 expression in TIMCs to be associated with, but not predictive of, prolonged survival.

Clinical investigation of expression of PD-L1 and PD-1 specifically in the NMIBC population was conducted by Inman et al. (2007). A total of 280 patients (44 with high-risk NMIBC) were assessed for PD-L1 status with use of IHC with an anti-PD-L1 antibody (clone 5H1) for assay. PD-L1 immunostaining was noted in 28% of the specimens. The prevalence of PD-L1 expression increased by stage category and was 7% for pTa, 16% for pT1, 23% for pT2, 30% for pT3/4, and 45% for CIS (Inman et al. 2007).

In the NMIBC cohort, 16 of 44 patients developed recurrent disease following BCG therapy. Only 3 of these patients were PD-L1 positive in their original tumor specimen. Upon further follow-up, 11 of 16 recurrences were observed to have BCG-induced granulomata positive for PD-L1 expression with diffuse and intense staining (>90% of the cells). Findings from this study were supportive of the hypothesis that the PD-L1/PD-1 pathway is involved with immune escape in NMIBC following exposure to BCG (Inman et al. 2007).

1.3 ATEZOLIZUMAB

Atezolizumab (MPDL3280A) is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human PD-L1 and inhibits its interaction with its receptors, PD-1 and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells.

Atezolizumab is being investigated as a potential therapy for patients with solid tumors and hematologic malignancies in humans.

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

1.3.1 Nonclinical Experience

Comprehensive pharmacologic, pharmacokinetic (PK), and toxicologic evaluations have been conducted to demonstrate in vitro and in vivo activity, to determine in vivo PK behavior, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose for atezolizumab.

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

1.3.2 Clinical Experience

As of 10 May 2016, atezolizumab has been administered to approximately 6053 patients (as monotherapy or in combination with other cancer therapies) in a broad range of malignancies including NSCLC, triple-negative breast cancer, melanoma, renal cell cancer, gastric cancer, colorectal cancer, head and neck cancer, and urothelial cancer (UC). Currently, no maximum tolerated dose, no dose-limiting toxicities, and no clear dose-related trends in the incidences of adverse events have been determined. Fatigue, decreased appetite, nausea, and cough are commonly reported adverse events observed with both monotherapy and combination therapy.

Atezolizumab is currently being studied in urothelial carcinoma in the adjuvant and metastatic settings. The following safety and efficacy data are from the Phase Ia study PCD4989g and the Phase II study IMvigor210 (GO29293), both of which studied atezolizumab monotherapy in patients with locally advanced or metastatic urothelial carcinoma.

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.

Study IMvigor210 is a multicenter, open-label, single-arm Phase II study evaluating atezolizumab monotherapy (1200 mg IV q3w) for the treatment of patients with metastatic urothelial carcinoma (mUC). Patients in Study IMvigor210 were enrolled into two cohorts. Cohort 1 comprised patients who were treatment naive (1L) and cisplatin-ineligible. Cohort 2 comprised patients who had disease progression following at least one platinum-containing regimen (2L+). Patients who had progressed within 12 months of treatment with a platinum-containing adjuvant/neoadjuvant regimen were also considered 2L patients.

1.3.3 Clinical Safety

As of the clinical cutoff date (CCOD) of 14 March 2016, 119 and 310 patients with mUC in Cohort 1 (treatment naive and cisplatin ineligible) and Cohort 2 (2L+), respectively, received atezolizumab as a single agent. Despite the different patient populations in these two cohorts, the safety profile of atezolizumab in each cohort was consistent with the other (see Table 3). Additionally, the safety profiles of these two cohorts were consistent with the UC cohort in Study PCD4989g (CCOD of 15 December 2015), where 95 safety-evaluable patients with UC from all lines of therapy received atezolizumab monotherapy.

1.3.4 IMvigor 210 Cohort 1

Of the 119 safety-evaluable Cohort 1 patients, 95.8% reported an adverse event (see Table 3). The most frequently reported adverse events (≥ 20%) included fatigue (45.4%), decreased appetite (2.7%), nausea (21.8%), and diarrhea (21.0%).

Table 3 Safety Profiles of IMvigor210 and Study PCD4989g (UC Cohort): Safety-Evaluable Population

Parameter	Cohort 1 [a, b] (n = 119)	Cohort 2 [a, c] (n = 310)	Study PCD4989g (UC Cohort) [d, e] (n = 95)
Any AE	114 (95.8%)	302 (97.4%)	93 (97.9%)
Related AE	79 (66.4%)	218 (70.3%)	63 (66.3%)
Grade 3–4	53 (44.5%)	177 (57.1%)	49 (51.6%)
Related Grade 3–4	18 (15.1%)	51 (16.5%)	8 (8.4%)
Grade 5	4 (3.4%)	3 (1.0%)	1 (1.1%)
Related Grade 5	1 (0.8%)	0	0
SAE	43 (36.1%)	143 (46.1%)	45 (47.4%)
Related SAE	10 (8.4%)	36 (11.6%)	5 (5.3%)
AEs leading to withdrawal from study treatment	7 (5.9%)	9 (2.9%)	4 (4.2%)

AE = adverse event; CCOD = clinical cutoff date; mUC = metastatic urothelial carcinoma; SAE = serious adverse event; UC = urothelial carcinoma.

[a] CCOD = 14 March 2016.

[b] Cohort 1 consisted of patients with mUC who were treatment naive and cisplatin ineligible.

[c] Cohort 2 consisted of 2L + patients with mUC.

[d] CCOD = 15 December 2015.

[e] Included patients from all lines of therapy.

Fewer than half (44.5%) of the Cohort 1 patients had a Grade 3–4 adverse event (see Table 3). The most commonly reported Grade 3–4 adverse events (≥ 2.5% or 3 patients) were fatigue and anemia (5% each), hyponatremia and blood creatinine increased (3.4% each), and small intestinal obstruction, and urinary tract infection, decreased appetite, increased ALT, and hypotension (2.5% each). Fatigue (3.4%) and increased ALT (2.5%) were the Grade 3–4 adverse events most commonly (≥ 2.5% or 3 patients) considered related to atezolizumab.

Four patients (3.4%) had a Grade 5 adverse event (see Table 3). These were cardiac arrest, myocardial infarction, sepsis (related to atezolizumab), and respiratory failure.

Approximately one-third of Cohort 1 patients (36.1%) had a serious adverse event (see Table 3). Most of these serious adverse events were each reported in 1 patient. Those that were reported in ≥2 patients (≥1.7%) are detailed in Figure 1. Ten patients (8.4%) had atezolizumab-related serious adverse events. Renal failure and diarrhea were the only related serious adverse events occurring in >2 patients.

Figure 1 Serious Adverse Events in ≥2 Patients: Safety-Evaluable Population in Cohort 1 of IMvigor 210

MedDRA System Organ Class MedDRA Preferred Term	All (N=119)
RENAL AND URINARY DISORDERS	
Total number of patients with at least one adverse event	8 (6.7%)
ACUTE KIDNEY INJURY	4 (3.4%)
RENAL FAILURE	4 (3.4%)
GASTROINTESTINAL DISORDERS	
Total number of patients with at least one adverse event	5 (4.2%)
SMALL INTESTINAL OBSTRUCTION	3 (2.5%)
DIARRHOEA	2 (1.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Total number of patients with at least one adverse event	4 (3.4%)
ASTHENIA	2 (1.7%)
PYREXIA	2 (1.7%)
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one adverse event	3 (2.5%)
SEPSIS	3 (2.5%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Total number of patients with at least one adverse event	2 (1.7%)
ANAEMIA	2 (1.7%)
INVESTIGATIONS	
Total number of patients with at least one adverse event	2 (1.7%)
BLOOD CREATININE INCREASED	2 (1.7%)
METABOLISM AND NUTRITION DISORDERS	
Total number of patients with at least one adverse event	2 (1.7%)
DEHYDRATION	2 (1.7%)

Investigator text for AEs encoded using MedDRA v18.1. Percentages are based on N in the column headings.
Table includes AEs occuring in at least 2 patients. For frequency counts by preferred term, multiple occurences of same AE in an individual are counted only once.
Safety summaries for treatment-emergent adverse events include all adverse events that occur on or after the first dose of study drug until 30 days after the last administration of study drug or initiation of another non-protocol anti-cancer therapy after the last administration of study drug, or clinical cutoff date, whichever occurs first.
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Cardiac arrest, myocardial infarction, autoimmune colitis, diarrhea, hypersensitivity, sepsis, and respiratory failure were the adverse events that led to 7 patients (5.9%) terminating atezolizumab.

1.3.4.1 IMvigor 210 Cohort 2

Of the 310 safety-evaluable patients in Cohort 2, 97.4% reported an adverse event of any grade (see Table 3). The most frequently reported adverse events (≥ 20%) included fatigue (50.3%), decreased appetite (26.8%), nausea (26.1%), constipation (25.2%), urinary tract infection (23.5%), pyrexia (21.6%), and diarrhea (21.3%).

Slightly more than half of the patients (57.1%) reported a Grade 3–4 adverse event (see Table 3), with the most common (≥ 2.3% or 7 patients) being anemia (9.4%), urinary tract infection (7.7%), fatigue (5.8%), hyponatremia (3.5%), dehydration and dyspnea (3.2% each), hematuria (2.9%), abdominal pain, back pain, and sepsis (2.6% each), and pain and pulmonary embolism (2.3% each). The Grade 3–4 adverse events considered related to atezolizumab were generally reported in 1 patient. Those reported in ≥ 2 patients (≥ 0.6%) were fatigue (1.6%), AST and ALT increased (1.3% each), and colitis, decreased appetite, dyspnea, pneumonitis, arthralgia, anemia, and hypotension (0.6% each).

Grade 5 adverse events of subileus, pulmonary sepsis, and cerebral hemorrhage occurred in 1 patient each (see Table 3). None of the events were considered related to atezolizumab.

Slightly fewer than half of the Cohort 2 patients (46.1%) reported a serious adverse event (see Table 3). Figure 2 summarizes the serious adverse events that were reported in ≥ 2 patients (≥ 0.6%). Urinary tract infection (7.1% or 22 patients) was the only serious adverse event that occurred in ≥ 5% of the patients. Thirty-six (11.6%) patients had an atezolizumab-related serious adverse event, with the most common (≥ 0.6% or ≥ 2 patients) being pneumonitis and pulmonary embolism (1.0% each) and encephalopathy, colitis, and pyrexia (0.6% each).

Figure 2 Serious Adverse Events in ≥2 Patients: Safety-Evaluable Population in Cohort 2 of IMvigor 210

MedDRA System Organ Class MedDRA Preferred Term	All (N=310)
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one adverse event	43 (13.9%)
URINARY TRACT INFECTION	22 (7.1%)
SEPSIS	8 (2.6%)
PNEUMONIA	6 (1.9%)
PYELONEPHRITIS	4 (1.3%)
UROSEPSIS	3 (1.0%)
BACTERAEMIA	2 (0.6%)
KIDNEY INFECTION	2 (0.6%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Total number of patients with at least one adverse event	20 (6.5%)
PULMONARY EMBOLISM	8 (2.6%)
DYSPNOEA	7 (2.3%)
PNEUMONITIS	3 (1.0%)
HAEMOPTYSIS	2 (0.6%)
HYPOXIA	2 (0.6%)
RENAL AND URINARY DISORDERS	
Total number of patients with at least one adverse event	18 (5.8%)
HAEMATURIA	11 (3.5%)
ACUTE KIDNEY INJURY	5 (1.6%)
HYDRONEPHROSIS	3 (1.0%)
METABOLISM AND NUTRITION DISORDERS	
Total number of patients with at least one adverse event	14 (4.5%)
DEHYDRATION	7 (2.3%)
HYPERCALCAEMIA	4 (1.3%)
HYPONATRAEMIA	4 (1.3%)
GASTROINTESTINAL DISORDERS	
Total number of patients with at least one adverse event	12 (3.9%)
SMALL INTESTINAL OBSTRUCTION	5 (1.6%)
ABDOMINAL PAIN	3 (1.0%)
NAUSEA	3 (1.0%)
SUBILEUS	2 (0.6%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Total number of patients with at least one adverse event	12 (3.9%)
PYREXIA	5 (1.6%)
ASTHENIA	3 (1.0%)
FATIGUE	3 (1.0%)
PAIN	3 (1.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Total number of patients with at least one adverse event	8 (2.6%)
BACK PAIN	6 (1.9%)
BONE PAIN	2 (0.6%)
NERVOUS SYSTEM DISORDERS	
Total number of patients with at least one adverse event	7 (2.3%)
ENCEPHALOPATHY	3 (1.0%)
CEREBROVASCULAR ACCIDENT	2 (0.6%)
SYNCOPE	2 (0.6%)
INVESTIGATIONS	
Total number of patients with at least one adverse event	5 (1.6%)
ASPARTATE AMINOTRANSFERASE INCREASED	3 (1.0%)
ALANINE AMINOTRANSFERASE INCREASED	2 (0.6%)
BLOOD CREATININE INCREASED	2 (0.6%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Total number of patients with at least one adverse event	4 (1.3%)
ANAEMIA	2 (0.6%)
LYMPH NODE PAIN	2 (0.6%)
PSYCHIATRIC DISORDERS	
Total number of patients with at least one adverse event	3 (1.0%)
CONFUSIONAL STATE	3 (1.0%)
VASCULAR DISORDERS	
Total number of patients with at least one adverse event	3 (1.0%)
DEEP VEIN THROMBOSIS	3 (1.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one adverse event	2 (0.6%)
HIP FRACTURE	2 (0.6%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	
Total number of patients with at least one adverse event	2 (0.6%)
PELVIC PAIN	2 (0.6%)

Investigator text for AEs encoded using MedDRA v18.1. Percentages are based on N i
column headings.
Table includes AEs occuring in at least 2 patients. For frequency counts by prefer
multiple occurences of same AE in an individual are counted only once.
Safety summaries for treatment-emergent adverse events include all adverse events
occur on or after the first dose of study drug until 30 days after the last admini
of study drug or initiation of another non-protocol anti-cancer therapy after the
administration of study drug, or clinical cutoff date, whichever occurs first.
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Nine adverse events led to 9 patients being withdrawn from atezolizumab treatment (2.9%) in Cohort 2 (see Table 3): pulmonary sepsis, retroperitoneal infection, sepsis, cerebral haemmorhage, posterior reversible encephalopathy syndrome, subileus, fatigue, acute kidney injury, and pruritus.

Refer to the current Atezolizumab Investigator's Brochure for details regarding immune-mediated adverse events observed in patients treated with atezolizumab.

1.3.4.2 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, as well as events of hepatitis/elevated liver function tests (LFTs) and influenza-like illness that are considered potential adverse drug reactions associated with atezolizumab. There is also a potential for immune activation being associated with generalized systemic features (e.g., hypotension, respiratory failure, and other organ impairment).

Refer to the current Atezolizumab Investigator's Brochure for details regarding immune-mediated adverse events observed in patients treated with atezolizumab.

1.3.5 Clinical Activity

1.3.5.1 PCD4989g: Clinical Activity in Patients with 2L + mUC

The single-arm Phase Ia Study PCD4989g evaluates the efficacy of single-agent atezolizumab in the treatment of patients with locally advanced or metastatic solid tumors or hematologic malignancies, including mUC. As of the CCOD of 15 December 2015, 94 1L+ patients with mUC (predominantly 2L+) were evaluable for efficacy.

IRF-assessed ORR (confirmed responses) per RECIST v1.1 was 25.5% in all patients, with 9 CRs and 15 PRs. An evaluation of ORR by PD-L1 expression subgroup suggested that higher levels of PD-L1 expression may be associated with higher ORRs (31.8% in IC2/3 vs. 20.8% in IC0/1). The median DOR was not estimable for the 94 efficacy-evaluable patients as 62.5% of patients were still event free at the point of the CCOD.

Table 4 IRF-Assessed ORR and DOR per RECIST v1.1 in PCD4989g (mUC Cohort): Efficacy-Evaluable Population

Efficacy Endpoint	IC0/1 (n=48)	IC2/3 (n=22)	Unknown (n=24)	All Patients (n=94)
ORR (%)	10 (20.8)	7 (31.8)	7 (29.2)	24 (25.5)
95% CI	(10.5, 35.0)	(13.9, 54.9)	(12.6, 51.1)	(17.1, 35.6)
Complete response	3	3	3	9
Partial response	7	4	4	15
Median DOR (months)	NE	NE	17.5	NE
95% CI	(7.5, NE)	(9.9, NE)	(17.3, NE)	(17.3, NE)
Patients with event (%)	4 (40.0)	2 (28.6)	3 (42.9)	9 (37.5)

CCOD=clinical cutoff date; DOR=duration of response; IC=tumor-infiltrating immune cell; IUO=investigational use only; mUC=metastatic urothelial carcinoma; ORR=objective response rate; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1.

Notes: The CCOD for these data was 15 December 2015. These responses were confirmed responses. PD-L1 diagnostic criteria were based on the IUO assay.

IMvigor210 Cohort 1: Clinical Activity in Patients with 1L Cisplatin-ineligible mUC

As of the clinical cutoff of 14 March 2016, efficacy analyses were performed on the 119 patients in Cohort 1 of from Study IMvigor210. The median age of this population was 73 years (range: 51–92 years), and the group represented a cisplatin-ineligible patient population who were previously untreated in the metastatic setting. The median duration on study treatment was 15 weeks.

With a median follow-up duration of 14.4 months, the cisplatin-ineligible mUC patients demonstrated clinically meaningful response rates after first-line treatment with atezolizumab in all PD–L1 IC subgroups: both IC0/1 and IC2/3 patients had an ORR of 28.1%. For patients with upper urinary tract urothelial carcinoma (UTUC) (n=33), the ORR was 42.4%.

As of 14 March 2016, the median duration of response (DOR) had not been reached in any of the IC subgroups (range: 3.7–16.6 months), with 21 patients with an ongoing response.

The median OS for all patients was 14.8 months (95% CI: 10.1, NE), and over half of the patients (52.9%) remained event-free (see Figure 3).

Table 5 IRF-Assessed ORR and DOR per RECIST v1.1 in 1L Patients with mUC: Efficacy-Evaluable Population in IMvigor 210 Cohort 1 (Primary and Updated Analyses)

	Primary Analysis [a]			Updated Analysis [b]		
Efficacy Endpoint	IC0/1 (n = 87)	IC2/3 (n = 32)	All Patients (n = 119)	IC0/1 (n = 87)	IC2/3 (n = 32)	All Patients (n = 119)
ORR (%)	16 (18.4)	7 (21.9)	23 (19.3)	19 (28.1)	9 (28.1)	28 (23.5)
95% CI	(10.9, 28.1)	(9.3, 40.0)	(12.7, 27.6)	(13.7, 32.0)	(13.8, 46.8)	(16.2, 32.2)
Complete response	5	1	6	6	2	8
Partial response	11	6	17	13	7	20
Median DOR (months)	NE	NE	NE	NE	NE	NE
95% CI	NE	NE	NE	(12.8, NE)	(11.1, NE)	(12.8, NE)
Patients with event (%)	1 (6.3)	0	1 (4.3)	4 (21.1)	3 (33..3)	7 (25.0)

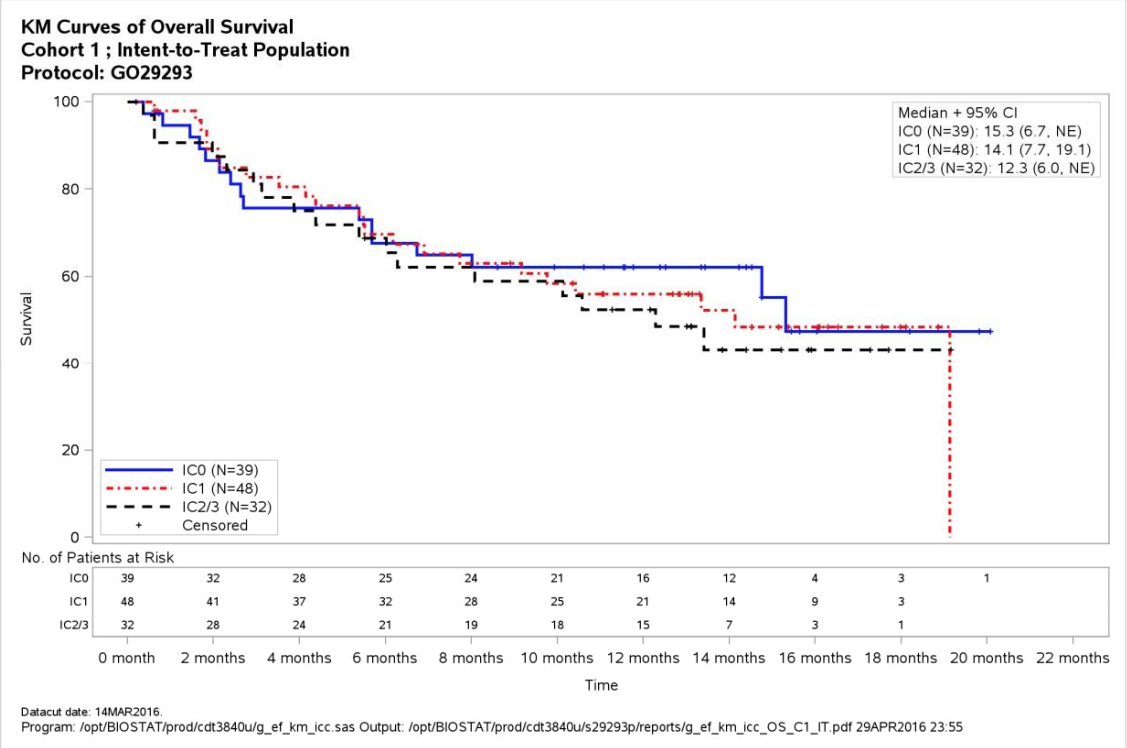
CCOD = clinical cutoff date; DOR = duration of response; IC = tumor-infiltrating immune cell; mUC = metastatic urothelial carcinoma; ORR = objective response rate; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: The responses were confirmed responses.

[a] The CCOD of the primary analysis was 14 September 2015.

[b] The CCOD of the updated analysis was 14 March 2016.

Figure 3 Overall Survival for All Cohort 1 Efficacy-Evaluable Patients



IMvigor210 Cohort 2: Clinical Activity in Patients with 2L+ mUC

As of the clinical cutoff of 14 March 2016, efficacy analyses were performed on the 310 Cohort 2 patients from Study IMvigor210. The median age of this population was 66 years (range: 32–91 years), and the group represented a 2L+ mUC patient population that was previously treated with at least one platinum-containing regimen. The median duration on study treatment was 12 weeks.

With a median follow-up duration of 14.4 months, atezolizumab treatment for 2L+ mUC patients demonstrated clinical activity in in all PD-L1 IC subgroups with higher ORRs associated with higher PD-L1 scores: The IC2/3 subgroup had a clinically meaningful ORR of 28.0% (15 CRs and 13 PRs) versus the 10% in the IC0/1 subgroup (6 CRs and 16 PRs). The ORR for all patients was 15.8%.

The median duration of response (DOR) for all responders (n = 49) has not been reached in any of the IC subgroups (range: 2.1+ to 19.2+ months), with 35 patients with an ongoing response.

With patient-event ratio at 70.3%, the median OS was 7.9 months (95% CI: 6.7, 9.3) for all patients (see Figure 4).

Table 6 IRF-Assessed ORR and DOR per RECIST v1.1 in 2L + Patients with mUC: Efficacy-Evaluable Population in IMvigor 210 Cohort 2 (Primary and Updated Analyses)

	Primary Analysis [a]			Updated Analysis [b]		
Efficacy Endpoint	IC0/1 (n = 211)	IC2/3 (n = 100)	All Patients (n = 311)	IC0/1 (n = 210)	IC2/3 (n = 100)	All Patients (n = 310)
ORR (%)	20 (9.5)	27 (27.0)	47 (15.1)	21 (10.0)	28 (28.0)	49 (15.8)
95% CI	(5.9, 14.3)	(18.6, 36.8)	(11.3, 19.6)	(6.4, 14.9)	(19.5, 37.9)	(11.9, 20.3)
Complete response	4	8	12	6	15	21
Partial response	16	19	35	16	13	28
Median DOR (months)	NE	NE	NE	NE	NE	NE
95% CI	NE	(6.0, NE)	(6.01, NE)	(10.6, NE)	NE	NE
Patients with event (%)	0	4 (14.8)	4 (8.5)	6 (28.6)	8 (28.6)	14 (28.6)

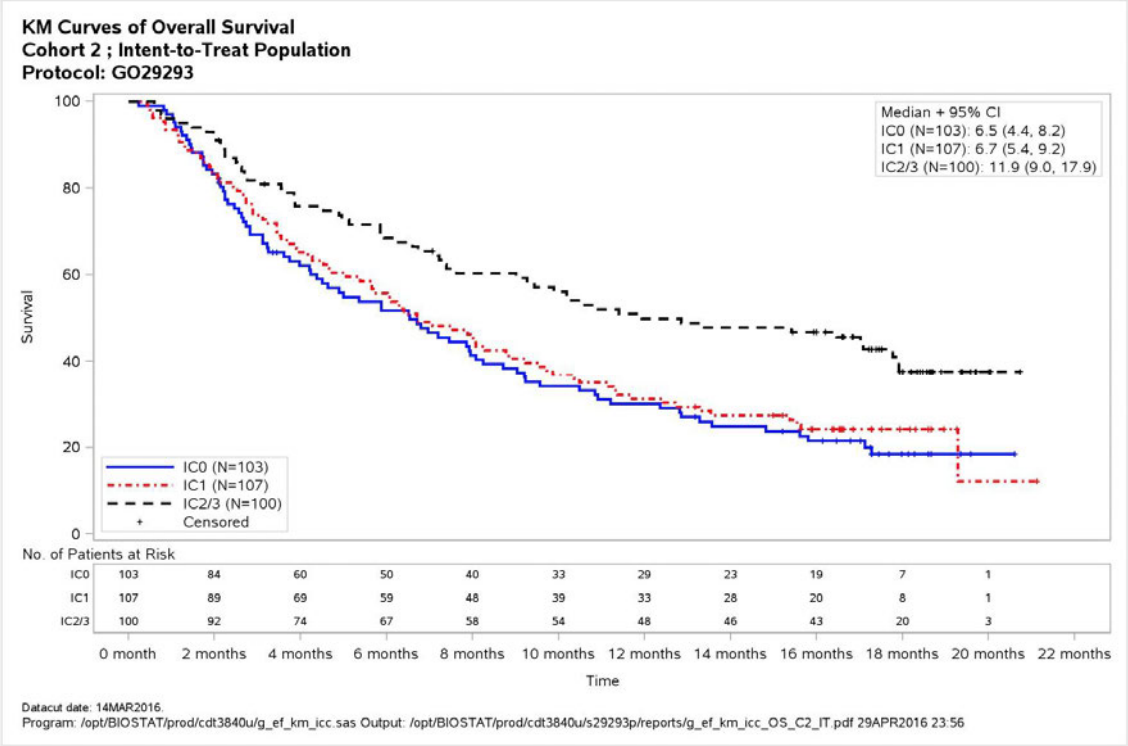
CCOD = clinical cutoff date; DOR = duration of response; IC = tumor-infiltrating immune cell; mUC = metastatic urothelial carcinoma; ORR = objective response rate; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: These responses were confirmed responses.

[a] The CCOD of the primary analysis was 5 May 2015.

[b] The CCOD of the updated analysis was 14 March 2016.

Figure 4 Overall Survival for All Cohort 2 Efficacy-Evaluable Patients



Refer to the Atezolizumab Investigator's Brochure for further information regarding efficacy data with atezolizumab.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Despite the activity of BCG in NMIBC, most patients will experience treatment failure with BCG with 50% having disease recurrence within the first year and up to 90% within 5 years (Lightfoot et al. 2011). In this group of BCG failures, approximately 55%–60% have BCG-unresponsive NMIBC. High risk factors for disease progression include BCG unresponsive disease and the presence of CIS (Shirakawa et al. 2012). Combination immune therapy with BCG and interferon has shown increased activity, but adoption has been limited because of toxicity.

Encouraging clinical data emerging in the field of cancer immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate

tumor-specific T-cell immunity. PD-L1 expression is prevalent in many human tumors, and elevated PD-L1 expression on tumor cells is associated with a poor prognosis in patients with UC (Nakanishi et al. 2007; Mu et al. 2011).

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies for whom standard-of-care therapies have failed or are not tolerated. In Study PCD4989g, a Phase Ia, dose-escalation and expansion study, objective responses with atezolizumab monotherapy were observed in a broad range of malignancies (see Section 1.3.2) including UC.

Recent studies suggest that BCG resistance or failure in NMIBC may occur via immune escape through PD-L1 tumor expression (Inman et al. 2007). These data, along with results of several studies investigating immunotherapy combinations for NMIBC, have formed the rationale to investigate the hypothesis of BCG activation with suppression of tumor resistance through PD-L1 blockade with use of a combination approach of atezolizumab and BCG in NMIBC (Inman et al. 2007; Zlotta et al. 2009).

Atezolizumab has been well tolerated in patients with advanced/metastatic urothelial carcinoma (see Section 1.3.2). Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, hypothyroidism, hepatitis/transaminitis, colitis, and myasthenia gravis, have been observed. To date, these events have been manageable with treatment. It is anticipated that treatment with atezolizumab in patients with NMIBC either alone or in combination with other treatment modalities (e.g., intravesical BCG) will have a manageable safety profile with an acceptable benefit-risk assessment for the conduct of the study.

NMIBC is an early disease state that is potentially curable. Toxicity deemed allowable in the advanced/metastatic setting would not be considered acceptable in this early disease setting. Thus, enrollment of BCG-relapsing (Cohort 2) and very high-risk BCG-naive (Cohort 3) patients will not commence until the benefit-risk of atezolizumab in BCG-unresponsive patients (as monotherapy and in combination with BCG) has been carefully reviewed.

2. OBJECTIVES

This study will evaluate the safety, pharmacokinetics, immunogenicity, patient-reported outcomes (PROs), and preliminary anti-tumor activity of atezolizumab administered as a single agent and in combination with BCG in patients with BCG-unresponsive NMIBC, and in combination with BCG in patients with BCG-relapsing, and VHR, BCG-naive NMIBC.

2.1 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab administered as a single agent and in combination with BCG
- To identify the dose-limiting toxicities (DLTs) and to determine the maximum tolerated dose (MTD) or tolerability at the maximum administered dose (MAD) of BCG when administered in combination with atezolizumab

2.2 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is as follows:

- To characterize the pharmacokinetics of atezolizumab administered as a single agent and in combination with BCG

2.3 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is as follows:

- To evaluate the immune response to atezolizumab, as measured by the incidence of ATAs

2.4 EFFICACY OBJECTIVE

The efficacy objective for this study is as follows:

- To make a preliminary assessment of the anti-tumor activity of atezolizumab administered as a single agent and in combination with BCG, as measured by the primary endpoint of 6-month CR rate. Secondary endpoints include 3-month CR rate, duration of CR, RFS rate, bladder-intact DFS, PFS, cystectomy-free survival (CFS), and overall survival.

2.5 PATIENT-REPORTED OUTCOME OBJECTIVE

The PRO objective for this study is as follows:

- To make a preliminarily assessment of patient-reported symptoms, function, and HRQoL associated with atezolizumab administered as a single agent and in combination with BCG, as measured by the EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30) and the EORTC QLQ-Non Muscle Invasive Bladder Cancer 24 (NMIBC24)

2.6 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To make a preliminary assessment of biomarkers that might act as indicators of anti-tumor activity of atezolizumab administered as a single agent and in combination with BCG
- To make a preliminary assessment of biomarkers that might act as indicators of the immunomodulatory effect of atezolizumab administered as a single agent and in combination with BCG

- To explore the potential relationship between immunogenic response and pharmacokinetics, safety, and efficacy

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a Phase Ib/II, open-label, multicenter study designed to assess the safety, tolerability, pharmacokinetics, immunogenicity, PROs, and preliminary anti-tumor activity of atezolizumab administered by IV infusion as a single agent and in combination with intravesical BCG in patients with high-risk NMIBC.

Atezolizumab will be evaluated in the following patient cohorts:

- Cohort 1: Patients with BCG-unresponsive NMIBC
  - Cohort 1A: Atezolizumab as a single agent
  - Cohort 1B: Atezolizumab in combination with BCG
- Cohort 2: Atezolizumab in combination with BCG in patients with BCG-relapsing NMIBC
- Cohort 3: Atezolizumab in combination with BCG in patients with VHR BCG-naive NMIBC

The study will be conducted at approximately 10 to 20 sites in the United States and will enroll up to approximately 70 patients across all cohorts. All patients will be required to have histologically confirmed non-muscle invasive urothelial carcinoma of the bladder with CIS. See Section 4.1.1 for definitions of BCG-unresponsive (Cohorts 1A and 1B), BCG-relapsing (Cohort 2), and VHR BCG-naive NMIBC (Cohort 3).

Atezolizumab will be administered at a fixed dose of 1200 mg q3w for a maximum of 96 weeks. BCG will be administered to evaluate DLTs, MTD, or MAD. De-escalation will be allowed for up to three dose levels of BCG (full dose [50 mg], 66% of a full dose, and 33% of a full dose [Cohort 1B only]).

The study will be conducted as follows (see Figure 5):

- Cohort 1A

  Cohort 1A will commence enrollment first. Cohort 1A will evaluate the safety and tolerability of atezolizumab as a single agent in patients with BCG-unresponsive NMIBC. Up to approximately 12 safety- and efficacy-evaluable patients will be enrolled into Cohort 1A.

- Cohort 1B

  Cohort 1B will commence enrollment once 3 patients in Cohort 1A have completed one cycle (21 days) of study therapy. Cohort 1B will evaluate the safety and tolerability, DLTs, and MTD or MAD of the combination of atezolizumab and BCG in patients with BCG-unresponsive NMIBC. Data from Cohort 1B will be used to inform on the safety and tolerability of combination treatment in NMIBC, as determined at the MTD or MAD, as well as the recommended starting BCG dose in Cohorts 2 (BCG-relapsing NMIBC) and 3 (VHR BCG-naive NMIBC). Approximately 8–18 patients will be enrolled into Cohort 1B. If fewer than 8 patients are required to establish MTD or MAD in this cohort, additional patients will be enrolled for a minimum of 8 patients in this cohort.

- Cohort 1 Expansion

  An expansion cohort will allow enrollment of up to approximately 10 additional patients from Cohorts 1A or 1B. The purpose of this expansion cohort is to provide additional safety and efficacy data on these patients, depending on the safety profile observed in Cohort 1B. If few or no DLTs are observed with the combination of atezolizumab and BCG, additional Cohort 1B patients will be enrolled to better characterize the safety clinical activity of combination therapy. Alternatively, if the combination of atezolizumab and BCG is deemed intolerable in the Cohort 1B population, additional Cohort 1A patients will be enrolled to provide additional safety and efficacy data for atezolizumab monotherapy in the BCG-unresponsive patients.

Enrollment into Cohorts 2 and 3 will not begin until safety and preliminary anti-tumor activity results from approximately 20 patients across Cohort 1 (1A and 1B) are obtained and the preliminary benefit/risk has been evaluated.

- Cohort 2

  Cohort 2 will commence once the preliminary risk/benefit assessment from Cohorts 1A and 1B has demonstrated an acceptable safety and efficacy profile. Cohort 2 will evaluate the safety, tolerability and preliminary efficacy of the combination of atezolizumab and BCG (dosed at the MAD or MTD defined by Cohort 1B) in patients with BCG-relapsing NMIBC. Approximately 10 patients will be enrolled into Cohort 2.

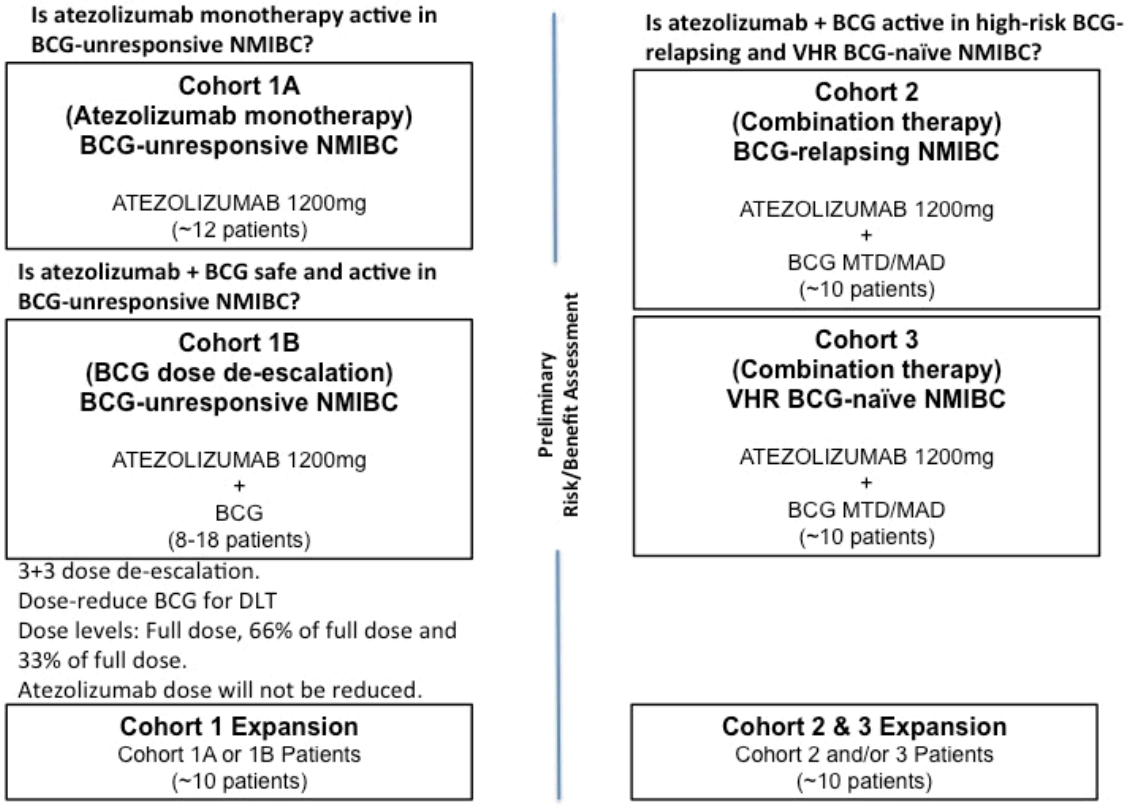
- Cohort 3

  Cohort 3 will commence simultaneously with Cohort 2. Cohort 3 will evaluate the safety, tolerability, and preliminary efficacy of the combination of atezolizumab and BCG (dosed at the MAD or MTD defined by Cohort 1B) in patients with VHR BCG-naive NMIBC. Approximately 10 patients will be enrolled in Cohort 3.

- Cohort 2 and 3 Expansion

  An expansion cohort will allow enrollment of up to approximately 10 patients in total from Cohorts 2 and/or 3. The purpose of this expansion cohort is to provide additional safety and efficacy data for these populations.

Figure 5 Study Schema



BCG = bacille Calmette-Guérin; DLT = dose-limiting toxicity; NMIBC = non–muscle-invasive bladder cancer.

Note: In the absence of unacceptable toxicity or evidence of disease progression, patients deriving clinical benefit may be offered continued atezolizumab for up to 96 weeks.

Cohort 1A

Enrollment in Cohort 1A will begin first. The treatment regimen for Cohort 1A patients is atezolizumab 1200 mg IV q3w monotherapy (see Figure 6). Patients may be treated for a maximum of 32 q3w cycles of atezolizumab (or for a maximum treatment duration of 96 weeks, whichever comes first). Dosing of the second and third patients will be staggered by a minimum of 1 week relative to the first patient.

Cohort 1B

Enrollment of patients into Cohort 1B will begin once 3 patients in Cohort 1A have completed one cycle (21 days) of therapy. Cohort 1B will follow a "3 + 3" BCG dose

de-escalation scheme evaluating up to three dose levels of BCG until the BCG MTD (or MAD) for the two-drug combination in BCG-unresponsive NMIBC is defined. The dose of atezolizumab will be fixed; dose de-escalation will occur only for BCG. The three BCG dose levels to be evaluated in Cohort 1B will be the full BCG dose (with a starting dose of 50 mg), followed by 66% of a full BCG dose (33 mg), followed by 33% of a full BCG dose (16.5 mg) [Cohort 1B only]. In the first course, patients will receive concurrent atezolizumab + BCG at the assigned dose. The MTD or MAD will be determined on the basis of DLTs observed during the DLT assessment window (defined as Days 1–21 of BCG Induction Course). After the MTD or MAD is determined for Cohort 1B, this dose will be used for all subsequent patients enrolled into Cohorts 1B, 2, and 3, unless the MTD is determined to be 33% of a full BCG dose. If MTD is determined to be 33% of a full BCG dose, then, no patients will be enrolled into Cohorts 2 and 3 until an assessment of the safety and activity of the combination of atezolizumab plus 33% of a full BCG dose is completed. Atezolizumab plus 33% of a full dose will not be carried into Cohorts 2 and 3 unless a favorable risk-benefit profile is demonstrated. If MTD or MAD is reached before 8 patients have been enrolled in Cohort 1B, additional patients will be enrolled up to a minimum of 8 total patients. These additional patients will be treated at the established MTD or MAD. See Section 3.1.3 for a description of the BCG dose de-escalation scheme and Section 3.1.4 for the definition of DLT.

A minimum of 3 patients will be enrolled into each BCG dose level evaluated. However, for the starting dose level in Cohort 1B, dosing of the second and third patients will be staggered by a minimum of 1 week relative to the first patient. If the first patient does not experience unacceptable toxicity during the first week of combination treatment, the second and third patients at the first dose level may start combination treatment without delay. Dosing for subsequent dose levels will not be staggered.

The treatment regimen for Cohort 1B patients is as follows (see Figure 6):

BCG

- BCG Induction Course (12 weeks): BCG induction will begin on study Day 1. BCG will be administered at the assigned dose (see Section 3.1.3) weekly for a total of six doses (BCG induction).
- BCG Maintenance Course 1 (12 weeks): BCG will be administered at the assigned dose weekly for a total of three doses (BCG maintenance).
- BCG Maintenance Courses 2–5 (every 24 weeks, beginning 12 weeks after initiation of Maintenance Course 1): BCG maintenance Courses 2–5 are optional for patients in Cohort 1B. BCG maintenance Courses 2–5 may be administered if, at the investigator's discretion, there is felt to be ongoing clinical benefit of BCG. The Medical Monitor will review and approve this on a case-by-case basis. These patients will receive BCG administered at the assigned dose weekly for a total of three doses per maintenance course.

Atezolizumab

- Atezolizumab therapy will begin on study Day 1. All patients will continue to receive atezolizumab 1200 mg IV q3w for a maximum of 32 q3w cycles or 96 weeks, whichever comes first.

Cohort 2

Patients in Cohort 2 will be treated with atezolizumab 1200mg IV q3w in combination with BCG dosed at the MAD or MTD determined by Cohort 1B (provided MAD or MTD is determined to be either full dose or 66% of a full BCG dose).

The treatment regimen for Cohort 2 patients is as follows (see Figure 6):

BCG

- BCG Induction Course (12 weeks): BCG induction will begin on study Day 1. BCG will be administered at the assigned dose weekly for a total of six doses (BCG induction).
- BCG Maintenance Course 1 (12 weeks): BCG will be administered at the assigned dose weekly for a total of three doses.
- BCG Maintenance Course 2–5 (every 24 weeks, beginning 12 weeks after initiation of Maintenance Course 1): BCG will be administered at the assigned dose weekly for a total of three doses per course.

Atezolizumab

- Atezolizumab therapy will begin on study Day 1. Patients will receive atezolizumab 1200 mg IV q3w for a maximum of 32 q3w cycles or 96 weeks, whichever comes first.

Cohort 3

Patients in Cohort 3 will be treated with atezolizumab 1200mg IV q3w in combination with BCG dosed at the MAD or MTD determined by Cohort 1B.

The treatment regimen for Cohort 3 patients is as follows (see Figure 6):

BCG

- BCG Induction Course (12 weeks): BCG induction will begin on study Day 1. BCG will be administered at the assigned dose weekly for a total of six doses (BCG induction).
- BCG Maintenance Course 1 (12 weeks): BCG will be administered at the assigned dose weekly for a total of three doses.
- BCG Maintenance Course 2–5 (every 24 weeks, beginning 12 weeks after initiation of Maintenance Course 1): BCG will be administered at the assigned dose weekly for a total of three doses per course.

Atezolizumab

- Atezolizumab therapy will begin on study Day 1. Patients will receive atezolizumab 1200 mg IV q3w for a maximum of 32 q3w cycles or 96 weeks, whichever comes first.

The total planned enrollment for this study is up to approximately 70 patients: up to approximately 12 patients in Cohort 1A, approximately 8–18 patients in Cohort 1B, up to approximately 10 patients in the Cohort 1 expansion, approximately 10 patients in Cohort 2, approximately 10 patients in Cohort 3, and approximately 10 patients in the Cohort 2 and 3 expansion.

3.1.2 Study Procedures for All Cohorts

Patients will be required to provide sample tumor tissue showing the presence of CIS, to be obtained within 60 days prior to study entry. Tissue should be submitted as formalin-fixed paraffin-embedded (FFPE) blocks (blocks preferred) or at least 10 unstained slides, with an associated pathology report, for central testing. Patients with fewer than 10 unstained slides available at baseline (but no fewer than five) may be eligible following discussion with the Medical Monitor. The Sponsor may replace patients who are later found to be unevaluable for tumor PD-L1 expression by central testing.

Tumor response assessment via cystoscopy and urine cytology will occur every 12 weeks for the first 2 years, and every 24 weeks thereafter until 5 years, and then yearly.

A mandatory tissue biopsy will be obtained from all patients 6 months after C1D1 of atezolizumab. For patients in Cohort 1A, biopsies should be obtained up to 21 days prior to atezolizumab administration. For patients in Cohorts 1B, 2, and 3, biopsies should be obtained 14–21 days prior to BCG intravesical instillation (e.g., Weeks 10, 22, 46, 70 and 94; see Appendix 3).

The Sponsor may replace patients who are discontinued from the study before the required tumor biopsy samples are obtained.

At the 6-month timepoint (Week 24 visit), documentation of a complete response (CR) is required to continue on study treatment.

Definition of Complete Response (must meet all 3 criteria):

- Cytology: not positive (see below)
- Upper Urinary Tract Imaging (if performed): normal, or abnormal but supportive of CR (with non-positive selective ureteral cytologies)

- Cystoscopy: bladder appears normal; or bladder appears abnormal but all biopsies are negative; or any grade papilloma, any grade papillary urothelial neoplasm of low malignant potential (PUNLMP), or low grade pTa

Interpretation of Urine Cytology:

- If results are Unsatisfactory, Atypical Cell, Suspicious, or Indeterminate, then assay must be repeated no less than 24 hours and up to 21 days later.
- If the results are again Unsatisfactory or Atypical Cell (2 in a row), then treat as if the result was negative.
- Two consecutive Suspicious or Indeterminate urine cytology specimens require further evaluation by cystoscopy and/or upper tract imaging as deemed appropriate by the investigator
- If cytology results are Suspicious or Indeterminate and the biopsies are negative, then treat as if the result was negative
- All occurrences of positive urine cytology will require further evaluation by cystoscopy and/or upper tract imaging. A positive cytology result only indicates presence of disease and cannot be used alone to determine disease progression.

  The date of a positive cytology result can be used for the date of recurrence, if the results of the cystoscopy, biopsy, or upper urinary tract assessment shows recurrence.

Patients with persistent and/or recurrent high grade NMIBC without progression (stage or grade progression of active disease, or the presence of new disease) at 12 weeks from treatment initiation may continue on study treatment.

Patients with recurrent low-grade papillary disease will be required to undergo resection with TURBT (unless medically contraindicated) and may continue on study and receive study treatment.

Indications for Discontinuation from Study for Disease Progression

- Stage or grade progression at any timepoint would require discontinuation from study therapy.
- Patients with persistent and/or recurrent high-grade NMIBC (any pT1, high grade pTa, or CIS) on or after the 6-month biopsy will be discontinued from study treatment and offered the option to undergo cystectomy or other bladder-sparing modalities as is clinically appropriate. Patients who undergo cystectomy will be requested to submit additional tissue from their cystectomy specimens.
- Patients with evidence of disease progression to muscle-invasive or metastatic disease at any timepoint will be discontinued from study treatment.

For all patients, additional evaluation (imaging, exam under anesthesia, biopsies) should be performed at investigator discretion for any of the following circumstances:

- Abnormal cystoscopy
- Positive urine cytology
- Two sequential suspicious or indeterminate urine cytology specimens

Study treatment with atezolizumab may be continued for a maximum of 32 q3w cycles or a total of 96 weeks of therapy. BCG treatment (induction and maintenance) may be continued for a maximum of 120 weeks (as clinically indicated; see Appendix 3). All study treatment will be discontinued in patients who undergo cystectomy or experience disease recurrence/progression or unacceptable toxicity, and in those who are not benefiting from study treatment (in the opinion of the investigator or the patient).

There may be circumstances in which either BCG or atezolizumab is permanently discontinued, but it may still be possible to continue the remaining study treatment with approval of the Medical Monitor. Patients in Cohorts 1B, 2, or 3 (atezolizumab plus BCG) who discontinue atezolizumab after receiving fewer than three cycles may be replaced.

All patients will be closely monitored for serious adverse events or protocol-defined events of special interest for 90 days or 30 days for adverse events, following their last dose of study therapy (atezolizumab and/or BCG) or initiation of non-protocol anti-cancer therapy, whichever occurs first. Safety assessments will include the incidence, nature, and severity of adverse events, changes in selected vital signs and laboratory abnormalities graded per NCI CTCAE v4.0.

Serum and plasma samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of antibodies to atezolizumab.

Patient samples, including archival tumor tissues, as well as plasma, whole blood, and urine will be collected for future exploratory biomarker assessments.

A treatment completion/discontinuation visit will be performed for all patients within 30 days after the last administration of study treatment.

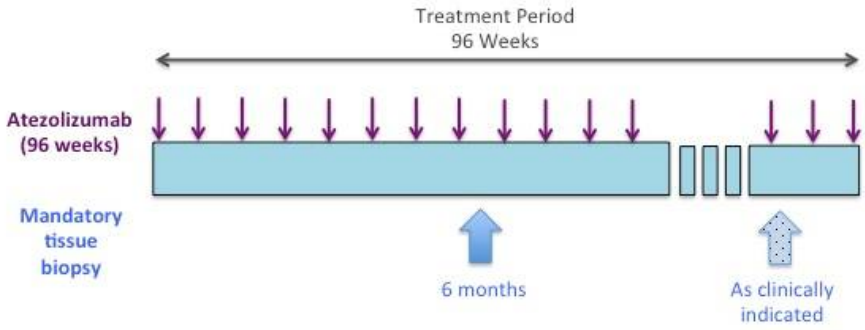
Patients who discontinue study treatment for a reason other than disease recurrence/progression or cystectomy (e.g., because of toxicity) will continue to undergo tumor assessments per protocol until they experience disease recurrence/progression or cystectomy, until the patient dies, withdraws consent, or until the study closes, whichever occurs first, for a maximum of 5 years after enrollment.

In addition, all patients will be followed for survival and subsequent anti-cancer therapy beginning 6 months after the treatment completion/discontinuation until loss to follow-up, death, withdrawal of consent, or study termination by the Sponsor, whichever occurs first, for a maximum of 5 years after enrollment.

Figure 6 presents the treatment plans for each cohort. The schedules of assessments are provided in Appendix 1 and Appendix 2.

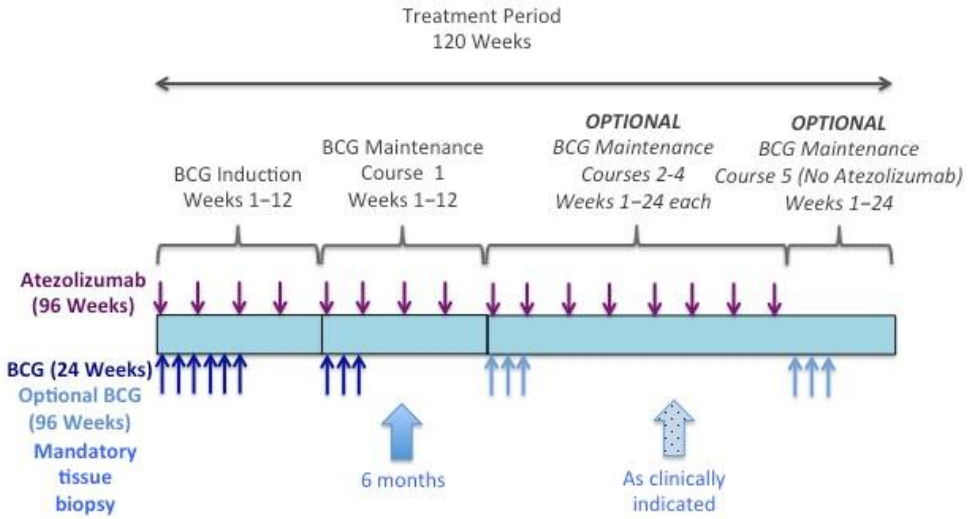
Figure 6 Treatment Plans

Cohort 1A



Cohort 1A: Patients receive atezolizumab 1200 mg IV q3w.

Cohort 1B



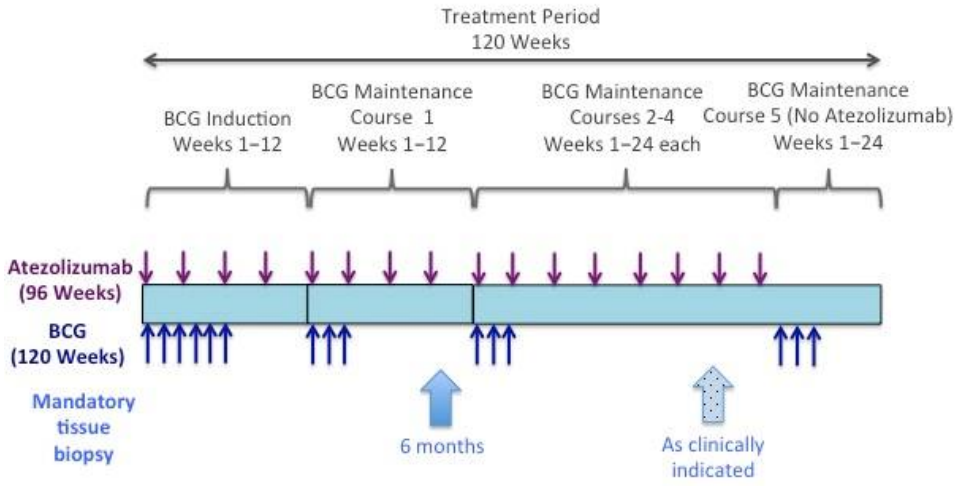
BCG = bacille Calmette-Guérin.

Notes: Cohort 1B: During BCG Induction Course, patients receive atezolizumab 1200 mg IV q3w for a total of four doses plus BCG at the assigned dose weekly for a total of six doses. During BCG Maintenance Course 1, patients receive atezolizumab 1200 mg IV q3w for a total of four doses plus BCG at the assigned dose weekly for a total of three doses. OPTIONAL BCG Maintenance Courses 2–5, patients receive atezolizumab 1200 mg IV q3w for a total of eight doses per course plus BCG at the assigned dose weekly for a total of three doses per course.

An optional collection of biopsy samples at disease progression/disease recurrence will be performed if clinically feasible.

Figure 6 Treatment Plans (cont.)

Cohorts 2 and 3



BCG = bacille Calmette-Guérin.

Notes: Cohorts 2 and 3: During BCG Induction Course, patients receive atezolizumab 1200 mg IV q3w for a total of four doses plus BCG at the assigned dose weekly for a total of six doses. During BCG Maintenance Course 1, patients receive atezolizumab 1200 mg IV q3w for a total of four doses plus BCG at the assigned dose weekly for a total of three doses. During BCG Maintenance Courses 2–5, patients receive atezolizumab 1200 mg IV q3w for a total of eight doses per course plus BCG at the assigned dose weekly for a total of three doses per course.

3.1.3 BCG Dose De-Escalation Scheme (Cohort 1B)

- This protocol will follow a 3 + 3 dose de-escalation scheme. MTD or MAD requires that either 0 of 3 or < 2 of 6 patients treated at a BCG dose level experience a DLT. If < 2 of 6 DLT-evaluable patients experience a DLT at the BCG dose level evaluated, that BCG dose level would be considered the MTD or MAD.
- A minimum of 3 patients will initially be treated at each BCG dose level evaluated.
- The following patients will not be considered evaluable for DLTs and will be replaced:

  Patients who withdraw from either study treatment during the DLT assessment window (Days 1–21 of BCG Induction Course) for any reason other than a DLT

  Patients who miss two or more doses of BCG or whose infusion of atezolizumab is delayed for ≥7 days during the DLT assessment window (Days 1–21 of BCG Induction Course) for any reason other than a DLT

Full-Dose BCG

Treatment starts at the full, standard doses of both BCG and atezolizumab:

- If 0 of 3 DLT-evaluable patients experience a DLT, MAD will be established and full-dose BCG and atezolizumab will be considered tolerable.

- If 1 of 3 DLT-evaluable patients experiences a DLT, 3 more patients will be enrolled at this dose level.
- If $<$ 2 of 6 DLT-evaluable patients experience a DLT, MAD will be established, full doses of BCG and atezolizumab will be considered tolerable, and no BCG dose de-escalation will be implemented.
- If $\geq$ 2 of 3 or $\geq$ 2 of 6 DLT-evaluable patients receiving the full standard doses experience a DLT, the BCG dose will be reduced to 66% of full dose, and a minimum of 3 patients will be enrolled at 66% of full-dose level.

Sixty-Six Percent Dose Level of BCG

- If 0 of 3 DLT-evaluable patients experience a DLT, MTD will be established and the 66% of full BCG dose and atezolizumab will be considered tolerable.
- If 1 of 3 DLT-evaluable patients experiences a DLT, 3 additional patients will be enrolled at this dose level.
- If $<$ 2 of 6 DLT-evaluable patients experience a DLT, MTD will be established as 66% of full dose BCG and full dose atezolizumab.
- If $\geq$ 2 of 3 or $\geq$ 2 of 6 DLT-evaluable patients receiving 66% of a full BCG dose experience a DLT, the BCG dose will be reduced to 33% of a full dose, and a minimum of 3 patients will be enrolled at the 33% of full dose level.

Thirty-Three Percent Dose Level of BCG

- If 0 of 3 DLT-evaluable patients experience a DLT, MTD will be established and the 33% of full BCG dose and atezolizumab will be considered tolerable.
- If 1 of 3 DLT-evaluable patients experiences a DLT, 3 additional patients will be enrolled at this dose level.
- If $<$ 2 of 6 DLT-evaluable patients experience a DLT, MTD will be established as 33% of full-dose BCG and full-dose atezolizumab.
- If $\geq$ 2 of 3 or $\geq$ 2 of 6 DLT-evaluable patients receiving the 33% of a full BCG dose experience a DLT at this dose level, this dosing schedule of combination BCG (33%) and atezolizumab will be considered intolerable, and Cohort 1B will be closed.
- BCG dose levels will be evaluated as described above until the MTD or MAD has been determined, or until the last of the BCG dose levels has been evaluated. For patients in Cohort 1B, if 33% of a full BCG dose is determined to be intolerable in combination with atezolizumab and further therapy with BCG is not permitted, patients may be allowed to continue in the study with single-agent atezolizumab 1200 mg IV q3w (for a total of 96 weeks)
- No atezolizumab dose reductions will be permitted.

On the basis of a review of available safety and PK data during this and other studies with both agents, BCG dose de-escalation may be halted or modified by the Sponsor in consultation with the Study Investigators and/or Steering Committee.

3.1.4 Definition of Dose-Limiting Toxicity

DLT definitions reflect the known and expected toxicities of atezolizumab and BCG.

A DLT is defined as one of the following toxicities occurring during the DLT assessment window (Induction Course, Days 1–21) that is considered by the investigator to be related to atezolizumab or the combination of atezolizumab and BCG (see Table 10 for causality assessment). For potential overlapping toxicities, including those described in Section 5.1.1, investigators are encouraged to perform additional tests to determine the underlying etiology and most appropriate attribution (see Appendix 6 for immune-related adverse event criteria). BCG dose reductions or delays will not, in themselves, constitute DLTs.

The following adverse events are considered to be DLTs (pending causality):

- Grade $\geq$4 neutropenia (ANC $<$500/μL)
- Grade $\geq$3 febrile neutropenia
- Grade $\geq$4 thrombocytopenia
- Grade $\geq$4 anemia
- Grade $\geq$3 symptomatic hepatic toxicities lasting for $>$48 hours, or Grade $\geq$3 asymptomatic hepatic toxicities lasting for $>$ 72 hours

  NOTE: Patients with Grade 2 AST, ALT, and/or alkaline phosphatase abnormality at baseline will be excluded from enrollment.
- Grade $\geq$3 dysuria lasting $\geq$ 72 hours following the BCG dose
- Grade $\geq$ 3 frequency (urinary) lasting $\geq$ 72 hours following the BCG dose
- Grade $\geq$ 3 hematuria lasting $\geq$ 48 hours following the BCG dose
- Grade $\geq$ 3 cystitis lasting $\geq$ 48 hours following the BCG dose
- Grade $\geq$ 3 urgency or nocturia lasting $\geq$ 72 hours following the BCG dose
- Grade $\geq$ 2 visual changes (limiting instrumental activities of daily living) that do not resolve to baseline within 72 hours
- Grade 4 visual disturbance of any duration
- Grade $\geq$3 non-hematologic, non-hepatic organ toxicity, excluding the following:

  Grade 3 nausea, vomiting, or diarrhea that resolves to Grade $\leq$1 within 7 days of appropriate supportive therapy

  Grade $\geq$3 asymptomatic or mildly symptomatic rash that can be adequately managed with supportive care, or resolves to become asymptomatic and/or Grade $\leq$2 within 7 days with appropriate supportive therapy

  Grade $\geq$3 fatigue that resolves to Grade $\leq$2 within 7 days

  Grade $\geq$3 elevation of serum creatinine kinase level that is asymptomatic (i.e., not accompanied by signs, symptoms, or other laboratory abnormalities associated with rhabdomyolysis or myocardial injury), that is deemed by the

investigator to be clinically insignificant, and that returns to Grade ≤ 2 within 14 days with treatment interruption

Grade 3 arthralgia that can be adequately managed with supportive care or that resolves to Grade ≤2 within 7 days

Grade 3 fever (in the absence of any clinically significant source of fever) that resolves to Grade ≤2 within 7 days with supportive care

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

Grade 3 autoimmune thyroiditis or other endocrine abnormality that can be managed by endocrine therapy that would not necessitate initiation of systemic corticosteroids

All DLTs must be reported via the paper Serious Adverse Event/Adverse Event of Special Interest Reporting Form (see Section 5.3). All DLTs will be considered adverse events of special interest for this protocol and must be reported to the Sponsor in an expedited manner, as indicated in Section 5.4.

BCG dose de-escalation decisions will be made by the Sponsor in consultation with the Study Investigators and/or the Steering Committee after review of available relevant data. See Section 4.5, Appendix 1, and Appendix 2 for the schedule of study assessments.

3.2 INDEPENDENT DATA MONITORING COMMITTEE

An external independent Data Monitoring Committee (iDMC) will monitor the study and assess the risk-benefit profile. The iDMC will evaluate study safety and efficacy data on a periodic basis, approximately every 4 months, according to policies and procedures detailed in the iDMC Charter. Members of the iDMC will be external to the Sponsor and will follow the charter that outlines their roles and responsibilities.

All summaries and analyses for iDMC review will be prepared by an external independent data coordinating center (iDCC). The safety and efficacy data will include but are not limited to demographic data, adverse events, serious adverse events, relevant laboratory data, as well as tumor assessment data. Following their data review, the iDMC will provide a recommendation as to risk-benefit; the final decision will rest with the Sponsor.

3.3 END OF STUDY AND LENGTH OF STUDY

END OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur approximately 120 weeks after the last patient is enrolled in the study (see Appendix 3).

LENGTH OF STUDY

The study is expected to last approximately 3.5 years after the first patient is enrolled.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Patient Population

This study is designed to obtain safety and efficacy data for single-agent atezolizumab as treatment for patients with BCG-unresponsive NMIBC and the combination of atezolizumab with BCG as treatment for patients with BCG-unresponsive, BCG-relapsing, or VHR BCG-naive NMIBC. Only patients who fulfill eligibility criteria will be enrolled into the study. These criteria are based on the safety data from Phase I/II studies (for atezolizumab) and Phase II/III studies (for BCG).

Cohort 1A (atezolizumab monotherapy) will enroll patients with BCG-unresponsive NMIBC. Selection of this population is on the basis of the high unmet need in patients who have experienced persistent/recurrent disease despite BCG treatment. Single-agent atezolizumab has already demonstrated significant single-agent activity in patients with advanced UC (Powles et al. 2014).

Cohort 1B (atezolizumab + BCG dose de-escalation) will enroll patients with BCG-unresponsive NMIBC. Selection of this population is on the basis of the high unmet need in patients who have experienced persistent/recurrent disease despite BCG treatment. Single-agent atezolizumab has already demonstrated significant single-agent activity in patients with advanced UC (Powles et al. 2014). Cohort 1B will evaluate both the safety and potential activity of the combination of BCG and atezolizumab.

Cohort 2 (atezolizumab + BCG) will enroll patients with BCG-relapsing NMIBC. No current standard therapies exist for this indication, with the exception of valrubicin, which while approved for use (United States only), is rarely used in NMIBC. Given the high unmet need in this population, these patients represent an appropriate population to first assess the safety, tolerability, and pharmacokinetics of novel therapies and combinations intended for the treatment of NMIBC with the aim of bladder preservation and delaying cystectomy.

Cohort 3 (atezolizumab + BCG) will enroll patients with VHR BCG-naive NMIBC. Selection of this population was based on the known mechanism of action of atezolizumab, the hypothesis that PD-L1 expression is a pathway for immune tolerance to BCG in NMIBC (Inman et al. 2007), and data from Lerner et al. (Lerner et al. 2007) demonstrating poorer outcomes in patients with high-risk NMIBC who fail to achieve a CR following BCG induction. This study will enroll patients with VHR BCG-naive NMIBC, as this population demonstrates significantly higher recurrence rates (up to 78% by 5 years) after BCG therapy and a 45% rate of progression to muscle-invasive disease by 5 years (Babjuk et al. 2008; Palou et al. 2012; Giannarini et al. 2014).

3.4.2 Rationale for Atezolizumab Dosage

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 the following: 1) 95% tumor-receptor saturation is needed for efficacy and 2) the tumor-interstitial concentration to plasma ratio is 0.30 based on tissue distribution data in tumor-bearing mice.

The atezolizumab dose is also informed by available clinical activity, safety, PK, and immunogenicity data. Anti-tumor activity has been observed with doses of 1 mg/kg to 20 mg/kg. The MTD of atezolizumab was not reached, and no DLTs 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 ATAs 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 whether administration of higher doses to patients with both detectable ATAs and reduced exposure would necessarily restore exposure to expected levels. No clear relationship between the development of measurable ATAs and safety or efficacy has been observed. Available data suggest that development of detectable ATAs does not appear to have a significant impact on pharmacokinetics for doses of 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 ATAs. Currently available PK and ATA 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 $C_{trough} \geq 6$ μg/mL and further safeguard against both interpatient variability and potential effect of ATAs 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 atezolizumab q3w 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 fixed dose or dose adjusted for weight (Bai et al. 2012). On the basis of this analysis, a fixed dose of 1200 mg was selected (equivalent to a body weight–based dose of 15 mg/kg).

Selection of a q3w dosing interval is supported by this preliminary PK evaluation and allows for a convenient integration with common chemotherapeutic regimens.

The optimal duration of immunotherapy for patients with NMIBC is not known. Current practice patterns in the use of BCG maintenance vary dramatically and support treatment for between 1 and 3 years. The EORTC meta-analysis of patients with NMIBC treated with BCG demonstrated that only patients treated with BCG maintenance therapy observed a reduction in progression. Maintenance schedules varied significantly; however, a separate meta-analysis demonstrated that at least 1 year of BCG maintenance was required to show an improvement in recurrence or progression. This supports a longer duration of therapy for immunotherapy to provide benefit.

In the studies of atezolizumab and other checkpoint inhibitors in patients with metastatic disease, delayed responses have been observed, and some of those patients remain long-term disease-free responders, suggesting that some patients require longer duration of immunotherapy. Additionally, while the majority of these responses have been durable, disease relapses have been observed in some responders who discontinued treatment after 1 or 2 years of therapy.

Considering the historical maintenance BCG studies as well as experience to date using immune checkpoint inhibitors, the Sponsor selected the 2-year treatment duration to ensure adequate exposure in potentially delayed responders yet balance patient-specific considerations such as inconvenience, toxicity, and economic impact.

3.4.3 Rationale for BCG Dosage

Dosing for BCG in this study was selected on the basis of prior immunotherapy combination studies investigating BCG in combination with IFN-α-2B. In a study of 1007 evaluable patients with NMIBC, combination therapy was assessed using full dose IFN and varying doses of BCG (full dose for BCG-naive patients and 1/3rd to 1/10th for patients with prior BCG exposure). Results from this study showed RFS rates of 59% and 45% for the BCG-naive and BCG-failure groups, respectively (Joudi et al. 2006). The lowest dose tested will be 33% of a full BCG dose. Thirty-three percent of a full BCG dose has been shown previously to be equivalent in efficacy to a full dose of BCG in all but the highest risk patients (Martínez-Piñeiro et al. 2002; Martínez-Piñeiro et al. 2005). The rationale for co-administration of BCG with atezolizumab is based on the observed improvement in DFS and RFS rates for combination immunotherapy in patients for whom BCG therapy has failed (O'Donnell et al. 2001) and also from data demonstrating PD-L1 expression as a potential pathway for resistance to BCG (Inman et al. 2007). If 33% of a full BCG dose is the MTD reached in Cohort 1B, further assessment would be needed for the combination of atezolizumab and BCG at 33% of a full dose to support using this dosing schedule in Cohorts 2 and 3.

3.4.4 Rationale for Pharmacokinetic Evaluation Schedule

The proposed sampling scheme for atezolizumab and BCG concentration assessments will contribute to the characterization of atezolizumab and BCG pharmacokinetics. The atezolizumab and BCG concentration results may be compared with available data from other atezolizumab clinical studies and correlated with safety events in this study as appropriate.

3.4.5 Rationale for Blood and Urine Sampling for Biomarkers

Changes in different blood and urine biomarkers may provide evidence for biologic activity of atezolizumab in humans and may allow for the development of a blood- or urine-based biomarker to help predict which patients may benefit from atezolizumab. An exploratory objective of this study is to evaluate changes in surrogate biomarkers in blood and urine samples.

3.4.6 Rationale for the Collection of Tumor Specimens at Screening

Published results suggest that expression of PD-L1 in tumor cells and tumor-infiltrating immune cells correlates with response to anti–PD-1 and anti–PD-L1 therapy (Herbst et al. 2014). This correlation was also observed with atezolizumab in a cohort of patients with advanced stage UC enrolled in Study PCD4989g (Powles et al. 2014). In the current study, tumor specimens from patients meeting eligibility criteria will be tested for PD-L1 expression by IHC at a central laboratory. Collection of tissue at screening may occur at the time of initial TURBT or repeat TURBT per institutional standard of care.

To enable evaluation of the potential for prior therapies to alter tumor expression of PD-L1, patients who have received at least one line of prior systemic therapy for UC should submit archival specimens obtained after completion of their most recent prior therapy. An archival specimen, if available, may also be submitted in patients who choose to undergo a fresh tissue biopsy.

In addition to assessment of PD-L1 status, other exploratory markers, such as potential markers that are related to response or clinical benefit of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type markers, may also be analyzed.

3.4.7 Rationale for the Collection of Tumor Specimens on Treatment and at Recurrence/Disease

The assessment of immunomodulation and PD-L1/PD-1 pathway inhibition in tumor tissue may guide selection of the appropriate dose and exposure for atezolizumab in combination BCG for future studies. Biopsy samples will be collected for the study of PD changes related to the additive or synergistic effects of atezolizumab and BCG (changes in PD-L1 and infiltration of CD8+ T cells and other exploratory biomarkers). The timing of on-treatment biopsy was selected to allow assessment of potential synergistic effect

of atezolizumab and BCG (following BCG induction) as well as to assess CR, disease recurrence, and/or disease progression (optional) and to allow adequate healing after biopsy and prior to the next BCG administration. A biopsy at tumor recurrence/progression will enable the evaluation of the role of immune and tumor type–related, as well other exploratory biomarkers (including but not limited to T-cell markers and tumor mutation status) associated with disease progression.

The presence of disease at 3 months after initiation of BCG induction has been shown to be predictive for disease recurrence and disease progression (Solsona et al. 2000; Sylvester et al. 2006); however, the use of maintenance BCG has been shown to increase response rates between 3 and 6 months. Therefore, 6 months is the recommended timepoint for disease response assessment (Lamm et al. 2000; Jarow et al. 2014).

3.4.8 Rationale for Patient-Reported Outcome Assessments

PROs provide an understanding of the impact a treatment has on a patient. The EORTC QLQ-C30 is a validated instrument that has been widely used in assessing quality of life in patients with cancer. The core instrument assesses global health status/quality of life, functions (physical, role, emotional, cognitive, and social), and general cancer symptoms. The EORTC QLQ-NMIBC24 is an NMIBC-specific module that can provide information on disease and treatment-related symptoms and functional interference that are specific to this patient population.

3.5 OUTCOME MEASURES

3.5.1 Safety Outcome Measures

The safety and tolerability of the combination of atezolizumab and BCG will be assessed using the following outcome measures:

- Incidence, nature, and severity of adverse events, graded according to the NCI CTCAE v4.0
- Changes in selected vital signs and clinical laboratory results during and following administration of atezolizumab alone and in combination with BCG

3.5.2 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Serum atezolizumab maximum serum concentration (C_{max}) after the first infusion of atezolizumab
- Serum atezolizumab minimum serum concentration (C_{min}) prior to the infusion at specified timepoints

3.5.3 Immunogenicity Outcome Measure

The immunogenicity outcome measure for this study is as follows:

- Incidence of ATA response to atezolizumab and potential correlation with PK, PD, safety, and efficacy parameters

3.5.4 Efficacy Outcome Measures

The primary efficacy outcome measure for this study is as follows:

- CR at the 6-month evaluations after the start of study treatment. Patients must be evaluated for CR by both cystoscopy and cytology and bladder biopsies will be required for the 6-month CR disease assessment.

The secondary efficacy outcome measures for this study are as follows:

- CR at the 3-month disease assessment, evaluated by both cystoscopy and cytology.
- Duration of CR, defined as time from first occurrence of a documented CR until the time of recurrence of NMIBC or death from any cause
- RFS rate at 6, 12, and 18 months, defined as the proportion of patients who are alive and free of persistent/recurrent high-risk NMIBC
- Bladder-intact DFS, defined as time from first study treatment to earliest evidence of progression to muscle-invasive disease in the bladder, regional pelvic progression, distant metastasis, bladder cancer–related death, or cystectomy or death from any cause
- PFS, defined as the time from first study treatment to the first occurrence of progression to muscle-invasive disease or death from any cause
- CFS, defined as the time from first study treatment to cystectomy or death from any cause
- Overall survival, defined as the time from first study treatment to death from any cause

3.5.5 Patient-Reported Outcome Measure

The exploratory PRO outcome measure for this study is as follows:

- Change from baseline in patient-reported symptoms, function, and HRQoL, as measured by the EORTC QLQ-C30 and EORTC QLQ-NMIBC24

3.5.6 Exploratory Biomarker Outcome Measures

The following biomarker endpoints will be assessed when appropriate:

- PD-L1 status by IHC in archival tissues and/or fresh biopsies
- Status of other exploratory biomarkers related to PD-L1 or immune cell biology (including but not limited to CD8 or PD-1) and tumor biology

The following exploratory biomarker outcome measures will be assessed when appropriate:

- Changes in immune-related markers (including but not limited to CD8, granzyme B, and other exploratory markers) in archival and/or fresh tumor tissue prior to and during atezolizumab and BCG treatment

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Ability to comply with protocol
- Age ≥ 18 years
- Histologically confirmed non–muscle-invasive TCC of the bladder with CIS

  Patients with mixed histologies, where the dominant (> 50% tumor volume) histology is TCC, may be considered on a case-by-case basis upon approval by the Medical Monitor.

  Patients may have Ta/T1 lesions, provided they have been completely resected.
- High-risk NMIBC defined by the following:

  BCG-unresponsive NMIBC (Cohorts 1A and 1B):

  Persistence of high-grade CIS at 6 months following an adequate course of BCG; OR

  Stage/grade progression at 3 months after induction BCG; OR

  Recurrence of high-grade CIS after achieving a disease-free state (i.e., CR) following an adequate course of BCG that occurs < 6 months after the last exposure to BCG

  BCG-relapsing NMIBC (Cohort 2):

  Recurrence of high-grade CIS after achieving a disease-free state following an adequate course of BCG that occurs ≥ 6 months after the last exposure to BCG

  VHR BCG-naive NMIBC (Cohort 3):

  VHR NMIBC, defined as having at least one of the following:

  Multiple and/or large (> 3 cm) T1, (HG/G3) tumors

  T1, (HG/G3) tumor with concurrent CIS

  T1, G3 with CIS in prostatic urethra

  Micropapillary variant of non-muscle invasive urothelial carcinoma

- For BCG-unresponsive and BCG-relapsing NMIBC, patients must have received an adequate course of BCG. An adequate course of BCG is defined as at least one course of induction (minimum of five weekly instillations) and one course of maintenance (minimum of two weekly instillations) with the following exceptions:

  Patients with grade/stage progression after induction BCG (minimum of five weekly instillations) are eligible.

  Patients with persistent or recurrence of high-grade disease after two BCG induction courses (minimum of five weekly instillations, each) are eligible.

  Patients who did not receive an adequate course of BCG as a result of the worldwide BCG shortage may be eligible following discussion with the Medical Monitor.

- Resection of all pTa/pT1 papillary disease

  Prior to enrollment, patients must have undergone repeat TURBT to ensure no evidence of residual papillary disease.

- No prior radiation to bladder or pelvic region
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 (see Appendix 7)
- Life expectancy ≥ 12 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment:

  ANC $\geq 1500/\mu L$ (without granulocyte colony-stimulating factor support within 2 weeks prior to the first dose of study treatment)

  WBC counts $> 2500/\mu L$ and $< 15,000/\mu L$

  Lymphocyte count $\geq 300/\mu L$

  Platelet count $\geq 100,000/\mu L$ (without transfusion within 2 weeks prior to the first dose of study treatment)

  Hemoglobin ≥ 9.0 g/dL

  Patients may be transfused or receive erythropoietic treatment to meet this criterion.

  AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ ULN

  Serum bilirubin $\leq 1.5 \times$ ULN

  Patients with known Gilbert disease who have serum bilirubin level $\leq 3 \times$ ULN may be enrolled.

  INR and aPTT $\leq 1.5 \times$ ULN

  This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.

  Creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault formula)

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

  Women must remain abstinent 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 study drug. Women must refrain from donating eggs during this same period.

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

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, 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 study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men receiving BCG: agreement to remain abstinent (refrain from sexual intercourse) or use a condom, as further explained in Section 4.3.1.2 and Section 5.1.2:

  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.

- Tumor tissue biopsy

  A sample of tumor tissue is required within 60 days prior to study entry. Fresh tissue biopsy is preferred; however, an archival specimen may be submitted in lieu of fresh tissue if a tissue biopsy is contraindicated owing to patient safety or tumor tissue accessibility and the archival specimen was obtained within 60 days of study screening. The specimen may consist of a FFPE tumor tissue block (preferred) or at least 10 unstained, serial sections. Patients with cystoscopy results indicating pTa/pT1 papillary disease must undergo a TURBT procedure for removal of residual papillary disease prior to study entry.

- Willingness to complete all study-related procedures including patient-reported questionnaires

Additional Cohort 3–Specific Inclusion Criteria

- No prior treatment with intravesical BCG

4.1.2 Exclusion Criteria

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

Cancer-Specific Exclusions

- Evidence of locally advanced or metastatic bladder cancer (including but not limited to disease involving renal pelvis, ureter, or prostatic urethra)
- Evidence of muscle-invasive bladder cancer
- Evidence of extravesical bladder cancer
- Any malignancy within 5 years prior to Cycle 1, Day 1, except adequately resected basal cell and squamous cell skin cancer or adequately treated carcinoma in situ of the cervix. Patients with malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death $< 5\%$ at 5 years) may be allowed after discussion with the Medical Monitor.

  Patients with prostate cancer who are at low risk and are undergoing active surveillance (Stage T1/T2a, Gleason score ≤ 7 and PSA ≤ 10 ng/mL) are eligible.
- Treatment with any approved anti-cancer therapy, including chemotherapy (systemic or intravesical), radiation therapy (to the bladder or pelvic region), or hormonal therapy within 3 weeks prior to the first dose of study treatment

  Use of hormone-replacement therapy and oral contraceptives is permitted.
- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to the first dose of study treatment

General Medical Exclusions

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

  Women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to the first dose of study treatment.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells
- Allergy or hypersensitivity to components of the atezolizumab formulation
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 6 for a more comprehensive list of autoimmune diseases)

  Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study after discussion with and approval by the Medical Monitor.

Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study after discussion with and approval by the Medical Monitor.

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

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Serum albumin $<$2.5 g/dL
- Positive test for HIV
- Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening)

  Patients with past or resolved hepatitis B (HBV) infection (defined as having a negative HBsAg test and a positive anti-hepatitis B core antigen [anti-HBc] antibody test) are eligible. HBV DNA must be obtained in these patients prior to the first dose of study treatment.
- Active hepatitis C

  Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction assay is negative for HCV RNA.
- Active tuberculosis
- Severe infections within 28 days prior to the first dose of study treatment, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of infection within 14 days prior to the first dose of study treatment
- Treatment with therapeutic oral or IV antibiotics within 14 days prior to the first dose of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible.
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within the previous 3 months, unstable arrhythmias, or unstable angina
- Major surgical procedure other than for diagnosis within 28 days prior to the first dose of study treatment, or anticipation of need for a major surgical procedure during the course of the study

- Administration of a live/attenuated vaccine within 28 days prior to the first dose of study treatment, within 5 months following the administration of the last dose of study drug, or anticipation that such a live/attenuated vaccine will be required during the study

  Influenza vaccination should be given during influenza season only (approximately October to May in the Northern Hemisphere and from April through September in the Southern Hemisphere). Patients must agree not to receive live/attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to first dose of study treatment, during treatment or within 5 months following the last dose of atezolizumab.

- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications.

Exclusion Criteria Related to BCG

- History of prior significant toxicity or intolerance to BCG requiring discontinuation of treatment
- History of prior systemic BCG infection

  Note: This is applicable to patients receiving combination BCG and atezolizumab therapy (Cohorts 1B or 2). Patients in Cohort 1A may be eligible, pending that they have received an adequate course of BCG and meet all other eligibility criteria.

- History of immunosuppression, or conditions associated with congenital or acquired immune deficiency, whether because of concurrent disease (e.g., AIDS, leukemia, lymphoma), cancer therapy (e.g., cytotoxic drugs, radiation), or immunosuppressive therapy (e.g., corticosteroids)
- Concurrent febrile illness, urinary tract infection, or gross hematuria

Exclusion Criteria Related to Medications

- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–cytotoxic T lymphocyte–associated antigen 4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including but not limited to IFNs and IL-2) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to the first dose of study treatment

- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to the first dose of study treatment, or anticipated requirement for systemic immunosuppressive medications during the study.

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.

  The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed. Use of physiologic doses of corticosteroids for adrenal insufficiency is allowed.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study. The investigator will determine the appropriate cohort for each patient.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab

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

4.3.1.2 Bacille Calmette-Guérin

OncoTICE® BCG for intravesical use is an attenuated, live culture preparation of the BCG strain of *Mycobacterium bovis*. The freeze-dried BCG preparation is delivered in glass vials, each containing 1 to 8×10^8 CFU of OncoTICE BCG, which is equivalent to approximately 50 mg wet weight. No preservatives have been added.

A single dose consists of one reconstituted vial. For intravesical use, the entire vial is reconstituted with sterile saline. OncoTICE BCG is viable upon reconstitution.

Patients should minimize fluid intake before treatment with BCG. Additionally, complete bladder drainage should occur via catheter drainage placed immediately prior to BCG administration.

In the event of a supply shortage of OncoTICE BCG, sites may be allowed to use a local stock of BCG on a case-by-case basis after approval by the Sponsor.

For detailed information on the formulation and handling of BCG, see the local OncoTICE prescribing information.

The following summarizes AUA voiding instructions and other precautions to patients following BCG exposure:

Precautions post procedure: after the first void and for the next 6 hours include:

a) Sit to void to avoid urine splashing. Do not use public toilets or void outside.

b) After each void, add 2 cups undiluted bleach to toilet, close the lid, and wait 15–20 minutes, and then flush the toilet. Repeat with each void for 6 hours.

c) Increase fluid intake to dilute the urine. Begin after the first void post procedure.

d) Common side effects within 24 hours post procedure: blood in urine; low-grade fever (99–100 °F); tiredness; urinary frequency, urgency, and burning with urination; and muscle or joint achiness. You will be given prescriptions to address the urinary symptoms (frequency, urgency, and burning on urination) if needed.

e) If sexually active, wear a condom with intercourse throughout the entire treatment course and for six weeks after treatment has ended.

f) Urinary incontinence: Immediately wash clothes in clothes washer. Do not wash with other clothes.

g) If wearing incontinence pad, pour bleach on pad, allow to soak in, then place in plastic bag, and discard in trash.

h) Call urology clinic or provider if patient develops fever more than 101.3 °F (38.5 °C), chills, or rigors.

i) May use acetaminophen or ibuprofen for fever and body aches.

j) May need antispasmodic medication to help with frequency and urgency.

4.3.2 Dosage, Administration, and Compliance

Atezolizumab and BCG are investigational medicinal products (IMPs) in this study.

4.3.2.1 Atezolizumab

The dose level of atezolizumab in this study is 1200 mg administered by IV infusion q3w. There will be no dose reduction of atezolizumab.

Cohort 1A: Patients receive atezolizumab 1200 mg IV q3w, for a maximum of 32 doses or 96 weeks of therapy, whichever comes first.

Cohort 1B: During BCG Induction Course (12 weeks), patients receive atezolizumab 1200 mg IV q3w for a total of four doses. During BCG Maintenance Course 1 (12 weeks), patients will receive atezolizumab 1200 mg IV q3w for a total of four doses. Additional BCG maintenance courses are not required for patients in Cohort 1B, but may be permitted following discussion with the Medical Monitor. During BCG Maintenance Courses 2–5 (each 24 weeks), patients receive atezolizumab 1200 mg IV q3w for a total of eight doses per course. Patients who stop BCG maintenance at any time may continue atezolizumab 1200mg IV q3w. The maximum atezolizumab treatment duration is 96 weeks. Atezolizumab may be administered before or after intravesical BCG on

days when these infusions coincide, however both the atezolizumab infusion and intravesical BCG infusion must be completed within 24 hours of one another.

Cohorts 2 and 3: During BCG Induction Course (12 weeks), patients receive atezolizumab 1200 mg IV q3w for a total of four doses. During BCG Maintenance Course 1 (12 weeks), patients will receive atezolizumab 1200 mg IV q3w for a total of four doses. During BCG Maintenance Courses 2–5 (each 24 weeks), patients receive atezolizumab 1200 mg IV q3w for a total of eight doses per course. Patients who stop BCG maintenance at any time may continue atezolizumab 1200mg IV q3w. The maximum treatment duration is 96 weeks. Atezolizumab may be administered before or after intravesical BCG on days when these infusions coincide; however, both the atezolizumab infusion and intravesical BCG infusion must be completed within 24 hours of one another.

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 regarding administration, refer to the 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 adverse events, 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 pressure, 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 infusion and at the end of 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 is indicated for the administration of atezolizumab in Cycle 1. Patients who experience an infusion-related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions (see Table 7).

Table 7 Guidelines for the Management of Infusion-Related Reactions during the First Atezolizumab Infusion

Toxicity	Severity	Management
Infusion-related reaction	Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If tolerated, the infusion rate may then be increased to the original rate.
	Grade 2	• Interrupt atezolizumab infusion. • Administer aggressive symptomatic treatment. • Restart 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 IRR. • At next cycle, administer oral premedication with antihistamine and anti-pyretic and monitor closely for infusion reaction.
	Grade 3 or 4	• Stop infusion. • Proper medical management which may include oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen. • Discontinue atezolizumab. • Contact the Medical Monitor if atezolizumab is discontinued.

For anaphylaxis precautions, see Appendix 8.

The atezolizumab dose may be interrupted for up to 12 weeks for Grade ≥ 3 toxicity or adverse event. If the adverse event does not resolve to Grade ≤ 1 within 12 weeks of last dose of atezolizumab, further treatment with atezolizumab will be discontinued.

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment for up to 12 weeks beyond the last dose if they experience adverse events that require a dose to be withheld. If atezolizumab is withheld because of adverse events for $>$12 weeks beyond the last dose, then the patient will be discontinued from atezolizumab treatment and will be followed up for safety and efficacy as specified in Section 4.5.11.

If, in the judgment of the investigator, the patient is likely to derive clinical benefit from atezolizumab after a hold of $>$12 weeks, study drug may be restarted with the approval of the Medical Monitor.

If a patient must be tapered off steroids used to treat adverse events, atezolizumab may be held for additional time beyond 12 weeks from the last dose until steroids are discontinued or reduced to prednisone dose $\leq$10 mg/day (or dose equivalent). The acceptable length of interruption will depend on an agreement between the investigator and the Medical Monitor.

Guidelines for treatment interruption or discontinuation and for the management of specific adverse events are provided in Section 5.1.3.

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

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

4.3.2.2 Bacille Calmette-Guérin

Cohort 1B: The three BCG dose levels to be evaluated in Cohort 1B will be full dose (starting dose of 50 mg), followed by 66% and 33% of a full BCG dose.

Cohorts 2 and 3: BCG will be administered at the MTD or MAD determined by dose de-escalation in Cohort 1B provided the MTD or MAD is determined to be full dose or 66% of a full BCG dose.

During BCG Induction Course (12 weeks), patients will receive BCG at the assigned dose weekly for a total of six doses. During BCG Maintenance Course 1 (12 weeks), patients receive BCG at the assigned dose weekly for a total of three doses. During BCG Maintenance Courses 2–5 (each 24 weeks), patients receive BCG at the assigned dose weekly for a total of three doses per course.

BCG will not be administered in Cohort 1A.

For detailed information on the formulation and handling of BCG, see the local OncoTICE prescribing information.

Guidelines for treatment interruption or discontinuation and for the management of specific adverse events are provided in Section 5.1.3.

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

4.3.3 Investigational Medicinal Product Accountability

The Sponsor or designee will provide BCG to investigational sites as an IMP. Following Sponsor notification, BCG may be sourced locally in emergency situations (e.g., site is out of stock of IMP and patient is ready to receive dose) in countries where BCG is commercially available. In these cases, sites will be responsible for sourcing and using the material according to local regulations. The Sponsor will provide atezolizumab as an IMP.

The study site will acknowledge receipt of study treatments with use of the interactive Web/voice response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

4.3.4 Post-Study Access to Atezolizumab

Currently, the Sponsor does not have any plans to provide atezolizumab or any other study treatments or interventions to patients who have completed the study. The Sponsor will evaluate whether to continue providing atezolizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:
http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

4.4.1 Permitted 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.

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist, as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 8).

Systemic corticosteroids and TNF-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. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for the second and subsequent infusions at the discretion of the treating physician after consultation with the Medical Monitor. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) 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.

Influenza vaccination should be given during influenza season only (approximately October to May in the Northern Hemisphere and from April through September in the Southern Hemisphere). Patients must not receive live/attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to the first dose of study treatment, during study treatment, or within 5 months following the last atezolizumab dose. Patients may receive inactivated vaccines.

Patients who use 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 should continue their use.

Females of reproductive potential should use highly effective means of contraception, as described in Section 4.1.1.

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 (outside of usage outlined in Section 4.4.1), immunotherapy, radiotherapy, investigational agents, or herbal therapy (except for maintenance therapies outlined in Section 4.4.1)

- Traditional herbal medicines should not be administered 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

Initiation or increased dose of granulocyte colony-stimulating factors (e.g., granulocyte colony-stimulating factor, GM-CSF, and/or pegfilgrastim) is strongly discouraged.

Patients are not allowed to receive immunostimulatory agents, including but not limited to 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.

Patients should also 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 and anti–TNF-α agents 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. If feasible, alternatives to these agents should be considered.

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.

4.5 STUDY ASSESSMENTS

EAU and NCCN guidelines recommend surveillance monitoring for high-risk NMIBC with cystoscopy and urine cytology every 3–6 months for the first 2 years, which is consistent with the tumor assessment schedule for this study (Babjuk et al. 2011; NCCN 2014).

See Appendix 1 and Appendix 2 for the schedules of assessments performed during the study.

Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

Patients should be assessed for toxicity prior to each dose of atezolizumab and BCG; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits scheduled according to the original schedule.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations.

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

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

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant 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, 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.

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

Cancer history will include an assessment of prior treatment for NMIBC (in the case of recurring disease) including but not limited to TURBT intravesical therapy, radiation, or a combination of these.

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic 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 pulse rate, respiratory 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 (pulse rate, respiratory rate, blood pressure, 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 infusion and at the end of 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.

4.5.5 Tumor and Response Evaluations

Screening and tumor response assessment will be in accordance with national (EAU AUA, and NCCN) guidelines, which recommend cystoscopic examination and urine cytology every 12 weeks for the first 2 years, and every 24 weeks thereafter (or as clinically appropriate) until 5 years, and then yearly. Upper tract imaging with CT urography or intravenous pyelogram will be performed at the 6- and 18-month disease assessments. Annual upper tract imaging thereafter is recommended as clinically indicated.

Screening assessments must include imaging of the upper tract collecting system, which may include any one or more of the following: intravenous pyelogram, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or magnetic resonance imaging urogram. Pelvic CT before TURBT may be considered, but is not required.

Primary assessment of tumor (at screening and while on study) will be with cystoscopy and urine cytology.

White-light cystoscopy, narrow band imaging cystoscopy, or fluorescent (blue-light) cystoscopy will be acceptable for baseline assessment. The same methodology used to assess disease sites at screening should be used throughout the study except when medical contraindicated (e.g., the same cystoscopy protocol and urine examination).

The Sponsor may replace patients who have had a change in the type of cystoscopy (e.g., screening with white-light cystoscopy and follow-up evaluation with blue-light cystoscopy) to ensure consistent evaluation over time. All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. A Bladder Map template (Appendix 11) has been provided and should be used to document the approximate size and location of abnormalities observed at screening, baseline, and on study cystoscopy/TURBT assessments.

Mandatory bladder biopsies will be performed at the 6-month tumor assessment. In absence of visible tumor, template biopsies should be obtained from all quadrants of the bladder. Template biopsies may be performed under anesthesia, at the discretion of the investigator. Regions of the template biopsies should include the trigone, left lateral wall, right lateral wall, posterior wall, and dome. Where feasible, the same evaluator should perform assessments if possible to ensure internal consistency across visits.

At the investigator's discretion, cystoscopy and/or urine cytology may be repeated at any time if progressive or recurrent disease is suspected.

At the 6 month timepoint (24 week visit), documentation of a complete response (CR) is required to continue on study treatment.

Definition of Complete Response (must meet all 3 criteria):

- Cytology: not positive (see below)
- Upper Urinary Tract Imaging (if performed): normal, or abnormal but supportive of CR (with non-positive selective ureteral cytologies)
- Cystoscopy: bladder appears normal; or bladder appears abnormal but all biopsies are negative; or any grade papilloma, any grade PUNLMP, or low grade pTa

Interpretation of Urine Cytology:

- If results are Unsatisfactory, Atypical Cell, Suspicious, or Indeterminate, then assay must be repeated no less than 24 hours and up to 21 days later
- If the results are again Unsatisfactory or Atypical Cell (2 in a row), then treat as if the result was negative
- Two consecutive Suspicious or Indeterminate urine cytology specimens require further evaluation by cystoscopy and/or upper tract imaging as deemed appropriate by the investigator
- If cytology results are Suspicious or Indeterminate and the biopsies are negative, then treat as if the result was negative
- All occurrences of positive urine cytology will require further evaluation by cystoscopy and/or upper tract imaging. A positive cytology result only indicates presence of disease and cannot be used alone to determine disease progression.

    The date of a positive cytology result can be used for the date of recurrence, if the results of the cystoscopy, biopsy, or upper urinary tract assessment shows recurrence.

Patients with persistent and/or recurrent high grade NMIBC without progression (stage or grade progression of active disease, or presence of new disease) at 12 weeks from treatment initiation may continue on study treatment. to muscle-invasive disease.

Patients with recurrent low-grade papillary disease will be required to undergo resection with TURBT (unless medically contraindicated) and may continue on study and receive study treatment.

Indications for Discontinuation from Study Treatment for Disease Progression

- Stage or grade progression at any timepoint would require discontinuation from study therapy.
- Patients with persistent and/or recurrent high-grade NMIBC (any pT1, high grade pTa, or CIS) on or after the 6-month biopsy will be discontinued from study treatment and offered the option to undergo cystectomy or other bladder-sparing modalities as is clinically appropriate. Patients who undergo cystectomy will be requested to submit additional tissue from their cystectomy specimens.
- Patients with evidence of disease progression to muscle-invasive or metastatic disease at any timepoint will be discontinued from study treatment.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Local laboratory assessments will include the following:

- 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, chloride, 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)
- Creatinine clearance (calculated using the Cockcroft-Gault formula)
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)
- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4)
- All patients will have a QuantiFERON blood test done locally prior to inclusion into the study
- HBV serology (HBsAg, antibodies against HBsAg, anti–hepatitis B core antibody [HBc Ab])

  HBV DNA should be obtained prior to the first dose of study treatment if the patient has positive serology for anti-HBc Ab.
- HCV serology (anti-HCV)
- HIV serology

Central laboratories will coordinate the collection of archival and tumor tissue as well as blood samples for the assessment of atezolizumab pharmacokinetics and biomarkers, ATA assays, and auto-antibody testing. The following assessments will be performed at a central laboratory or at Roche:

- ATA assays

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

- PK assay

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

- Biomarker assays in blood

  Blood samples will be obtained at various timepoints, including at disease progression, for biomarker evaluation (including but not limited to biomarkers that are related to bladder or tumor immune biology) from all eligible patients according to the schedule in Appendix 4 and Appendix 5. Specifically, at disease progression, samples will be processed to obtain EDTA plasma for the determination of changes in blood-based biomarkers. Whole blood samples may be processed to obtain peripheral blood mononuclear cells (PBMCs) and their derivatives (e.g., RNA).

  Blood samples will also be evaluated using the TruCulture® System. TruCulture system is designed to test the ex vivo immune response of peripheral blood immune cells to BCG. The supernatant of this culture will be tested for immune cell cytokine production (e.g., IL2, IFNg). Of note, TruCulture tubes stimulated with BCG will be processed based on the site's own local rules. The Institutional Biosafety Committee (IBC) at each site will review the requirements for handling BCG.

- Biomarker assays in urine

  Urine samples will be obtained for biomarker evaluation (including but not limited to biomarkers that are related to bladder or tumor immune biology) from all eligible patients according to the schedule in Appendix 4 and Appendix 5.

Serum samples collected for PK and immunogenicity analysis, which may be used for additional method development, assay validation, and characterization, will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

Refer to the laboratory manual for additional details on laboratory assessments and sample handling.

- Tumor tissue and archival samples collected at screening:

  Fresh TURBT representative tumor specimens either FFPE (preferred) or at least 10 unstained slides, with an associated pathology report is required for study entry; tumor specimens will be evaluated for PD-L1 expression.

In addition, exploratory biomarkers (including but not limited to markers related to immune or UC biology) may be evaluated.

Tumor tissue obtained from TURBT should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status).

Additional archival tumor specimens should be submitted if available.

For archival samples, the remaining tumor tissue block for all patients enrolled will be returned to the site upon request or 18 months after final closure of the study database, whichever is sooner. Tissue samples from patients who are not eligible to enroll in the study will be returned no later than 6 weeks after eligibility determination.

- Bladder biopsy while in the study

  Patients will undergo a mandatory biopsy within 60 days prior to study entry. Fresh tissue biopsy is preferred; however, an archival specimen may be submitted in lieu of fresh tissue if a tissue biopsy is contraindicated owing to patient safety or tumor tissue accessibility and the archival specimen was obtained within 60 days of study screening. The specimen may consist of a formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred) or at least 10 unstained, serial sections. Patients with cystoscopy results indicating pTa/pT1 papillary disease must undergo a TURBT procedure for removal of residual papillary disease prior to study entry.

  Patients will undergo a mandatory biopsy at 6 months (see Appendix 1 and Appendix 2) and as clinically indicated. Tissue biopsies should include any foci of disease (if present) as well as template biopsies obtained from all quadrants of the bladder. Regions of the template biopsies should include the trigone, left lateral wall, right lateral wall, posterior wall, and dome. Additional tissue biopsies may also be obtained over the course of the study to evaluate disease per investigator assessment.

- Bladder biopsy at disease progression/recurrence

  Collection of biopsy samples at disease progression/disease recurrence will be optional and should include any foci of disease as well as template biopsies obtained from all quadrants of the bladder.

- For patients who consent to the optional collection of tumor samples for the Roche Clinical Repository (RCR):

  Patients may agree to provide optional tumor biopsy samples by providing consent on the Optional RCR Informed Consent Form, which is separate from the main study Informed Consent Form. For patients who agree to optional biopsies, tissue samples for biopsy may be collected preferably, per investigator discretion, at the time of disease progression.

  Optional biopsies should consist of core-needle biopsies for deep tumor tissue or organs or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

- Use and storage of remaining samples from study-related procedures

  The remaining samples obtained for study-related procedures will be destroyed no later than 5 years after the end of the study or earlier depending on local regulations. If the patient provides optional consent for storing samples into the RCR for future research (see Section 4.5.12), the samples will be destroyed no later than 15 years after the date of final closure of the clinical database.

- The status of immune-related and tumor type–related and other exploratory biomarkers (including but not limited to T-cell markers and non-inherited biomarkers identified through next generation sequencing (NGS) on extracted DNA and/or RNA) in tumor tissue samples may be evaluated.

  NGS may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator can obtain results from the samples collected at the time of disease progression in the form of an NGS report, which is available upon request directly from Foundation Medicine. The investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by the U.S. Food and Drug Administration (FDA); results from these investigational tests should not be used to guide future treatment decisions.

- Please refer to the laboratory manual for additional details on laboratory assessments and sample handling.

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

Remaining biological samples obtained for study-related procedures will be destroyed no later than 5 years after the end of the study, or earlier depending on local regulations. If the patient provides optional consent for storing samples into the RCR for future research (see Section 4.5.12), the samples will be destroyed no later than 15 years after the date of final closure of the clinical database.

4.5.7 Electrocardiograms

A 12-lead ECG is required at screening and as clinically indicated. ECGs should be obtained on the same machine whenever possible. Lead placement should be as consistent as possible. ECG recordings should 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 or electronic 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.

4.5.8 Patient-Reported Outcomes

PRO data will be collected via questionnaires to more fully characterize the clinical profile of atezolizumab as a single agent and in combination with BCG. The questionnaires will be translated as required into the local language. To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit should be completed prior to the performance of non-PRO assessments and the administration of study treatment. PROs are required at C1D1, and then every 6 weeks/2 cycles starting with C2D1.

The EORTC QLQ-C30 is a validated and reliable self-report measure (Aaronson et al. 1993; Hjermstad et al. 1995; Osoba et al. 1997) that consists of 30 questions assessing global HRQoL, five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea, and vomiting, and pain), and six single-items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) (see Appendix 9). Scale scores can be obtained for the multi-item scales. The EORTC QLQ-C30 takes approximately 5–10 minutes to complete.

The EORTC QLQ-NMIBC24 is a NMIBC-specific module that accompanies the EORTC. The validated and reliable self-report measure (Blazeby et al. 2014) consists of 24 questions assessing the following NMIBC-specific disease and treatment domains: urinary symptoms; malaise; future worries; bloating and flatulence; sexual function, enjoyment, intimacy, and problems; and intravesical treatment. Scale scores can be obtained for the multi-item scales (see Appendix 10).

4.5.9 Assessments during Treatment

All visits must occur within ±3 days from the scheduled date unless otherwise noted (see Appendix 1 and Appendix 2). All assessments involving cystoscopy and urine cytology will be performed within 21 days prior to atezolizumab treatment and for patients in Cohorts 1b, 2, and 3, 14–21 days prior to BCG dosing unless otherwise specified.

See the study flowchart provided in Appendix 1 and Appendix 2 for the schedule of treatment period assessments.

If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on the original 12-week schedule (for atezolizumab and BCG Induction course/Maintenance Course 1), 24-week schedule (for atezolizumab and BCG Maintenance Courses 2–5), or 21-day cycle schedule (for single-agent atezolizumab). If treatment was postponed for fewer than 3 days, the patient can resume the original schedule. Resumption of therapy beyond 3 days will require approval by the Medical Monitor.

Following the eighth cycle of atezolizumab, one of three subsequent administrations may be delayed by 28 days in the combination cohorts to allow for vacations. Following the eighth cycle of atezolizumab, one of three subsequent administrations may be delayed by 1 week for atezolizumab alone cohort to allow for vacations.

4.5.10 Treatment Discontinuation Visit

Patients who discontinue early from treatment for recurrence/progression or toxicity will be asked to return to the clinic within 30 days after the last administration of study treatment or before another anti-cancer therapy is initiated, whichever is earlier. The visit at which a tumor assessment shows progressive disease resulting in treatment discontinuation may be used as the treatment discontinuation visit.

See the study flowcharts provided in Appendix 1 and Appendix 2 for assessments to be performed at the treatment discontinuation visit.

4.5.11 Follow-Up Assessments

See the study flowchart provided in Appendix 1 and Appendix 2 for specified follow-up assessments.

Ongoing Tumor Assessments

Patients who discontinue study treatment for a reason other than disease recurrence/progression or cystectomy will continue to undergo tumor assessments per study protocol, until they experience disease recurrence/progression or cystectomy, until the patient dies, or withdraws consent, or until the study closes, whichever occurs first, for a maximum of 5 years after enrollment.

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

Adverse Events

See Sections 5.2–5.5 for information on reporting adverse events.

Survival and Subsequent Anti-Cancer Therapy Follow-Up

All patients will be followed for survival and subsequent anti-cancer therapy beginning 6 months after the treatment completion/discontinuation visit. Survival and subsequent anti-cancer therapy follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months until loss to follow-up, death, withdrawal of consent, or study termination by the Sponsor, whichever occurs first, for a maximum of 5 years after enrollment. Request to withdraw from follow-up must be documented in the source documents and signed by the investigator. If the patient

withdraws from study treatment but not from follow-up, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

4.5.12 Samples for Roche Clinical Repository

4.5.12.1 Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) 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, and peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR 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

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR 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 RCR sampling, this section of the protocol (see Section 4.5.10) will not be applicable at that site.

4.5.12.3 Sample Collection

The following samples may be collected for patients who have signed the RCR optional consent:

- Optional freshly collected biopsy samples during the study (preferably at disease progression, if clinically feasible)
- Remaining fluids (urine, plasma, and whole blood derivatives) after study-related tests have been performed
- Remaining FFPE tissue (with the exception of archival FFPE blocks, which will be returned to sites) after study-related tests have been performed.

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.12.4 Confidentiality

Confidentiality for All RCR Specimens

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

Patient medical information associated with RCR 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.

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

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted.
The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

Additional Confidentiality for Specimens Used for Genetic Research

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens collected for genetic research.
Upon receipt by the RCR, specimens for genetic research are "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A “linking key” between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure.

Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

4.5.12.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. 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 RCR 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 by completing the RCR Research Sample Informed Consent eCRF.

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

4.5.12.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. *After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient.* If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the study is closed. A patient's withdrawal from Study WO29635 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study WO29635.

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

global_rcr-withdrawal@roche.com

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time

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

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

4.6.2 Study Treatment Discontinuation

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

- Persistence/recurrence of disease with high grade lesion (any pT1, high-grade Ta, or CIS) detected any time on or after the 6-month bladder biopsy.

  Patients with persistent and/or recurrent high-grade NMIBC without progression at 12 weeks may continue in the study, provided there is no evidence of progression to muscle-invasive disease.
- Disease progression (e.g., muscle–invasive or metastatic UC)
- Symptomatic deterioration (i.e., uncontrollable pain secondary to disease or unmanageable ascites, etc.) attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status.
- Intolerable toxicity related to atezolizumab or the combination of BCG and atezolizumab, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment
- Use of another non-protocol anti-cancer therapy (see Section 4.4.2)
- Pregnancy

The primary reason for study treatment discontinuation must be documented in the eCRF.

4.6.3 Study and Site Discontinuation

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

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

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

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Measures will be taken to ensure the safety of patients participating in this study, including the use of inclusion and exclusion criteria (see Section 4.1.1 and Section 4.1.2) and close monitoring (as indicated below and in Section 4.5).

An iDMC has also been incorporated into the study design to periodically review aggregate safety and efficacy data (please refer to the iDMC Charter for a detailed monitoring plan).

BCG is an approved treatment for patients with NMIBC. Additional information on the risks and precautions associated with BCG therapy are provided in the OncoTICE prescribing information.

Eligibility

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies with atezolizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were taken into account. Specifically, patients at risk for study-emergent autoimmune conditions or with a prior diagnosis of autoimmune disease, patients with evidence of acute infections, and patients who have received a live-attenuated viral vaccine within 28 days before Day 1 are excluded from the study (see Section 4.1.2).

Monitoring

Safety will be evaluated in this study through the monitoring of all serious adverse events, defined and graded according to NCI CTCAE v4.0. General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Appendix 1 and Appendix 2 for the list and timing of study assessments). Laboratory values must be reviewed prior to each infusion.

During the study, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection. All serious adverse events and protocol-defined events of special interest (see Sections 5.2.2 and 5.2.3) will be reported in an expedited fashion (see Section 5.4.2). In addition, the Medical Monitor will review and evaluate observed adverse events on a regular basis. An iDMC will review safety and efficacy data as described in the Section 3.2.

Patients who experience a serious adverse event or protocol defined events of special interest will be followed for safety for 90 days following their last dose of study drug or until they receive another anti-cancer therapy, whichever comes first. Patients who experience all other adverse events will be followed for safety for 30 days following their last dose of study drug or until they receive another anti-cancer therapy, whichever comes first.

Patients who have an ongoing study treatment–related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections. Refer to the Atezolizumab Investigator's Brochure for a complete summary of safety information.

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*, and myositis. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab).* Refer to Appendix 12 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with BCG

Although intravesical BCG is generally well tolerated, the potential for adverse effects and severe complications exists with prolonged therapy and include local and systemic infectious complications. Adverse events commonly seen with BCG treatment include but are not limited to the following: urinary tract infection, anorexia, unclassified cardiac disorders, nausea/vomiting, diarrhea, liver involvement, skin rash, arthralgia/myalgia/arthritis, dysuria, hematuria, urinary frequency, urinary urgency, BCG cystitis, bladder cramps/pain, urinary incontinence, contracted bladder, fever, malaise,

and chills (Lamm et al. 1991). Additional complications include clinical granulomatous prostatitis, pneumonitis, hepatitis, ureteral obstruction, epididymitis, renal abscess, sepsis, arthritis, osteomyelitis, and cytopenias (Brausi et al. 2014).

The proper administration of BCG is essential for avoiding intravascular dissemination of the bacillus.

The following is a summary of AUA guidelines for avoiding BCG transmission to others after BCG exposure:

To avoid transmission of BCG to others, for 6 hours after treatment, patients should void (urinate) while seated to avoid splashing of urine. Urine voided during this time should be disinfected with 2 cups of household bleach in the toilet water and allowing it to stand for 15–2 minutes before flushing.

Men receiving BCG treatment can pass on BCG during sex. To protect their partner from coming into contact with BCG, men should not have sex for 48 hours after each treatment. Men should use condoms while taking BCG and for six weeks after treatment has ended.

Both men and women should not conceive a child (get pregnant) while taking BCG treatments. Barrier methods of contraception, such as condoms, are recommended while taking BCG. Men and women should discuss with their doctor when it is safe to conceive a child after therapy.

Women should not breastfeed while taking this medication.

5.1.2.1 Constitutional Symptoms (Flu-like Symptoms)

Flu-like symptoms (malaise, fever and chills) may occur with both BCG treatment and atezolizumab. In patients who develop flu-like symptoms, disseminated BCG infection should be evaluated and ruled out before attributing to atezolizumab. The management of disseminated BCG infection requires the administration of antibiotics and steroids would be contraindicated. Patients should be monitored for the presence of symptoms and signs of toxicity after each intravesical treatment. Flu-like symptom attributable to BCG may be managed per the OncoTICE prescribing information.

Additional guidelines for management of patients who develop flu-like symptoms are provided in Table 8.

5.1.2.2 Local Bladder Symptoms

Symptoms of bladder irritability (i.e., bladder pain, bladder spasm), related to the inflammatory response induced, are reported in approximately 60% of patients receiving BCG (Brausi et al. 2014). The symptoms typically begin 4–6 hours after instillation and last 24–72 hours.

Grade ≥3 dysuria occurs in 11% of patients and usually seen after the third instillation and tends to increase in severity with each subsequent administration. The mechanism of action has not been firmly established, but is most consistent with an immunological mechanism. Then is no evidence that dose reduction or anti-tuberculous drug therapy can prevent or lessen the irritative toxicity of BCG.

Guidelines for management of patients who develop local bladder symptoms are provided in Table 8.

5.1.3 Management of Patients Who Experience Specific Adverse Events

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend atezolizumab for up to 12 weeks beyond last dose if they experience adverse events that require a dose to be withheld. If atezolizumab is withheld because of related adverse events for > 12 weeks beyond the last dose, then the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in Section 5.5. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming atezolizumab after a hold > 12 weeks, atezolizumab may be restarted with the approval of the Medical Monitor.

If a patient must be tapered off steroids used to treat adverse events, atezolizumab may be withheld for an additional time beyond 12 weeks from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤ 10 mg/day. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Note, if systemic corticosteroids must be initiated in patients receiving weekly BCG installations, either during BCG induction or any BCG maintenance course, BCG must be withheld throughout the duration of systemic corticosteroid therapy to minimize the risk of systemic BCG infection. BCG instillations should not be resumed until the patient has discontinued systemic corticosteroids.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Guidelines for the management of fever, local bladder symptoms, and influenza-like illness are presented in Table 8, as these events may result from or be potentiated by the combination of BCG and atezolizumab. Refer to Appendix 12 for additional management guidelines for immune-mediated adverse events.

See Section 4.3.2.1 for guidelines for the management of infusion-related reactions and Appendix 8 for precautions for anaphylaxis.

Table 8 Guidelines for Management of Specific Adverse Events

Severity	Management
Influenza-like illness Arthralgia/chills	
Grade ≤2	• Continue atezolizumab. • Treat symptoms with non-steroidal anti-inflammatory drugs (e.g., ibuprofen).
Grade 3/4	• Withhold atezolizumab. • Consider starting 10 mg/day oral prednisone or equivalent, with taper over 1–2 weeks. • Resume atezolizumab if symptoms resolve and corticosteroid dose is equivalent to 10 mg/day. • Refer to the TICE prescribing information for additional management guidelines pertaining to BCG.
Fever < 101° F (38.3° C)	• Continue atezolizumab and BCG (patients receiving induction or maintenance BCG at time of symptom) • Treat symptoms with non-steroidal anti-inflammatory drugs (e.g., ibuprofen). • Withhold BCG and atezolizumab.
≥ 101° F (38.3° C)	• For fever < 24 hours, and in absence of other new grade ≥ 2 symptoms, evaluate and rule out co-existing infection including urine and blood culture, blood tests, and chest X-ray. Consider consultation with infectious disease specialist. • For fever > 24hours, would recommend immediate consultation with infectious disease specialist, discontinuation of BCG instillations, urine and blood culture, blood tests, and chest X-ray. Consider initiation of ≥2 antimicrobial agents including coverage with anti-tuberculosis therapy while diagnostic evaluation is being conducted. • Refer to the TICE prescribing information for additional management guidelines pertaining to BCG.
Local bladder symptoms	
Dysuria	• Refer to the TICE prescribing information for management guidelines pertaining to BCG.
Frequency	• Refer to the TICE prescribing information for management guidelines pertaining to BCG.
Hematuria	• Refer to the TICE prescribing information for management guidelines pertaining to BCG.
Local inflammation (e.g., epididymitis, prostatitis, orchitis)	• Refer to the TICE prescribing information for management guidelines pertaining to BCG.

BCG = bacille Calmette-Guérin; GGO = ground-glass opacity; IV = intravenous; LFT = liver function test; TNF-α = tumor necrosis factor-α; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

According to the International Council for Harmonisation (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 5.3.5.9
- 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 5.3.5.10)

- 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) criteria; 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:

- DLTs
- 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 and based on the following observations:

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

  Treatment-emergent ALT or AST $>$ 3 $\times$ baseline value in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study drug, as defined below:

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

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>$ 10 $\times$ ULN
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barre syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- BCG infection
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, *and* systemic inflammatory reaction syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade $>$2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4, Section 5.5, Section 5.6.

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events and serious adverse events regardless of attribution will be collected until 90 days following the last administration of study treatment or until study discontinuation/termination or until initiation of subsequent anti-cancer therapy, whichever occurs first. Patients will be contacted at 30 days after the last dose of study treatment to determine if any new adverse events have occurred. After this period, investigators should report only serious adverse events that are considered to be related to prior study treatment (see 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

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

The adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity. See Table 9 for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 9 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
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 one's self, 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 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 10):

- 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 (where 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 10 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	Adverse events will be considered related, unless they fulfill the criteria as 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).

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 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.

5.3.5.2 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.

5.3.5.3 Persistent or Recurrent Adverse Events

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

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

5.3.5.4 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms

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

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin $5 \times$ 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 if 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 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN
- Treatment-emergent ALT or AST $> 3 \times$ 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 (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.6 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 5.3.5.3 for details on recording persistent adverse events).

5.3.5.7 Deaths

All on-study deaths, regardless of relationship to study drug, must be recorded on the eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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

During survival follow-up, deaths attributed to progression of UC should be recorded only on the Death Page eCRF.

5.3.5.8 Preexisting Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of Non–Muscle-Invasive Bladder Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on cystoscopic assessment. 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 a result of disease progression, it should be reported as an adverse event.

5.3.5.10 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
- Hospitalization to perform an efficacy measurement for the study
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The patient has not suffered an adverse event.

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

- Hospitalization for outpatient care outside of normal clinic operating hours that is required per protocol or per local standard of care

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

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

5.3.5.12 Patient-Reported Outcome Data

The PRO measurements are described in Section 4.5.8. The methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Because of these differences, PRO data will not be reported as adverse events and no attempt will be made to resolve any noticeable discrepancies between PRO data and observed or volunteered adverse events. The PRO data will be presented in separate tables, figures, and data listings from the adverse event data, and will be included in the appropriate section of the final study report.

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 study. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

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

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

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

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

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, 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 and Medical Monitor contact information will be distributed to all investigators (see Protocol Administrative and Contact Information & List of Investigators).

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted] M.D.
E-mail: [redacted]
Telephone No.: [redacted]
Mobile Telephone No.: [redacted]

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. For reports of serious adverse events and adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the Adverse Event eCRF and submit the report via the Serious Adverse Event/Adverse Event of Special Interest Reporting Form.

The Serious Adverse Event/Adverse Event of Special Interest Reporting Form and Fax Coversheet should be completed and faxed or e-mailed immediately (i.e., no more than 24 hours after learning of the event), as follows. Ensure that information is also entered in the EDC system.

Fax: 1-866-807-4325
E-mail: cann.sae@scri-innovations.com

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug or until they receive another anti-cancer therapy, whichever comes first. After initiation of study drug, all adverse events will be reported until 30 days (see guidance and table in Section 5.3.1) after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the Serious Adverse Event/Adverse Event of Special Interest Reporting Form.

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 e-mailing the form with use of the fax number or e-mail address provided to investigators. All information will also need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and faxed or e-mailed immediately as follows below (i.e., no more than 24 hours after learning of the event).

Fax:	1-866-807-4325
Email:	Cann.sae@scri-innovations.com

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

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor or designee immediately via the Serious Adverse Event/Adverse Event of Special Interest Reporting Form (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 or designee immediately via the Serious Adverse Event/Adverse Event of Special Interest Reporting Form (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 study-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. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

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 adverse event reporting period (see Section 5.3.1), all deaths, regardless of cause, should be reported through use of the Survival Follow-Up eCRF. In addition, if the investigator becomes aware of a serious adverse event or adverse event of special interest that is believed to be related to prior study drug treatment or study procedure, 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 with use of the following reference documents:

- Atezolizumab Investigator's Brochure
- Local prescribing information for BCG (OncoTICE)

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

All analyses will be performed by cohort. Selected analyses may also be performed for all cohorts combined as specified below.

All patients treated with any amount of study drug (atezolizumab or BCG) will be included in all analyses unless specified otherwise.

Analyses of DLTs will be performed on an ongoing basis as described in Section 3.1. Analyses of endpoints related to anti-tumor activity will be performed periodically among patients with sufficient follow-up. Final analyses will be performed after the LPLV has occurred.

Continuous variables will be summarized using means, SDs, medians, and ranges. Categorical variables will be summarized by proportions. The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

6.1 DETERMINATION OF SAMPLE SIZE

The sample sizes for Cohorts 1A, 2, and 3 were based on clinical and operational considerations. The sample size for Cohort 1B was based on a 3+3 dose de-escalation design appropriate for assessing DLTs and MTD or MAD of BCG in combination with atezolizumab.

An evaluation of results from Cohorts 1A and 1B will be performed prior to initiation of enrollment in Cohorts 2 and 3. Table 11 shows the 95% CI for selected observed CR rates for a range of sample sizes for Cohorts 1A and 1B pooled.

Table 11 95% CI for Selected Observed 6-Month Complete Response Rates in Cohorts 1A and 1B

Cohort	N	Number of Patients with CR (Observed CR Rate)	95% CI for CR Rate [a]
Cohorts 1A and 1B pooled	12	5 (42%)	(15%, 72%)
		6 (50%)	(21%, 79%)
	15	6 (40%)	(16%, 68%)
		7 (47%)	(21%, 73%)
	20	8 (40%)	(19%, 64%)
		9 (45%)	(23%, 68%)

CR = complete response.

[a] Clopper-Pearson method.

Table 12 shows the 95% CI for selected observed CR rates with the planned maximum enrollment of patients in either Cohorts 2 or 3.

Table 12 95% CI for Selected Observed 6-Month Complete Response Rates with the Planned Maximum Enrollment of Patients in Either Cohort 2 or 3

Cohort	N	Number of Patients with CR (Observed CR rate)	95% CI for CR Rate [a]
Cohorts 2 or 3	20	10 (50%)	(27%, 73%)
		12 (60%)	(36%, 81%)
		14 (70%)	(46%, 88%)
		16 (80%)	(56%, 94%)
		18 (90%)	(68%, 99%)

CR = complete response.

[a] Clopper-Pearson method.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol deviations including major deviations of inclusion/exclusion criteria, and reasons for discontinuation from the study will be summarized by cohort and among pooled cohorts for the treated population. Study treatment administration and reasons for discontinuation from the study treatment will be summarized by cohort and among pooled cohorts for all treated patients.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables such as age, sex, race/ethnicity, baseline characteristics (e.g., prior therapy, time since initial diagnosis, site[s] of disease, number of site[s], EORTC risk score, smoking status, and ECOG performance status) will be summarized by cohort and among pooled cohorts for all treated patients.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy outcome measure for this study is CR at 6 months after the start of study treatment as assessed by the investigator on the basis of cystoscopic assessment and urine cytology. The CR rate will be summarized by timepoint for each cohort, and the corresponding 95% CI will be calculated on the basis of the Clopper-Pearson method.

6.4.2 Secondary Efficacy Endpoints

All assessments will be based on investigator assessments of tumor response/recurrence/progression and cause of death. The secondary efficacy endpoints for this study are as follows.

- CR at the 3-month disease assessment, evaluated by both cystoscopy and cytology.
- Duration of CR will be defined for patients with a CR as the time from the first occurrence of a documented complete response to recurrence of high-grade NMIBC or death from any cause. Data for patients without an event will be censored at the last date known to be alive and recurrence free.
- RFS rate at 6, 12, and 18 months, defined as the proportion of patients who are alive and free of persistent/recurrent high-grade NMIBC. Data for patients without an event will be censored at the last date known to be alive and free of persistent/recurrent NMIBC.
- Bladder-intact DFS will be defined as the time from the first study treatment to earliest evidence of progression to muscle-invasive disease in the bladder, regional pelvic progression, distant metastasis, bladder cancer–related death, or cystectomy. Data for patients without an event will be censored at the last date known to be alive and event-free. Data for patients who died from causes other than bladder cancer will be censored at the day of death.

- PFS, defined as the time from the first study treatment to the first occurrence of progression to muscle-invasive disease based on cystoscopy and urine cytology or death from any cause. Data for patients without a PFS event will be censored at the last date known to be alive and progression-free.
- Cystectomy-free survival, defined as from start of study treatment to bladder removal for any cause or death from any cause. Data for patients alive without cystectomy will be censored at the last date known to be alive without cystectomy.
- Overall survival, defined as the time from the first dose of study treatment to death from any cause. Data for patients who have not died will be censored at the last date known to be alive.

Data for patients without the respective post-baseline assessment will be censored at the time of start of treatment plus one day. Time-to-event endpoints (duration of CR, bladder-intact DFS, PFS, cystectomy-free survival, and overall survival) will be summarized by cohort with use of the Kaplan-Meier method. Kaplan-Meier curves will be presented. Kaplan-Meier estimates of event rates at landmark timepoints (e.g., 6-, 12-, and 18-months) and median time to the event will be presented with the corresponding 95% CI. RFS rates and the corresponding 95% CI will be summarized at the 6-, 12-, and 18-month timepoints.

6.4.2.1 Exploratory Efficacy Analyses

Summaries of efficacy endpoints may be provided by subgroups defined by demographic and baseline characteristics as appropriate.

6.5 SAFETY ANALYSES

Safety will be assessed through summaries of adverse events, changes in laboratory test results, and changes in selected vital signs. Safety analyses will be performed for treated patients by cohort. Selected analyses will be performed by BCG dose level.

All adverse events with onset on or after treatment on Day 1 (treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v4 toxicity grade. All adverse events, NCI CTCAE v4 Grade $\geq$3 adverse events, adverse events leading to withdrawal of treatment and serious adverse events will be summarized overall and for treatment related events. In addition, all deaths including cause of death will be summarized. All adverse events and deaths will be listed.

All DLTs will be listed for DLT-evaluable patients (see Section 3.1.3 for a definition of DLT-evaluable patients).

NCI CTCAE v4 Grade 3 and 4 laboratory data will be listed; in addition changes in selected laboratory data will be summarized by grade with use of the NCI CTCAE v4. Selected vital signs and selected laboratory data will be summarized. The incidence of antibodies to atezolizumab will be summarized.

6.6 PHARMACODYNAMIC ANALYSES

PD analyses will include assessments of PD biomarkers in both tumor tissue and whole blood. Changes in PD and biomarkers potentially related to outcomes will be listed by dose, cohort, and response status. Change from baseline will be reported descriptively as means, medians, and ranges and as a function of the response.

6.7 PHARMACOKINETIC ANALYSES

Available atezolizumab serum concentrations data (C_{min} and C_{max}) will be tabulated and summarized for each course or cycle, as appropriate. Descriptive statistics will include means, medians, ranges, and SDs, as appropriate.

Additional PK analyses may be conducted as appropriate.

6.8 PATIENT-REPORTED OUTCOME ANALYSES

Cycle scores and change from baseline in symptoms, function, and HRQoL, as measured by the EORTC QLQ-C30 and the EORTC QLQ-NMIBC24 will be reported descriptively by cohort as means, SDs, medians, and ranges.

6.9 INTERIM ANALYSIS

6.9.1 Planned Interim Analyses

A preliminary assessment of anti-tumor activity and safety will be performed on Cohorts 1A and 1B prior to initiation of enrollment into Cohorts 2 and 3.

Given the nature of this study, the Sponsor may choose to perform additional periodic analyses of safety or efficacy on any cohort.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC with use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the CRO, with use of the CRO's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's

standard procedures will be used to handle and process the electronic transfer of these data.

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification 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 study.

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) *and applicable local, regional, and national laws*.

8.2 INFORMED CONSENT

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

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

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

8.4 CONFIDENTIALITY

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 *MANAGEMENT OF STUDY QUALITY*

The Sponsor will implement 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 will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include 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 will be 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, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

A Steering Committee will consist of expert investigators selected from three academic institutions participating in the study. During the study, the Committee's role will be to review safety data with the Sponsor.

The study site will acknowledge receipt of study treatments with use of the IxRS to confirm the shipment condition and content.

Central laboratories will coordinate the collection of archival tumor, fresh tumor and leftover tumor tissue, and blood samples for the assessment of atezolizumab pharmacokinetics and biomarkers, ATA assays, and auto-antibody testing. Specified laboratory tests may be performed at a central laboratory.

9.6 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, at scientific congresses*, in clinical trial registries,* and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. *Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request.* For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical studies 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 study results within 6 months after the availability of the respective clinical study report. In addition, for all clinical studies 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 studies 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).

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Appendix 1
Schedule of Assessments: Cohort 1A

Study Procedures	Screening Days –28 to –1	Weeks 1–96 [a]	Disease Progression	Treatment Completion/ DC Visit [b]	Follow-Up
Signed Informed Consent Form [c]	x				
Review of eligibility criteria	x				
Medical, surgical, and cancer histories [d]	x				
Demographic [e]	x				
ECOG performance status	x	x [f]		x	
Complete physical examination [g]	x				
Limited physical examination [h]		x [f]		x	
Weight	x				
Height	x				
Vital signs [i]	x	x [f]		x	
12-lead ECG [j]	x				
Upper tract imaging with CT urography or IV pyelogram [k, l]	x	Prior to atezolizumab treatment Cycles 9 and 29, then annually as indicated			
Hematology [m, n]	x [n]	x [f]		x	
Serum chemistry [n, o]	x [n]	x [f]		x	
Coagulation panel (aPTT, INR) [n]	x [n]			x	
Urinalysis [n, p]	x				
Creatinine clearance	x				
TSH, free T3, free T4	x	q6w [C2D1 and then every other cycle thereafter (e.g., C4D1, C6D1, etc.)]			
HIV, HBV, HCV serology [q]	x				

Appendix 1
Schedule of Assessments: Cohort 1A (cont.)

Study Procedures	Screening Days –28 to –1	Weeks 1–96 [a]	Disease Progression	Treatment Completion/ DC Visit [b]	Follow-Up
TB test [r]	x				
Serum pregnancy test [n, s]	x	q3w [f]		x	
Archival/screening FFPE tumor tissue specimen or 10 unstained slides [t]	x				
Serum PK sample [u]		See Appendix 4			
Serum ATA sample [u]		See Appendix 4			
Plasma PD biomarker		See Appendix 4			
Atezolizumab infusion [v]		x			
Tissue biopsy (mandatory sample) [w]		Prior to Cycle 9 (before Week 24)			
Tumor biopsy (optional sample)			x	x	x
Tumor assessment [x]	x	Every 12 weeks [x, l]		x	x [y]
Patient reported outcomes [z]		Cycle 1 Day 1, Cycle 2 Day 1, and every 6 weeks thereafter		x	
Concomitant medications [aa]	x [aa]	x		x	
Adverse events [bb]	x [aa]	x		x	x
Survival and anti-cancer therapy follow-up assessment [cc]					x
Blood samples for pharmacodynamics and biomarkers [dd]		See Appendix 4			

Appendix 1
Schedule of Assessments: Cohort 1A (cont.)

Study Procedures	Screening Days –28 to –1	Weeks 1–96 [a]	Disease Progression	Treatment Completion/ DC Visit [b]	Follow-Up
Urine samples for biomarker analysis [ee]		See Appendix 4			
Whole blood TruCulture		See Appendix 4			
Whole blood FACS		See Appendix 4			

ATA = anti-therapeutic antibody; BCG = bacille Calmette-Guérin; CT = computed tomography; DC = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC = European Organisation for the Research and Treatment of Cancer; FACS = Fluorescence-activated cell sorting; FFPE = formalin-fixed paraffin-embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; IV = intravenous; MRI = magnetic resonance imaging; NMIBC = non–muscle-invasive bladder cancer; NMIBC24 = QLQ non–muscle-invasive bladder cancer; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PK = pharmacokinetic; PPD = purified protein derivative; q3w = every 3 weeks; q6w = every 6 weeks; QLQ-C30 = Quality of Life Questionnaire Core 30; qw = weekly; TB = tuberculosis; TSH = thyroid-stimulating hormone; TURBT = transurethral resection of bladder tumor; UC = urothelial carcinoma.

Note: Each atezolizumab cycle is 3 weeks. All assessments should be performed within ±3 days of the scheduled visit, unless otherwise specified. Assessments scheduled on the days of study treatment administration should be performed before the infusion unless otherwise noted.

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits scheduled according to the original schedule.

[a] In the absence of unacceptable toxicity or compelling evidence of disease progression, patients deriving clinical benefit may be offered continued study treatments for up to 96 weeks (in total).

[b] Patients will be asked to return to the clinic within 30 days after the last administration of study treatment or before another anti-cancer therapy is initiated, whichever is earlier. The visit at which a tumor assessment shows progressive disease resulting in treatment discontinuation may be used as the treatment discontinuation visit.

[c] Written informed consent is required before performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1, Day 1 (except where otherwise specified) may be used for screening assessments rather than repeating such tests.

Appendix 1
Schedule of Assessments: Cohort 1A (cont.)

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[d] Cancer history includes stage, date of diagnosis, and surgical resection procedure used as frontline treatment (if applicable).

[e] Demographic information includes sex, age, and self-reported race/ethnicity.

[f] Required on Day 1 of every atezolizumab cycle.

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

[h] Perform a limited, symptom-directed examination at every atezolizumab cycle and at treatment completion/DC visit, or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Vital signs include heart rate, respiratory rate, blood pressures, and temperature. For the first atezolizumab infusion, the patient's vital signs should be determined within 60 minutes before, during (every 15 [$\pm$5] minutes), and 30 ($\pm$10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and at the end of the infusion.

[j] ECG recordings will be obtained during the screening period and when clinically indicated. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[k] Baseline upper urinary tract imaging with CT urography, intravenous pyelogram, renal ultrasound with retrograde pyelogram, ureteroscopy or MRI urogram. Pelvic CT before TURBT may be considered but is not required. Assessment should be within 28 days prior to starting study treatment. Upper tract imaging using the same modality as was used at baseline should be performed at the 6-month (atezolizumab Cycle 9, Day 1) and 18-month (atezolizumab Cycle 29, Day 1) assessments, and then annually as indicated.

[l] Patients with recurrent low-grade papillary disease will be required to undergo resection with TURBT (unless medically contraindicated) and may continue in the study and receive study treatment. Patients with persistent and/or recurrent high-grade NMIBC without progression at 12 weeks may continue in the study, provided there is no evidence of progression to muscle-invasive disease. Patients with persistent and/or recurrent high-grade NMIBC at the 6-month assessment will be discontinued from study therapy. Patients with progression to muscle invasion at any time will be discontinued from study therapy.

[m] Includes RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated.

[n] Laboratory results to be obtained within 14 days prior to the first dose of atezolizumab treatment.

[o] Includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.

Appendix 1
Schedule of Assessments: Cohort 1A (cont.)

[p] Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood).

[q] HIV testing to be performed in accordance with national and/or institutional guidelines. HBV DNA must be collected on or before Cycle 1, Day 1 in patients who have negative serology for hepatitis B surface antigen and positive serology for anti-HCV.

[r] All patients will have a QuantiFERON® test done locally prior to inclusion into the study.

[s] 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 Cycle 1, Day 1, q3w, and at treatment completion/discontinuation.

[t] A sample of tumor tissue is required at study entry. Fresh tissue biopsy is preferred; however, an archival specimen may be submitted in lieu of fresh tissue if a tissue biopsy is contraindicated owing to patient safety or tumor tissue accessibility and the archival specimen was obtained within 2 months of study screening. The specimen may consist of a FFPE tumor tissue block (preferred) or at least 10 unstained, serial sections.

[u] See Appendix 4 for a detailed schedule of sample collection timepoints. Plasma PD biomarker, whole blood PBMC, urine biomarker, and whole blood FACS analysis will be performed at disease progression. Post-atezolizumab dose samples should be collected 30 ± 10 minutes after the end of atezolizumab infusion.

[v] Atezolizumab will be administered by IV infusion q3w for a maximum of 32 cycles of 96 weeks, whichever occurs first.

[w] All patients will undergo a mandatory tumor biopsy sample collection at 6 months (prior to Cycle 9 of atezolizumab). Biopsy must be scheduled 14–21 days prior to BCG administration. Fresh tissue biopsies will also be obtained as clinically indicated (e.g., if patient experiences signs of progression). Mandatory fresh tissue biopsies should include any foci of disease (if present) as well as template biopsies obtained from all quadrants of the bladder. Regions of the template biopsies should include the trigone, left lateral wall, right lateral wall, posterior wall, and dome. The Bladder Map template (Appendix 11) should be used to document the approximate size and location of any abnormalities, as well as the approximate location of template biopsies. Additional tissue biopsies may also be obtained over the course of the study to evaluate disease per investigator assessment.

[x] Primary assessment of tumor will be with cystoscopy and urine cytology. Tumor response assessment will occur every 12 weeks for the first 2 years, and every 24 weeks thereafter (or as clinically appropriate) until 5 years, and then yearly. White-light cystoscopy, narrow band imaging cystoscopy, or fluorescent (blue-light) cystoscopy will be acceptable for baseline assessment. The same methodology used to assess disease sites at screening should be used throughout the study except when medically contraindicated (e.g., the same cystoscopy protocol and urine examination). All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Random biopsies must include all four quadrants of the bladder. The same evaluator should perform assessments if possible to ensure internal consistency across visits. The Bladder Map template (Appendix 11) should be used to document the approximate size and location of any abnormalities, as well as the approximate location of any biopsies performed. For all patients, additional evaluation (imaging, exam under anesthesia, biopsies) should be performed at investigator discretion for any of the following circumstances:

- Abnormal cystoscopy
- Positive urine cytology
- Two sequential suspicious/indeterminate urine cytology specimens

[y] Patients who discontinue all study treatment for a reason other than disease recurrence/progression or cystectomy will continue to undergo tumor assessments every 6 months until they experience disease recurrence/progression or cystectomy, until the patient dies, or withdraws consent, or until the study closes, whichever occurs first, for a maximum of 5 years after enrollment.

[z] Health-related quality of life will be assessed using the EORTC QLQ-C30 and EORTC QLQ-NMIBC24.

[aa] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to informed consent should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

[bb] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all serious adverse events or protocol-defined events of special interest will be followed for 90 days following their last dose of study drug or until they receive another anti-cancer therapy, whichever comes first. All other adverse events will be followed for safety for 30 days following their last dose of study drug or until they receive another anti-cancer therapy, whichever comes first. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events or adverse events of special interest considered to be related to the study drug or study-related procedures until a final outcome can be reported. Treatment-related serious adverse events or adverse events of special interest should be reported regardless of the time after the end of treatment or study.

[cc] All patients will be followed for survival and subsequent anti-cancer therapy beginning 6 months after the treatment completion/discontinuation visit. Survival and subsequent anti-cancer therapy follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits every 6 months (±1 month) until loss to follow-up, withdrawal of consent, or study termination by the Sponsor, for a maximum of 5 years after enrollment. Request to withdraw from follow-up must be documented in the source documents and signed by the investigator. If the patient withdraws from treatment but not from follow-up, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

[dd] See Appendix 4 for details of the pharmacodynamic sampling schedule.

[ee] Acquisition of urine biomarker samples will be performed prior to administration of study drug.

Appendix 2
Schedule of Assessments: Cohorts 1B, 2, and 3

Study Procedures	Screening (Days –28 to –1)	Weeks 1–96 [a]	Disease Progression	Treatment Completion/ DC Visit [b]	Follow-Up
Signed Informed Consent Form [c]	x				
Review of eligibility criteria	x				
Medical, surgical, and cancer histories [d]	x				
Demographic [e]	x				
ECOG performance status	x	x [f]		x	
Complete physical examination [g]	x				
Limited physical examination [h]		x [f]		x	
Weight	x				
Height	x				
Vital signs [i]	x	x [f]		x	
12-lead ECG [j]	x				
Upper tract imaging with CT urography or IV pyelogram [k, l]	x	Prior to atezolizumab Cycles 9 and 29, then annually as indicated			
Hematology [m, n]	x [n]	x [f]		x	
Serum chemistry [m, n,o]	x [n]	x [f]		x	
Coagulation panel (aPTT, INR) [n]	x [n]			x	
Urinalysis [n, p]	x				
Creatinine clearance	x				
TSH, free T3, free T4 [n]	x [m]	q6w [C2D1 and then every other cycle thereafter (e.g., C4D1, C6D1, etc.)]			

Appendix 2
Schedule of Assessments: Cohorts 1b, 2, and 3 (cont.)

Study Procedures	Screening (Days –28 to –1)	Weeks 1–96 [a]	Disease Progression	Treatment Completion/ DC Visit [b]	Follow-Up
HIV, HBV, HCV serology [q]	x				
TB test [r]	x				
Serum pregnancy test [n, s]	x	q3w [f]		x	
Archival/screening FFPE tumor tissue specimen or 10 unstained slides [t]	x				
Serum PK sample [u]		See Appendix 5			
Serum ATA sample [u]		See Appendix 5			
Plasma PD Biomarker		See Appendix 5			
Atezolizumab infusion [v]		x			
BCG administration [w]		BCG Induction: weekly for 6 weeks (Weeks 0–11) BCG Maintenance Course 1: weekly for 3 weeks (Weeks 12–23) BCG Maintenance Course 2: weekly for 3 weeks (Weeks 24–47) BCG Maintenance Course 3: weekly for 3 weeks (Weeks 48–71) BCG Maintenance Course 4: weekly for 3 weeks (Weeks 72–95) BCG Maintenance Course 5: weekly for 3 weeks (Weeks 96–120)			
Tissue biopsy (mandatory sample) [x]		Prior to Cycle 9			

Appendix 2
Schedule of Assessments: Cohorts 1b, 2, and 3 (cont.)

Study Procedures	Screening (Days –28 to –1)	Weeks 1–96 [a]	Disease Progression	Treatment Completion/ DC Visit [b]	Follow-Up
Tissue biopsy (optional sample)			x	x	x
Tumor assessment [y]	x	Every 12 weeks following initiation of atezolizumab [y, l]		x [z]	x [z]
Patient-reported outcomes [aa]		Cycle 1, Day 1, Cycle 2 Day 1, and every 6 weeks thereafter		x	
Concomitant medications [bb]	x [bb]	x		x	
Adverse events [cc]	x [cc]	x		x	x
Survival and anti-cancer therapy follow-up assessment [dd]					x
Blood samples for pharmacodynamics and biomarkers [ee]		See Appendix 5			
Urine samples for biomarker analysis [ff]		See Appendix 5			
Whole blood TruCulture		See Appendix 5			
Whole blood FACS		See Appendix 5			

Appendix 2
Schedule of Assessments: Cohorts 1b, 2, and 3 (cont.)

ATA = anti-therapeutic antibody; BCG = bacille Calmette-Guérin; CT = computed tomography; DC = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC = European Organisation for the Research and Treatment of Cancer; FACS = Fluorescence-activated cell sorting; FFPE = formalin-fixed paraffin-embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; IV = intravenous; MRI = magnetic resonance imaging; NMIBC = non–muscle-invasive bladder cancer; NMIBC24 = QLQ non–muscle-invasive bladder cancer; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamic; PK = pharmacokinetic; PPD = purified protein derivative; q3w = every 3 weeks; q6w = every 6 weeks; QLQ-C30 = Quality of Life Questionnaire Core 30; qw = every week; TB = tuberculosis; TSH = thyroid-stimulating hormone; TURBT = transurethral resection of bladder tumor; UC = urothelial carcinoma.

Note: All assessments should be performed within ±3 days of the scheduled visit, unless otherwise specified. Assessments scheduled on the days of study treatment administration should be performed before the infusion unless otherwise noted. All assessments (with cystoscopy and urine cytology) will be performed within 21 days prior to treatment and must occur 14 days prior to BCG dosing (for patients receiving BCG) unless otherwise specified.

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits scheduled according to the original schedule.

[a] In the absence of unacceptable toxicity or compelling evidence of disease progression, patients deriving clinical benefit may be offered continued atezolizumab treatments for up to 96 weeks (in total).

[b] Patients will be asked to return to the clinic within 30 days after the last administration of study treatment or before another anti-cancer therapy is initiated, whichever is earlier. The visit at which a tumor assessment shows progressive disease resulting in treatment discontinuation may be used as the treatment discontinuation visit.

[c] Written informed consent is required before performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to atezolizumab Cycle 1, Day 1 (except where otherwise specified) may be used for screening assessments rather than repeating such tests.

[d] Cancer history includes stage, date of diagnosis, and surgical resection procedure used as frontline treatment (if applicable).

[e] Demographic information includes sex, age, and self-reported race/ethnicity.

[f] Required on Day 1 of every atezolizumab cycle.

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

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

Appendix 2
Schedule of Assessments: Cohorts 1b, 2, and 3 (cont.)

[i] Vital signs include heart rate, respiratory rate, blood pressures, and temperature. For the first atezolizumab infusion, the patient's vital signs 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 infusion and at the end of the infusion.

[j] ECG recordings will be obtained during the screening period and when clinically indicated. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[k] Baseline upper urinary tract imaging with CT urography, intravenous pyelogram, renal ultrasound with retrograde pyelogram, ureteroscopy or MRI urogram. Pelvic CT before TURBT may be considered but is not required. Assessment should be within 28 days prior to starting study treatment. Upper tract imaging using the same modality as was used at baseline should be performed at the 6-month (atezolizumab Cycle 9, Day 1) and 18-month (atezolizumab Cycle 29, Day 1) assessments, and then annually as indicated.

[l] Patients with recurrent low-grade papillary disease will be required to undergo resection with TURBT (unless medically contraindicated) and may continue in the study and receive study treatment. Patients with persistent and/or recurrent high-grade NMIBC without progression at 12 weeks may continue in the study provided there is no evidence of progression to muscle invasive disease. Patients with persistent and/or recurrent high-grade NMIBC at the 6-month assessment will be discontinued from study therapy. Patients with progression to muscle invasion at any time will be discontinued from study therapy.

[m] Includes RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated.

[n] Laboratory results to be obtained within 14 days prior to the first dose of atezolizumab treatment.

[o] Includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.

[p] Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood).

[q] HIV testing to be performed in accordance with national and/or institutional guidelines. HBV DNA must be collected on or before Cycle 1, Day 1 in patients who have negative serology for hepatitis B surface antigen and positive serology for anti HCV.

[r] All patients will have a QuantiFERON® test done locally prior to inclusion into the study.

[s] 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 Cycle 1, Day 1 and at treatment completion/discontinuation.

[t] A sample of tumor tissue is required at study entry. Fresh tissue biopsy is preferred; however, an archival specimen may be submitted in lieu of fresh tissue if a tissue biopsy is contraindicated owing to patient safety or tumor tissue accessibility and the archival specimen was obtained within 2 months of study screening. The specimen may consist of a FFPE tumor tissue block (preferred) or at least 10 unstained, serial sections.

[u] See Appendix 5 for a detailed schedule of sample collection timepoints. Plasma PD biomarker, whole blood PBMC, urine biomarker, and whole blood FACS analysis will be performed at disease progression. Post-atezolizumab dose samples should be collected 30 ± 10 minutes after the end of atezolizumab infusion.

[v] Atezolizumab will be administered by IV infusion. During BCG Induction Course (12 weeks), patients receive atezolizumab 1200 mg IV q3w for a total of four doses.

Appendix 2
Schedule of Assessments: Cohorts 1b, 2, and 3 (cont.)

During BCG Maintenance Course 1 (12 weeks), patients will receive atezolizumab 1200 mg IV q3w for a total of four doses. During BCG Maintenance Course 2–5 (each 24 weeks), patients receive atezolizumab 1200 mg IV q3w for a total of eight doses per course. The maximum treatment duration is 96 weeks or 32 cycles, whichever occurs first.

[w] BCG will be administered intravesically. During BCG Induction Course (12 weeks), patients will receive BCG at the assigned dose weekly for a total of six doses. During BCG Maintenance Course 1 (12 weeks), patients receive BCG at the assigned dose weekly for a total of three doses.

During BCG Maintenance Courses 2–5 (each 24 weeks), patients receive BCG at the assigned dose weekly for a total of three doses per course. In the absence of unacceptable toxicity or compelling evidence of disease progression, patients deriving clinical benefit may be offered continued study treatments for up to 24 months (in total).

[x] All patients will undergo a mandatory tumor biopsy sample collection at 6 months (prior to Cycle 9 of atezolizumab). Biopsy must be scheduled 14–21 days prior to BCG administration. Fresh tissue biopsies will also be obtained as clinically indicated (e.g., if patient experiences signs of progression. Mandatory fresh tissue biopsies should include any foci of disease (if present) as well as template biopsies obtained from all quadrants of the bladder. Regions of the template biopsies should include the trigone, left lateral wall, right lateral wall, posterior wall, and dome. Bladder Map template (Appendix 11) should be used to document the approximate size and location of any abnormalities, as well as the approximate location of template biopsies. Additional tissue biopsies may also be obtained over the course of the study to evaluate disease per investigator assessment.

[y] Primary assessment of tumor will be with cystoscopy and urine cytology. Tumor response assessment will occur every 12 weeks for the first 2 years, and every 24 weeks thereafter (or as clinically appropriate) until 5 years, and then yearly. Cystoscopy that falls prior to BCG should be performed at least 14 days prior to BCG administration. White-light cystoscopy, narrow band imaging cystoscopy, or fluorescent (blue-light) cystoscopy will be acceptable for baseline assessment. The same methodology used to assess disease sites at screening should be used throughout the study except when medically contraindicated (e.g., the same cystoscopy protocol and urine examination). All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Random biopsies must include all four quadrants of the bladder. The same evaluator should perform assessments if possible to ensure internal consistency across visits. Bladder Map template (Appendix 11) should be used to document the approximate size and location of any abnormalities, as well as the approximate location of any biopsies performed. For all patients, additional evaluation (imaging, exam under anesthesia, biopsies) should be obtained as clinical indicated or if progression is suspected, performed at investigator discretion for any of the following circumstances:

- Abnormal cystoscopy
- Positive urine cytology
- Two sequential suspicious/indeterminate urine cytology specimens

[z] Patients with recurrent low-grade papillary disease will be required to undergo resection with TURBT (unless medically contraindicated) and may continue in the study and receive study treatment. Patients with persistent and/or recurrent high-grade NMIBC without progression at 12 weeks may continue in the study provided there is no evidence of progression to muscle invasive disease. Patients with persistent and/or recurrent high-grade NMIBC at the 6-month assessment will be discontinued from study therapy. Patients with progression to muscle invasion at any time will be discontinued from study therapy.

[aa] Health-related quality of life will be assessed using the EORTC QLQ-C30 and EORTC QLQ-NMIBC24.

Appendix 2
Schedule of Assessments: Cohorts 1b, 2, and 3 (cont.)

[bb] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to informed consent should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

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

[dd] All patients will be followed for survival and subsequent anti-cancer therapy beginning 6 months after the treatment completion/discontinuation visit. Survival and subsequent anti-cancer therapy follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits every 6 months (± 1 month) until loss to follow-up, withdrawal of consent, or study termination by the Sponsor, for a maximum of 5 years after enrollment. Request to withdraw from follow-up must be documented in the source documents and signed by the investigator. If the patient withdraws from treatment but not from follow-up, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

[ee] See Appendix 5 for details of the pharmacodynamic sampling schedule.

[ff] Acquisition of urine biomarker samples will be performed prior to administration of study drugs.

Appendix 3
BCG and Atezolizumab Treatment and Tumor Assessment Calendar for Study Weeks 0–108: Cohorts 1B, 2, and 3

Week on Study	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Study Month													3												6						
Atezolizumab Cycle # (Day 1)[a,b]	1			2			3			4			5			6			7			8			9			10			11
BCG Administration [b,c]	x	x	x	x	x	x							x	x	x										x	x	x				
Cystoscopy/ Cytology [d]											x												x								
Upper Tract Imaging [b,e]																									x						

Week on Study	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Study Month																						12								
Atezolizumab Cycle # (Day 1) [a,b]			12			13			14			15			16			17			18			19			20			21
BCG Administration [b,c]																		x	x	x										
Cystoscopy/ Cytology [d]						x										x														x
Upper Tract Imaging [b,e]																														

Appendix 3
BCG and Atezolizumab Treatment and Tumor Assessment Calendar for Study Weeks 0–108: Cohorts 1B, 2 and 3 (cont.)

Week on Study	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90
Study Month																		18												
Atezolizumab Cycle # (Day 1) [a,b]			22			23			24			25			26			27			28			29			30			31
BCG Administration [b,c]												x	x	x																
Cystoscopy/ Cytology [d]										x														x						
Upper Tract Imaging [b,e]																								x						

Week on Study	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108 [f]
Study Month														24				
Atezolizumab Cycle # (Day 1) [a,b]			32															
BCG Administration [b,c]						x	x	x										
Cystoscopy/ Cytology [d]				x														x
Upper Tract Imaging [b,e]																		

Appendix 3
BCG and Atezolizumab Treatment and Tumor Assessment Calendar for Study Weeks 0–108: Cohorts 1B, 2 and 3 (cont.)

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[a] Atezolizumab will be administered by IV infusion. During BCG Induction Course (12 weeks), patients receive atezolizumab 1200 mg IV q3w for a total of four doses. During BCG Maintenance Course 1 (12 weeks), patients will receive atezolizumab 1200 mg IV q3w for a total of four doses. During BCG Maintenance Course 2–5 (each 24 weeks), patients receive atezolizumab 1200 mg IV q3w for a total of eight doses per course. The maximum treatment duration is 96 weeks or 32 cycles, whichever occurs first.

[b] All visits must occur within ± 3 days from the scheduled date unless otherwise noted.

[c] BCG will be administered intravesically. During BCG Induction Course (12 weeks), patients will receive BCG at the assigned dose weekly for a total of six doses. During BCG Maintenance Course 1 (12 weeks), patients receive BCG at the assigned dose weekly for a total of three doses. During BCG Maintenance Courses 2–5 (each 24 weeks), patients receive BCG at the assigned dose weekly for a total of three doses per course.

[d] All assessments involving cystoscopy and urine cytology will be performed within 21 days prior to atezolizumab treatment and must occur 14–21 days prior to BCG dosing (for patients receiving BCG) unless otherwise specified. All patients will undergo a mandatory tumor biopsy sample collection at 6 months (prior to Cycle 9 of atezolizumab). Biopsy must be scheduled 14–21 days prior to BCG administration. Fresh tissue biopsies will also be obtained as clinically indicated (e.g., if patient experiences signs of progression). Mandatory fresh tissue biopsies should include any foci of disease (if present) as well as template biopsies obtained from all quadrants of the bladder. Regions of the template biopsies should include the trigone, left lateral wall, right lateral wall, posterior wall, and dome. Additional tissue biopsies may also be obtained over the course of the study to evaluate disease per investigator assessment.

[e] Baseline upper urinary tract imaging with CT urography, intravenous pyelogram, renal ultrasound with retrograde pyelogram, ureteroscopy or MRI urogram. Pelvic CT before TURBT may be considered but is not required. Assessment should be within 28 days prior to starting study treatment. Upper tract imaging using the same modality as was used at baseline should be performed at the 6-month (atezolizumab Cycle 9, Day 1) and 18-month (atezolizumab Cycle 29, Day 1) assessments, and then annually as indicated.

[f] The 2-year timepoint falls between Week 96 and Week 108 cystoscopy/cytology assessments. The Week 108 cystoscopy/cytology assessment should be performed and then the every 24 week assessment schedule should be followed after the Week 108 UC assessment, until 5 years.

Appendix 4
Schedule of Pharmacodynamic, Pharmacokinetic and Biomarker Assessments: Cohort 1A

Visit [a]	Timepoint	Sample Type
Study Week 0/ Atezolizumab Cycle 1	Pre-atezolizumab dose	Serum atezolizumab PK
		Serum atezolizumab ATA
		Plasma PD biomarker
		Whole blood TruCulture®
		Whole blood PBMC
		Urine Biomarker
		Whole blood FACS
	Post-atezolizumab dose [b]	Serum atezolizumab PK
Study Week 3/ Atezolizumab Cycle 2	Pre-atezolizumab dose	Serum atezolizumab PK
		Serum atezolizumab ATA
		Plasma PD biomarker
		Whole blood PBMC
		Urine Biomarker
		Whole blood FACS
Study Week 6/ Atezolizumab Cycle 3	Pre-atezolizumab dose	Serum atezolizumab PK
		Serum atezolizumab ATA
Study Week 9/ Atezolizumab Cycle 4	Pre-atezolizumab dose	Serum atezolizumab PK
		Serum atezolizumab ATA
		Plasma PD Biomarker
		Whole blood TruCulture®
		Whole blood PBMC
		Urine Biomarker
		Whole blood FACS
Study Weeks 21, 45, and 69 Atezolizumab Cycles 8, 16, and 24	Pre-atezolizumab dose	Serum atezolizumab PK
		Serum atezolizumab ATA
Disease Progression	NA	Plasma PD Biomarker
		Whole blood PBMC
		Urine Biomarker
		Whole blood FACS

Appendix 4
Schedule of Pharmacodynamic, Pharmacokinetic and Biomarker Assessments: Cohort 1A (cont.)

Visit [a]	Timepoint	Sample Type
Atezolizumab treatment completion/discontinuation visit [c]	NA	Serum atezolizumab PK
		Serum atezolizumab ATA
		Plasma PD biomarker
		Whole blood PBMC
		Urine Biomarker
		Whole blood FACS
120 days ± 30 days after last atezolizumab dose [d]	NA	Serum atezolizumab PK
		Serum atezolizumab ATA

ATA = anti-therapeutic antibody; FACS = fluorescence-activated cell sorting; NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic; PBMC = peripheral blood mononuclear cells.

Note: Each atezolizumab cycle is 3 weeks. All pre-atezolizumab PK, ATA, and PD sample collection will be just prior to study treatment administration on the specified day.

[a] For each specified visit, samples should be collected on Day 1 of each cycle.

[b] Post-atezolizumab dose samples should be collected 30 ± 10 minutes after the end of atezolizumab infusion.

[c] PK, ATA, Plasma PD biomarker samples, urine biomarker, whole blood PBMC, and whole blood FACS will be obtained from patients at the time of atezolizumab treatment completion or discontinuation.

[d] A sample will be obtained 120 days (± 30 days) after the final dose of atezolizumab, unless the patients has withdrawn consent of is lost to follow-up.

Appendix 5
Schedule of Pharmacodynamic and Pharmacokinetic Assessments: Cohorts 1B, 2 and 3

Visit [a]	Timepoint	Sample Type
BCG Induction		
Study Week 0/ Atezolizumab Cycle 1	Pre-atezolizumab dose	Serum atezolizumab PK
		Serum atezolizumab ATA
		Plasma PD biomarker
		Whole blood TruCulture®
		Whole blood PBMC
		Urine Biomarker
		Whole blood FACS
	Post-atezolizumab dose [b]	Serum atezolizumab PK
Study Week 3/ Atezolizumab Cycle 2	Pre-atezolizumab dose	Serum atezolizumab PK
		Serum atezolizumab ATA
		Plasma PD biomarker
		Whole blood PBMC
		Urine Biomarker
		Whole blood FACS
Study Week 6/ Atezolizumab Cycle 3	Pre-atezolizumab dose	Serum atezolizumab PK
		Serum atezolizumab ATA
Study Week 9/ Atezolizumab Cycle 4	Pre-atezolizumab dose	Serum atezolizumab PK
		Serum atezolizumab ATA
		Plasma PD Biomarker
		Whole blood TruCulture®
		Whole blood PBMC
		Urine Biomarker
		Whole blood FACS
BCG Maintenance Course 1		
Study Week 21/ Atezolizumab Cycle 8	Pre-atezolizumab dose	Serum atezolizumab PK
		Serum atezolizumab ATA

Appendix 5
Schedule of Pharmacodynamic and Pharmacokinetic Assessments: Cohorts 1B, 2 and 3 (cont.)

Visit [a]	Timepoint	Sample Type
BCG Maintenance Courses 2–5		
Study Weeks 45 and 69/ Atezolizumab Cycles 16 and 24	Pre-atezolizumab dose	Serum atezolizumab PK
		Serum atezolizumab ATA
Disease Progression	NA	Plasma PD Biomarker
		Whole blood PBMC
		Urine Biomarker
		Whole blood FACS
Atezolizumab treatment completion/discontinuation visit [c]	NA	Serum atezolizumab PK
		Serum atezolizumab ATA
		Plasma PD biomarker
		Whole blood PBMC
		Urine Biomarker
		Whole blood FACS
120 days ± 30 days after last Atezolizumab dose [d]	NA	Serum atezolizumab PK
		Serum atezolizumab ATA

ATA = anti-therapeutic antibody; BCG = bacille Calmette-Guérin; FACS = fluorescence-activated cell sorting; NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic; PBMC = peripheral blood mononuclear cells.

Note: Each atezolizumab cycle is 3 weeks. All pre-atezolizumab PK, ATA, and PD sample collection will be just prior to study treatment administration on the specified day.

[a] For each specified visit, samples should be collected on Day1 of each cycle.

[b] Post-Atezolizumab dose samples should be collected 30 ± 10 minutes after the end of atezolizumab infusion.

[c] PK, ATA, Plasma PD biomarker samples, Urine biomarker, Whole Blood PBMC, and Whole Blood FACS will be obtained from patients at the time of atezolizumab treatment completion or discontinuation.

[d] A sample will be obtained 120 days (± 30 days) after the final dose of atezolizumab, unless the patients has withdrawn consent or is lost to follow-up.

Appendix 6
Preexisting Autoimmune Diseases

Acute disseminated encephalomyelitis	Dysautonomia	Ord's thyroiditis
Addison's disease	Epidermolysis bullosa acquista	Pemphigus
Ankylosing spondylitis	Gestational pemphigoid	Pernicious anemia
Antiphospholipid antibody syndrome	Giant cell arteritis	Polyarteritis nodusa
Aplastic anemia	Goodpasture's syndrome	Polyarthritis
Autoimmune hemolytic anemia	Graves' disease	Polyglandular autoimmune syndrome
Autoimmune hepatitis	Guillain-Barré syndrome	Primary biliary cirrhosis
Autoimmune hypoparathyroidism	Hashimoto's disease	Psoriasis
Autoimmune hypophysitis	IgA nephropathy	Reiter's syndrome
Autoimmune myocarditis	Inflammatory bowel disease	Rheumatoid arthritis
Autoimmune oophoritis	Interstitial cystitis	Sarcoidosis
Autoimmune orchitis	Kawasaki's disease	Scleroderma
Autoimmune thrombocytopenic purpura	Lambert-Eaton myasthenia syndrome	Sjögren's syndrome
Behcet's disease	Lupus erythematosus	Stiff-Person syndrome
Bullous pemphigold	Lyme disease – chronic	Takayasu's arteritis
Chronic fatigue syndrome	Mooren's ulcer	Ulcerative colitis
Chronic inflammatory demyelinating polyneuropathy	Morphea	Vitiligo
Chung-Strauss syndrome	Multiple sclerosis	Vogt-Kovanagi-Harada disease
Crohn's disease	Myasthenia gravis	Wegener's granulomatosis
Dermatomyositis	Neuromyotonia	
	Opsoclonus myoclonus syndrome	
	Optic neuritis	

Note: Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Please contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Appendix 7
Eastern Cooperative Oncology Group
Performance Status Scale

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

Appendix 8
Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

1. Stop the study drug infusion.
2. Maintain an adequate airway.
3. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
4. Continue to observe the patient and document observations.

Appendix 9
EORTC QLQ-C30 Questionnaire

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): 31 ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

	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 9
EORTC QLQ-C30 Questionnaire (cont.)

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

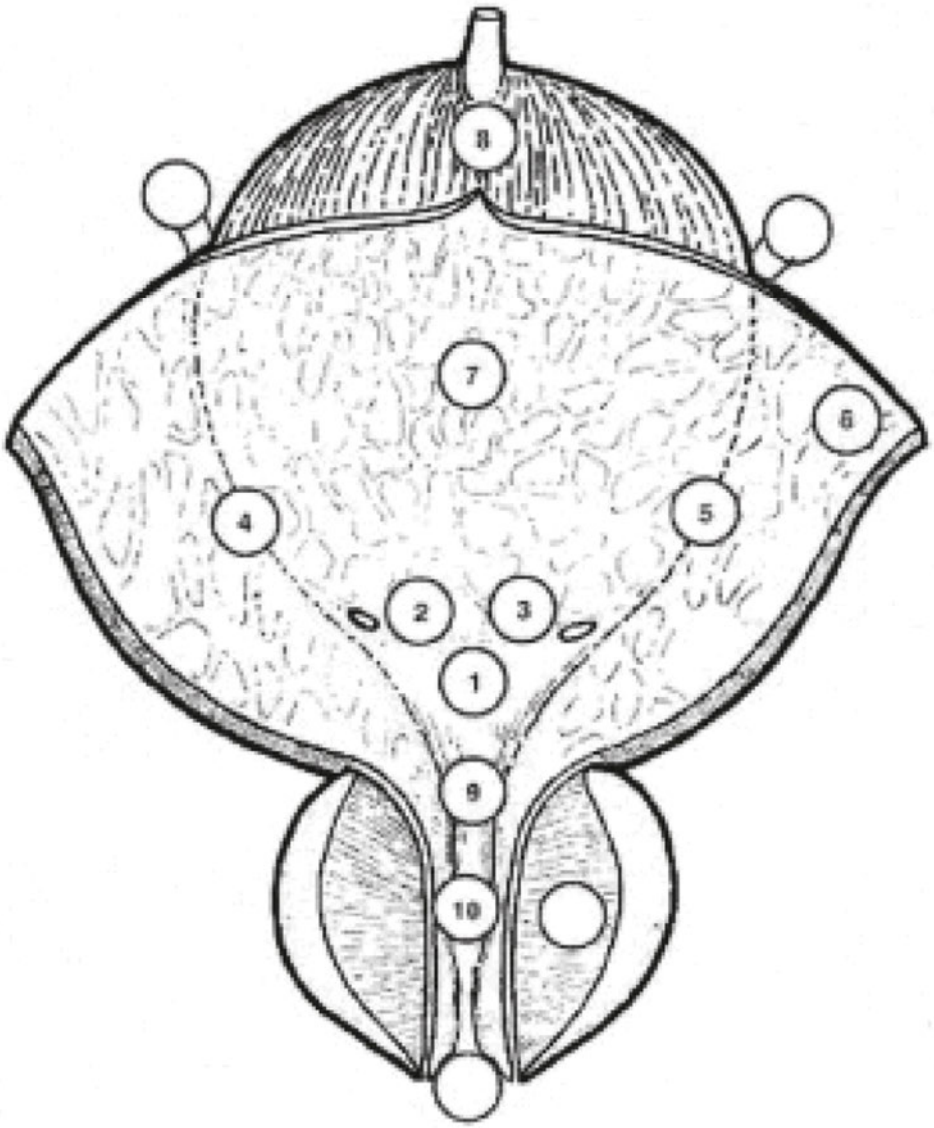
Appendix 10
EORTC QLQ-NMIBC24 Questionnaire

EORTC QLQ–NMIBC24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had to urinate frequently during the day?	1	2	3	4
32. Have you had to urinate frequently at night?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house, because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Have you had pain or a burning feeling when urinating?	1	2	3	4
38. Did you have a fever?	1	2	3	4
39. Did you feel ill or unwell?	1	2	3	4
40. Did you have trouble arranging your life around the repeated bladder treatment appointments (cystoscopies or instillations)?	1	2	3	4
41. Did you worry about having repeated bladder treatments (cystoscopies or instillations)?	1	2	3	4
42. Were you worried about your health in the future?	1	2	3	4
43. Did you worry about the results of examinations and tests?	1	2	3	4
44. Did you worry about possible future treatments?	1	2	3	4
45. Did you have a bloated feeling in your abdomen?	1	2	3	4
46. Have you had flatulence or gas?	1	2	3	4
47. To what extent were you interested in sex?	1	2	3	4
48. To what extent were you sexually active (with or without sexual intercourse)?	1	2	3	4
49. For men only: Did you have difficulty gaining or maintaining an erection?	1	2	3	4
50. For men only: Did you have ejaculation problems (e.g. dry ejaculation)?	1	2	3	4
51. Have you felt uncomfortable about being sexually intimate?	1	2	3	4
52. Have you worried that you may contaminate your partner during sexual contact with the bladder treatment you have been receiving?	1	2	3	4
53. To what extent was sex enjoyable for you?	1	2	3	4
54. For Women only: did you have a dry vagina or other problems during intercourse?	1	2	3	4

Appendix 11
Bladder Map



1 = Trigone
2 = Right ureteral orifice
3 = Left ureteral orifice
4 = Right wall
5 = Left wall
6 = Anterior wall
7 = Posterior wall
8 = Dome
9 = Neck
10 – Posterior urethra

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

Although most *immune-mediated* adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, *immune-mediated* toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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 $\geq$1 month to $\leq$10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for $>$12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for $>$12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for $>$12 weeks if the Medical Monitor agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

MANAGEMENT GUIDELINES

PULMONARY EVENTS

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

LFT = liver function 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 2 Management Guidelines for Hepatic Events (cont.)

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

LFT = liver function 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

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.

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

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.

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events

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

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

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

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

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

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-MEDIATED MYOCARDITIS

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

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated myocarditis, Grade 3–4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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 7.

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 7 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.*

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

Grade 2 [a] *Fever [b] with hypotension not requiring vasopressors* ***and/or*** *Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by*	• I*mmediately* 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.* [e] • *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.* • *If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered.* • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs *and/or CRS.* • *If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.*

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

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. [f] • *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. [e]* • *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. [f]* • *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. [e] For patients who are refractory to anti-cytokine therapy, experimental treatments [g] may be considered at the discretion of the investigator and in consultation with the Medical Monitor.* • *Hospitalize patient until complete resolution of symptoms.*

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table7 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: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] *Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE 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] *There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.*

[f] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. *For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after consulting the Medical Monitor and considering the benefit–risk ratio.*

[g] *Refer to Riegler et al. (2019) for information on experimental treatments for CRS.*

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

IMMUNE-MEDIATED MENINGOENCEPHALITIS

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

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

RENAL EVENTS

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. *Renal* function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies

(including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-MEDIATED MYOSITIS

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

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 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 agreed upon by the investigator and the Medical Monitor.*

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

[a] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

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

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

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

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

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 ×10^9/L (100,000/μL)*
  - *ANC <1.0 ×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 ≤181 ×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.

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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 and/or an immunosuppressive agent.* • *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.*

HLH =hemophagocytic lymphohistiocytosis; MAS =macrophage activation syndrome.

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