# PROTOCOL

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| **TITLE:** | **A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) VERSUS OBSERVATION AS ADJUVANT THERAPY IN PATIENTS WITH HIGH-RISK MUSCLE-INVASIVE UROTHELIAL CARCINOMA AFTER SURGICAL RESECTION** |
| **PROTOCOL NUMBER:** | WO29636 |
| **VERSION NUMBER:** | 10 |
| **EUDRACT NUMBER:** | 2014-005603-25 |
| **IND NUMBER:** | 120827 |
| **NCT NUMBER:** | NCT02450331 |
| **TEST PRODUCT:** | Atezolizumab (MPDL3280A; RO5541267) |
| **MEDICAL MONITOR:** | [redacted], M.D. |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **DATE FINAL:** | Version 1: 1 April 2015 |
| **DATES AMENDED:** | Version 2: 2 June 2015<br>Version 3 (UK Only): 28 July 2015<br>Version 4: 24 September 2015<br>Version 5: 4 April 2016<br>Version 6: 14 July 2016<br>Version 7: 4 October 2017<br>Version 8: 19 November 2018<br>Version 9: 3 February 2020<br>Version 10: See electronic date stamp below. |

## PROTOCOL AMENDMENT APPROVAL

| Date and Time (UTC) | Title | Approver's Name |
|---|---|---|
| 13-Apr-2020 22:30:49 | Company Signatory | [redacted] |

## PROTOCOL AMENDMENT, VERSION 10: RATIONALE

Protocol WO29636 has been amended primarily to allow more flexibility on the timing of disease assessment visits following the primary analysis. Changes to the protocol, along with a rationale for each change, are summarized below:

- Following the primary analysis, patients who are in Years 1–3 or Years 2–3, as applicable, of the study and are in disease recurrence follow-up may now be assessed for recurrence every 24 weeks (Sections 3.1, 4.5.5, 4.6.1, and Appendix 1).
- The requirement to have a confirmatory tumor biopsy at the time of disease recurrence has been made optional (Sections 3.1, 3.3.8, 4.5.5, 4.5.7.2, and Appendix 1).
- EQ-5D-5L assessments are no longer required for patients who are in disease recurrence follow-up or for patients who have had a DFS event (Section 4.5.10 and Appendix 1).
- The survival follow-up schedule has been updated to further clarify that follow-up and clinic visits will be approximately every 3 months from the completion or discontinuation of the treatment/observation period, and that patients who have completed the treatment or observation phase and continue in disease recurrence follow-up should have survival follow-up in parallel approximately every 3 months (Section 4.6.4 and Appendix 1).

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

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return a copy of the form to the Sponsor or their designee. Contact details will be provided to the investigator prior to the study start. Please retain the original copy for your study files.

## PROTOCOL SYNOPSIS

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| **TITLE:** | **A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) VERSUS OBSERVATION AS ADJUVANT THERAPY IN PATIENTS WITH HIGH-RISK MUSCLE-INVASIVE UROTHELIAL CARCINOMA AFTER SURGICAL RESECTION** |
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| **NCT NUMBER:** | NCT02450331 |
| **TEST PRODUCT:** | Atezolizumab (MPDL3280A; RO5541267) |
| **PHASE:** | III |
| **INDICATION:** | Muscle-invasive urothelial carcinoma |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

### Objectives

**Efficacy Objectives:**

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of adjuvant atezolizumab treatment in patients with muscle-invasive urothelial carcinoma (UC), as measured by disease-free survival (DFS)

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of adjuvant atezolizumab treatment, as measured by overall survival (OS)
- To evaluate the efficacy of adjuvant atezolizumab treatment, as measured by disease-specific survival (DSS)
- To evaluate the efficacy of adjuvant atezolizumab treatment, as measured by distant metastasis-free survival (DMFS)
- To evaluate the efficacy of adjuvant atezolizumab treatment, as measured by non-urinary tract recurrence-free survival (NURFS)

**Safety Objectives**

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab in the adjuvant setting
- To evaluate the incidence of anti-therapeutic antibodies (ATAs) against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

**Pharmacokinetic Objective**

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

- To characterize the pharmacokinetics of atezolizumab

**Patient-Reported Outcome Objective**

The patient-reported outcome (PRO) objective for this study is as follows:

- To assess health status as measured by the EuroQol 5-dimension, 5-level version (EQ-5D-5L) questionnaire

**Exploratory Objective**

The exploratory objective for this study is as follows:

- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease recurrence

## Study Design

**Description of Study**

Study WO29636 is a global Phase III, open-label, randomized, controlled trial designed to evaluate the efficacy and safety of adjuvant treatment with atezolizumab compared with observation in patients with muscle-invasive UC, who are at high risk for recurrence following resection.

Male and female patients aged ≥ 18 years with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 who have histologically confirmed muscle-invasive UC (also termed TCC) of the bladder or upper urinary tract (i.e., renal pelvis or ureters) are eligible. Patients with upper urinary tract urothelial carcinoma (UTUC) will be limited to no more than approximately 10% of the study population.

Patients with bladder as the site of primary involvement must have undergone radical cystectomy with lymph node dissection. Patients with UTUC as the site of primary involvement must have undergone radical nephroureterectomy (RNU) with excision of the bladder cuff regardless of the location of the tumor in the upper urinary tract. RNU must include lymph node dissection.

Patients who have received prior neoadjuvant chemotherapy are eligible, but must have tumor staging of ypT2–4a or ypN+ (ypT2-4 or ypN+ for patients with UTUC) and M0 at pathological examination of the surgical resection specimen. Patients who have not received prior neoadjuvant chemotherapy must be ineligible for or declined treatment with cisplatin-based adjuvant chemotherapy and have tumor staging of pT3–4a or pN+ (pT3-4 or pN+ for patients with muscle-invasive UTUC) and M0.

Tumor specimens from surgical resection (i.e., radical cystectomy, RNU, or lymph node dissection) from patients who have signed the Informed Consent Form will be evaluated for PD-L1 expression by IHC. Only patients whose tumors have sufficient amounts of viable tumor and are evaluable for PD-L1 expression as confirmed by a central pathology laboratory prior to enrollment of the patient in the study will be eligible.

Patients will be randomized to one of the following arms in a 1:1 ratio:

- Arm A (experimental arm): atezolizumab 1200 mg q3w
- Arm B (control arm): observation

Randomization will be stratified by the following factors:

- Number of lymph nodes resected (< 10 vs. ≥ 10)
- Nodal status (positive vs. negative)
- Tumor stage after surgical resection (≤ pT2 vs. pT3/pT4)
- PD-L1 IHC status (IHC score of IC0/1 vs. IHC score of IC2/3)
- Prior neoadjuvant chemotherapy (yes vs. no)

Randomization must occur within 14 weeks after surgical resection of the primary tumor and study drug administration should begin within 7 calendar days after randomization.

For patients in Arm A, atezolizumab will be administered intravenously (IV) on Day 1 of each 21-day cycle for 16 cycles (up to 1 year). In Arm B, patients will continually undergo observation starting on Day 1 of each 21-day cycle for 16 cycles (up to 1 year). Treatment/observation will be discontinued in the event of disease recurrence, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor.

To ensure the same frequency of study assessments between the treatment arms, including assessments for disease recurrence and safety, patients in Arm B will be required to undergo q3w medical contacts for assessments during the first year, which will consist of formal clinic visits alternating with clinical contacts (either via telephone call or formal outpatient clinic visit) for symptom and adverse event assessment.

Patients in the control arm will not be allowed to cross over to receive atezolizumab treatment within this study.

All patients will undergo scheduled assessments for tumor recurrence at baseline and every 12 weeks (approximately every 4 cycles) in the first year following randomization. Upon completion of the treatment/observation period, surveillance for tumor recurrence will be performed every 12 weeks for Years 2–3; every 24 weeks for Years 4–5; and at Year 6 (approximately 48 weeks after the last assessment in Year 5). *After the primary analysis, patients in Years 2–3 of the study may be assessed for tumor recurrence every 24 weeks.* In the absence of a DFS event (defined as any of the following: local [pelvic] recurrence of UC; upper urinary tract or urethral recurrence of UC; distant metastasis of UC; or death from any cause), surveillance for tumor recurrence should continue regardless of whether patients start new anticancer therapy, until withdrawal of consent, loss to follow-up, or study termination by the Sponsor, whichever occurs first. For patients with muscle-invasive bladder cancer (MIBC), surveillance for tumor recurrence will include physical examination, laboratory evaluation, and imaging studies of the chest, abdomen, upper urinary tracts, and pelvis. Disease recurrence will be as determined by the investigator based on radiographic evidence (visual appearance of UC with histological confirmation is acceptable for recurrence in bladder). For patients with UTUC, surveillance for tumor recurrence must include physical examination, cystoscopy, urine cytology and imaging studies of the chest, abdomen, and pelvis. A confirmatory tumor biopsy is mandatory at the time of disease recurrence. Cases for which biopsy results definitively rule out recurrence of UC will not be considered as disease recurrence for this study. *After the primary analysis, a confirmatory tumor biopsy is optional at the time of disease recurrence.*

Safety assessments will include the incidence, nature, and severity of adverse events, changes in vital signs, and laboratory abnormalities graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0. Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of ATAs to atezolizumab. A sample of archived tumor tissues, as well as serum and plasma samples, will be collected for future exploratory biomarker assessments.

An external independent Data Monitoring Committee (iDMC) will evaluate safety data according to policies and procedures detailed in an iDMC Charter.

**Number of Patients**

Approximately 800 patients will be enrolled in the study.

**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 muscle-invasive UC (also termed TCC) of the bladder or upper urinary tract (i.e., renal pelvis or ureters)

  Patients with mixed histologies are required to have a dominant transitional cell pattern.
- TNM classification (UICC/AJCC 7th edition) at pathological examination of surgical resection specimen as follows:

  For patients treated with prior neoadjuvant chemotherapy: tumor stage of ypT2 -4a or ypN+ (ypT2-4 or ypN+ for patients with UTUC) and M0

For patients who have not received prior neoadjuvant chemotherapy: tumor stage of pT3–4a or pN+ (pT3-4 or pN+ for patients with UTUC) and M0

- Surgical resection of muscle-invasive UC of the bladder, or UTUC upper tract

  For patients with MIBC, radical cystectomy may be performed by the open, laparoscopic, or robotic approach. Cystectomy must include bilateral lymph node dissection, the extent of which will be at the discretion of the treating surgeon but optimally should extend at a minimum from the mid common iliac artery proximally to Cooper's ligament distally, laterally to the genitofemoral nerve, and inferiorly to the obturator nerve. The method of urinary diversion for patients undergoing cystectomy will be at the discretion of the surgeon and choice of the patient.

  Patients with a negative surgical margin (i.e., R0 resection) or with carcinoma in situ (CIS) at the distal ureteral or urethral margin will be eligible.

  Patients with a positive R2 margin (which is defined as a tumor identified at the inked perivesical fat margin surrounding the cystectomy specimen) or R1 margin (which is defined as evidence of microscopic disease identified at the tumor margin), except for CIS at the distal ureteral or urethral margin, will be excluded.

  For patients with UTUC, RNU with excision of the bladder cuff is required and may be performed by the open or laparoscopic approach. RNU must include lymph node dissection (LND), the extent of which will be at the discretion of the treating surgeon but optimally should include the para-aortic, paracaval or interaortocaval nodes from the renal hilum to the inferior mesenteric artery in renal pelvis and proximally ureteral tumors, or nodes from the renal hilum to the bifurcation of the common iliac artery and ipsilateral pelvic nodes in mid and lower ureteral tumors, respectively.

  Patients must have a negative surgical margin (i.e., R0 resection). Patients with a positive R1 or R2 surgical margin will be excluded.

- Patients who have not received prior platinum-based neoadjuvant chemotherapy, have refused, or are ineligible ("unfit") for cisplatin-based adjuvant chemotherapy

  Patients who have received at least two cycles of a platinum-containing regimen will be considered as those who have received prior neoadjuvant chemotherapy.

  Cisplatin ineligibility is defined by any one of the following criteria:

  Impaired renal function (glomerular filtration rate [GFR] $<$ 60 mL/min); GFR should be assessed by direct measurement (i.e., creatinine clearance or ethyldiaminetetra-acetate) or, if not available, by calculation from serum/plasma creatinine (Cockcroft-Gault formula)

  A hearing loss (measured by audiometry) of 25 dB at two contiguous frequencies

  Grade 2 or greater peripheral neuropathy (i.e., sensory alteration or parasthesis including tingling)

  ECOG performance status of 2

- Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens from surgical resection (i.e., radical cystectomy, nephroureterectomy, or lymph node dissection) in paraffin blocks (blocks preferred) or at least 15 unstained slides, with an associated pathology report, for central testing and determined to be evaluable for tumor PD-L1 expression prior to study enrollment

  Patients with fewer than 15 unstained slides available at baseline (but no fewer than 10) may be eligible following discussion with Medical Monitor.

  Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.

Tumor tissue of bladder or upper tract should be of good quality based on total and viable tumor content and must contain a muscle invasive component (i.e., T2 or greater) of the tumor as verified by local pathology review. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation. In situations where multiple specimens were received from different sites or at different times, the score from the surgical resection of the primary tumor or lymph node dissection specimen will be used for both primary and secondary analyses.

- Muscle-invasive UC with PD-L1 expression per IHC prospectively determined on the surgical resection or lymph node dissection tumor specimens by a central laboratory
- Absence of residual disease and absence of metastasis, as confirmed by a negative baseline computed tomography (CT) or magnetic resonance imaging (MRI) scan of the pelvis, abdomen, and chest no more than 4 weeks prior to randomization.

  For patients with MIBC, imaging of the upper urinary tracts must include one or more of the following: intravenous pyelogram (IVP), CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy or MRI urogram, and must be completed no more than 4 weeks prior to randomization.

  For patients with UTUC, cystoscopy and urine cytology must be completed no more than 4 weeks prior to randomization, however upper tract imaging is not needed.

  Other examinations should be performed as clinically indicated.

  For patients with both primary MIBC and primary UTUC, imaging of the upper urinary tracts, cystoscopy, and urine cytology is not required.
- Full recovery from cystectomy or nephroureterectomy within 14 weeks following surgery
- ECOG performance status of $\leq 2$
- Life expectancy $\geq 12$ weeks
- Adequate hematologic and end-organ function, as defined by the following laboratory results obtained within 14 days prior to the first study treatment:

  ANC $\geq 1500$ cells/$\mu$L (without granulocyte colony–stimulating factor support within 2 weeks prior to Cycle 1, Day 1)

  WBC counts $> 2500/\mu L$

  Lymphocyte count $\geq 300/\mu L$

  Platelet count $\geq 100{,}000/\mu L$ (without transfusion within 2 weeks prior to Cycle 1, Day 1)

  Hemoglobin $\geq 9.0$ g/dL

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

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

  Serum bilirubin $\leq 1.0 \times$ ULN

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

  PTT/PT $\leq 1.5 \times$ ULN or INR $< 1.7 \times$ ULN

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

  Calculated creatinine clearance $\geq$ 20 mL/min (Cockcroft-Gault formula)

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 5 months after the last dose of atezolizumab, and agreement to 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 trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

**Exclusion Criteria**

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

**Cancer-Specific Exclusion Criteria:**

- Any approved anti-cancer therapy, including chemotherapy, or hormonal therapy within 3 weeks prior to initiation of study treatment

  Hormone-replacement therapy or oral contraceptives are allowed.

- Adjuvant chemotherapy or radiation therapy for UC following surgical resection

  Patients who have received primary chemoradiation for bladder preservation before cystectomy are eligible and will be treated as the same as patients who have received prior neoadjuvant chemotherapy.

  Postsurgical intrapelvic/intravesical chemotherapy or BCG is not allowed for patients with UTUC.

- Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days or five half-lives of the drug, whichever is longer, prior to enrollment

- Malignancies other than UC within 5 years prior to Cycle 1, Day 1

  Patients with high risk UTUC (defined as tumor stage ypT2–4a or ypN+) within 5 years prior to Cycle 1 Day 1 will be ineligible after the UTUC limit of approximately 10% has been met.

  Patients with localized low risk prostate cancer (defined as Stage $\leq$T2b, Gleason score $\leq 7$, and PSA at prostate cancer diagnosis $\leq 20$ ng/mL [if measured]) treated with curative intent and without prostate-specific antigen (PSA) recurrence are eligible.

  Patients with low risk prostate cancer (defined as Stage T1/T2a, Gleason score $\leq 7$ and PSA $\leq 10$ ng/mL) who are treatment-naive and undergoing active surveillance are eligible.

  Patients with malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death <5% at 5 years) are eligible provided they meet all of the following criteria:

  - Malignancy treated with expected curative intent (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent)
  - No evidence of recurrence or metastasis by follow-up imaging and any disease-specific tumor markers

**General Medical Exclusion Criteria:**

- Pregnancy or breastfeeding
- 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 or any component 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 antiphospholipid 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.

    Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen may be eligible for this study.
- 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
- Patients with active hepatitis B virus (HBV; chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

    Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBc Ab] and absence of HBsAg) are eligible. HBV DNA must be obtained in these patients prior to Cycle 1, Day 1.

    Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Active tuberculosis
- Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia

Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1

- Receipt of therapeutic oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1

    Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent 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

    Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction $< 50\%$ must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
- Major surgical procedure other than for diagnosis within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study
- Prior allogeneic stem cell or solid organ transplant

- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 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 through May in the Northern Hemisphere and approximately 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 randomization, during treatment or within 5 months following the last dose of atezolizumab (for patients randomized to atezolizumab).
- Any other disease, 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

**Medication-Related Exclusion Criteria:**

- Prior treatment with CD137 agonists or immune checkpoint–blockade therapies, including anti-CD40, anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including but not limited to interferons, IL-2) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to Cycle 1, Day 1
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1, or anticipated requirement for systemic immunosuppressive medications during the trial

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea, multiple doses for contrast allergy) may be enrolled in the study.

  The use of inhaled or low-dose (e.g., ≤ 10 mg/day prednisone) corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, and mineralocorticoids (e.g., fludrocortisone for adrenal insufficiency) and low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

**End of Study**

The end of the study as planned will occur when the required number of events for the final analysis of OS has occurred (projected to be approximately Month 95 from FPI). However, the Sponsor may decide to terminate the study at any time.

**Length of Study**

The study is expected to last approximately 8 years after the first patient is randomized.

## Outcome Measures

### Efficacy Outcome Measures

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

- Investigator-assessed DFS, defined as the time from randomization to the time of first occurrence of a DFS event, defined as any of the following:

  Local (pelvic) recurrence of UC (including soft tissue and regional lymph nodes)

  Urinary tract recurrence of UC (including all pathological stages and grades)

  Distant metastasis of UC

  Death from any cause

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

- OS, defined as the time from randomization to the date of death from any cause
- DSS, defined as the time from randomization to the date of death from UC per investigator assessment of cause of death

- DMFS, defined as the time from randomization to the date of diagnosis of distant (i.e., non-locoregional) metastases or death from any cause
- NURFS, defined as the time from randomization to the time of first occurrence of a NURFS event, defined as any of the following:

  Local (pelvic) recurrence of UC (including soft tissue and regional lymph nodes)

  Distant metastasis of UC

  Death from any cause

**Safety Outcome Measures**

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events graded according to NCI CTCAE v4.0
- Changes in vital signs and clinical laboratory results
- Incidence of ATA response to atezolizumab and potential correlation with PK, pharmacodynamic, safety, and efficacy parameters

**Pharmacokinetic Outcome Measures**

The PK outcome measures for this study are as follows:

- Maximum observed serum atezolizumab concentration ($C_{max}$) after infusion on Day 1 of Cycle 1
- Minimum observed serum atezolizumab concentration ($C_{min}$) prior to infusion on Day 1 of Cycles 1, 2, 3, and 4; every 8 cycles starting on Cycle 8; at treatment discontinuation; and at 120 days (±30 days) after the last dose of atezolizumab

**Patient-Reported Outcome Measure**

The PRO outcome measure for this study is as follows:

- EQ-5D-5L as a measure of patient-reported health status

**Exploratory Outcome Measures**

The exploratory outcome measures for this study are as follows:

- Status of tumor immune-related or disease type−related exploratory biomarkers in archival and/or freshly obtained tumor tissues and association with disease recurrence
- Status of exploratory biomarkers in plasma, whole blood, or serum (including but not limited to cytokines such as IL-6) collected before or during treatment with atezolizumab or at recurrence and association with disease recurrence

**Investigational Medicinal Products**

**Test Product (Investigational Drug)**

The dose level of atezolizumab to be tested in this study is 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) administered by IV infusion every 3 weeks (21 [±3] days) for 16 cycles or 1 year (whichever occurs first).

**Statistical Methods**

**Primary Analysis**

The primary efficacy endpoint is investigator-assessed DFS, defined as the time from randomization to the time of first occurrence of a DFS event, defined as any of the following: local (pelvic) recurrence of UC; urinary tract recurrence of UC; distant metastasis of UC; or death from any cause. Data for patients without a DFS event will be censored at the last date the patient was assessed to be alive and recurrence free as determined with radiographic evidence. Data for patients with no post-baseline disease assessment will be censored at the randomization date.

For United States registrational purposes, the primary efficacy endpoint of DFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with a DFS event who missed two or more scheduled assessments immediately prior to the DFS event will be censored at the last tumor assessment as determined with radiographic evidence prior to the missed visits. Type I error control will be applied to this analysis of DFS.

DFS will be analyzed in the ITT population. The following analyses will be performed for both DFS endpoints described above. DFS will be compared between treatment arms using the stratified log-rank test. The hazard ratio (HR) for recurrence or death will be estimated using a stratified Cox proportional hazards model and the 95% CI for the HR will be provided. The stratification factors will be the same as the randomization stratification factors; however, stratification factors may be combined for analysis purposes if necessary to minimize small stratum cell sizes. Combination of stratification factors, if any, would be specified in the Statistical Analysis Plan (SAP) prior to analysis. The stratification factors will be obtained from the IxRS at the time of randomization. Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate median DFS for each treatment arm; Kaplan-Meier curves will be produced. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median DFS for each treatment arm. The DFS rate at various timepoints (i.e., every 6 months after randomization) will be estimated by Kaplan-Meier methodology for each treatment arm, and the 95% CI will be calculated using Greenwood's formula.

The following additional analyses will be performed for both DFS endpoints described above:

- Analyses at landmark timepoints
- Subgroup analyses

**Determination of Sample Size**

Approximately 800 patients will be randomized in this study.

The type I error (alpha) for this study is 0.05 (two-sided). Type I error will be controlled for the primary endpoint of DFS and the key secondary endpoint of OS. To control the Type I error at alpha = 0.05 (two-sided) for DFS and OS endpoints, the treatment arms will be compared in a hierarchical fashion as follows: If the DFS analysis results (as defined for United States registrational purposes) are statistically significant at alpha = 0.05 (two-sided), then the analysis of OS will be performed at alpha = 0.05 (two-sided) and the interim analysis boundaries for OS will be calculated according to alpha = 0.05 (two-sided).

The analysis of the primary endpoint of DFS will take place when approximately 377 DFS events have occurred and at least 12 months after the last patient is enrolled have elapsed. The estimated number of events required for the analysis is based on the following assumptions:

- Two-sided log-rank test at the 0.05 significance level (two-sided)
- 80% power
- 1:1 randomization ratio
- Median DFS for the control (observation) arm of 20 months and estimated median DFS in the atezolizumab arm of 26.7 months (corresponding to a HR of 0.75)
- No interim analysis of DFS

Accrual of the planned 800 patients is projected to occur over 32 months, assuming a ramp-up period of 13 months to a projected accrual rate of 35 patients per month. On the basis of these assumptions, and the projected probability of loss to follow-up for DFS of approximately 32% over 24 months after enrollment, the required number of DFS events is projected to occur at Month 50 from the time the first patient is randomized. Also on the basis of these assumptions, it is projected that an observed HR of 0.82 or lower will result in a statistically significant difference between treatment arms (i.e., an HR of 0.82 will be the minimally detectable difference at the analysis; this corresponds to an improvement of 4.5 months in median DFS, from 20 months in the control [observation] arm to 24.5 months in the atezolizumab arm).

The final analysis of the secondary endpoint of OS will take place when approximately 428 deaths have occurred on the basis of the following assumptions:

- Two-sided log-rank test at the 0.05 significance level (two-sided)

- 80% power
- 1:1 randomization ratio
- Median OS for the control (observation) arm of 34 months and estimated median OS in the atezolizumab arm of 44.7 months (corresponding to HR of 0.76)
- Two interim analyses of OS

On the basis of these assumptions, the projected probability of loss to follow-up for OS of approximately 24% over 24 months after enrollment, and projected accrual, the required number of OS events for the final analysis of OS is projected to occur 95 months from the time the first patient is randomized. It is projected that an observed HR of 0.82 or lower will result in a statistically significant difference between treatment arms (i.e., an HR of 0.82 will be the minimally detectable difference at the analysis; this corresponds to an improvement of 7.4 months in median OS, from 34 months in the control [observation] arm to 41.4 months in the atezolizumab arm).

Two interim analyses of OS are planned.

**Interim Analyses**

No interim efficacy analyses of DFS are planned for this study.

A total of three analyses of OS will be performed by the Sponsor (two interim analyses and one final analysis). The final analysis of OS will be performed when approximately 428 deaths (54% of 800 patients) have occurred in the ITT population. On the basis of accrual projections and projected median OS for each treatment arm, the final analysis of OS is projected to occur 95 months from the time the first patient is randomized. The interim analysis boundaries for statistical significance at each interim analysis will be determined on the basis of the Lan-DeMets implementation of the O'Brien-Fleming use function.

The first interim analysis of OS will be performed at the time of the DFS analysis. On the basis of the projected median OS for each treatment arm and the projected time of the final analysis of DFS, it is projected that approximately 280 deaths (35% of 800 patients) will have occurred at the first interim analysis of OS, which corresponds to approximately 65% of the 428 deaths required for the final analysis of OS. It is projected that an observed HR of 0.74 or lower will result in a statistically significant difference between treatment arms at this analysis.

The second interim analysis of OS will be performed when approximately 342 deaths (43% of 800 patients) have occurred, which corresponds to 80% of the 428 deaths required for the final analysis of OS. The required number of OS events for the second interim analysis of OS is projected to occur 63 months from the time the first patient is randomized. It is projected that an observed HR of 0.78 or lower will result in a statistically significant difference between treatment arms at this analysis.

The interim analyses of OS will be performed by the Sponsor. The boundary for statistical significance at each interim analysis and the final analysis will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming use function. For example, with $\alpha = 0.05$ (two-sided) and using the two-sided log-rank test, if 280 deaths have occurred at the time of the first OS interim analysis, statistical significance will be declared $p \leq 0.011$; if 342 deaths have occurred at the time of the second OS interim analysis, statistical significance will be declared if $p \leq 0.021$; and if 428 deaths have occurred at the time of the final OS analysis, statistical significance will be declared if $p \leq 0.042$.

An iDMC will be convened to evaluate safety results approximately every 6 months after enrollment of the first patient until the analysis of the primary endpoint (DFS).

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ACCI | age-adjusted Charlson comorbidity index |
| ATA | anti-therapeutic antibody |
| CL | clearance |
| $C_{max}$ | maximum observed serum concentration |
| $C_{min}$ | minimum observed serum concentration |
| CBC | complete blood count |
| CIS | carcinoma *in situ* |
| CMV | methotrexate, vinblastine, and cisplatin |
| CR | complete response |
| CT | computed tomography (scan) |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DFS | disease-free survival |
| DLT | dose-limiting toxicity |
| DMFS | distant metastasis-free survival |
| DOR | duration of response |
| DSS | disease-specific survival |
| EAU | European Association of Urology |
| EC | Ethics Committee |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| EQ-5D-5L | EuroQol 5-dimension, 5-level version (questionnaire) |
| ESMO | European Society of Medical Oncology |
| FDA | U.S. Food and Drug Administration |
| FDG-PET | fludeoxyglucose ($^{18}F$) positron emission tomography |
| FFPE | formalin-fixed paraffin-embedded |
| FPI | first patient in |
| GC | gemcitabine and cisplatin |
| GFR | glomerular filtration rate |
| HBc Ab | hepatitis B core antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIPAA | Health Insurance Portability and Accountability Act |
| IC | tumor-infiltrating immune cell (score) |

| Abbreviation | Definition |
|---|---|
| ICH | International Conference on Harmonisation |
| iDCC | independent data coordinating center |
| iDMC | independent Data Monitoring Committee |
| Ig | immunoglobulin |
| IHC | immunohistochemistry |
| IMP | investigational medicinal product |
| IND | Investigational New Drug (application) |
| IRB | Institutional Review Board |
| IRF | independent review facility |
| IxRS | interactive voice/web response system |
| IV | intravenous |
| IVP | intravenous pyelogram |
| MIBC | muscle-invasive bladder cancer |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| mUC | metastatic urothelial carcinoma |
| MVAC | methotrexate, vinblastine, doxorubicin, and cisplatin |
| NCCN | National Cancer Clinical Network |
| NCI | National Cancer Institute |
| NMIBC | non–muscle-invasive bladder cancer |
| NSCLC | non–small cell lung cancer |
| NU | nephroureterectomy |
| NURFS | non-urinary tract recurrence-free survival |
| ORR | objective response rate |
| OS | overall survival |
| PBMCs | peripheral blood mononuclear cells |
| pCR | pathologic complete response |
| PD-1 | programmed death-1 |
| PD-L1 | programmed death-ligand 1 |
| PK | pharmacokinetic |
| PO | polyolefin |
| PR | partial response |
| PRO | patient-reported outcome |
| PSA | prostate-specific antigen |
| pTa | papillary urothelial carcinoma |
| PUNLMP | papillary urothelial neoplasm of low malignant potential |
| PVC | polyvinyl chloride |

| Abbreviation | Definition |
|---|---|
| q3w | every 3 weeks |
| QoL | quality of life |
| QTcF | QT interval corrected using Fridericia's formula |
| RCC | renal cell carcinoma |
| RCR | Roche Clinical Repository |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RFS | recurrence-free survival |
| RNU | radical nephroureterectomy |
| TCC | transitional cell carcinoma |
| TNF | tumor necrosis factor |
| TSH | thyroid-stimulating hormone |
| TURBT | transurethral resection of bladder tumor |
| UC | urothelial carcinoma |
| UBC | urothelial bladder cancer |
| ULN | upper limit of normal |
| UTUC | upper urinary tract urothelial cancer |
| VAS | visual analog scale |
| $V_{ss}$ | volume of distribution at steady state |

# 1. BACKGROUND

## 1.1 BACKGROUND ON MUSCLE-INVASIVE UROTHELIAL CARCINOMA

Urothelial carcinoma (UC, also termed transitional cell carcinoma [TCC] or urothelial bladder cancer [UBC]) is the most common cancer of the urinary system worldwide, with UC of the bladder being the predominant histologic type and location. Although less common, UC may originate in the renal pelvis, ureter, or urethra.

Globally, there were an estimated 429,793 new cases of bladder cancer and 165,084 deaths in 2012 (GLOBOCAN 2012). In 2012, it was estimated that there were 151,297 new cases of bladder cancer and 52,411 deaths in Europe, including 124,188 new cases and 40,635 deaths in the 28 member states of the European Union (EU). In 2014, it was estimated that there would be 74,690 new cases of bladder cancer and 15,580 deaths in the United States (American Cancer Society 2014). In 2012, it was estimated that there were 55,486 new cases of bladder cancer and 26,820 deaths in China (GLOBOCAN 2012).

The median age at diagnosis is 69 years in men and 71 years in women (Lynch and Cohen 1995; Scosyrev et al. 2009). Multiple risk factors have been linked to the development of bladder cancer and include cigarette smoking, which is the most common risk factor, as well as various occupational exposures such as those experienced by metal workers; painters; electrical workers; miners; cement workers; transport operators; workers in the rubber, leather, and textile industries; and workers who manufacture plastics and industrial chemicals (Kogevinas et al. 2003; Gaertner et al. 2004; Smailyte et al. 2004). High concentrations of arsenic in drinking water have been linked to bladder cancer (Tsai et al. 1998; Marshall et al. 2007). Other risk factors for the development of bladder cancer include chronic cystitis (Delnay et al. 1999) and human papillomavirus (HPV), especially HPV 16 (Li et al. 2011). Iatrogenic causes of bladder cancer include radiation therapy to the pelvic region and chemotherapy such as cyclophosphamide.

Bladder cancer presents as non-muscle-invasive (NMIBC), muscle-invasive (MIBC), or metastatic disease. For patients with MIBC (pT2–T4a, N0–Nx, M0), radical cystectomy with bilateral pelvic lymphadenectomy forms the backbone of the management of MIBC. The surgery involves resection of the bladder, adjacent organs, and regional lymph nodes. There are also gender-based differences in the surgical approach: For men, the surgery includes removal of the prostate and seminal vesicles, and for women, the surgery includes removal of the uterus, cervix, ovaries, and anterior vagina. Urinary diversion is required after removal of the bladder. The perioperative mortality rate is approximately 2%–3% when cystectomy is performed at centers of excellence (Stein et al. 2001; Madersbacher et al. 2003). In spite of this surgery, many patients recur and present with pain (e.g., flank pain due to ureteral obstruction; abdominal or right upper quadrant pain due to liver metastasis or an abdominal lymph node; bone pain

secondary to bone metastases) or constitutional symptoms such as fatigue, weight loss, anorexia, and failure to thrive. Approximately half of the patients with MIBC will develop a local and/or metastatic recurrence of their disease within 2 years of cystectomy and will eventually die from their disease (Raghavan et al. 1990; Stein et al. 2001; Stenzl et al. 2009). For those with high-risk features (pT3–T4a or pN+), the overall 5-year survival ranges from 10%–40% (Sternberg et al. 2007).

Because of the high risk of relapse with surgery alone, neoadjuvant and adjuvant treatment have been utilized in conjunction with radical cystectomy for MIBC. The rationale for perioperative chemotherapy is based on the response in patients with locally advanced or metastatic UC, in which cisplatin-based chemotherapy has demonstrated efficacy with a median survival of approximately 15 months with responses in 40%–60% of patients (von der Maase et al. 2005). However, there is an urgent need for effective regimens for patients with poor performance status, comorbidities, or renal insufficiency, for whom carboplatin-based regimens appear to generate suboptimal outcomes in both perioperative and advanced settings (De Santis et al. 2009; Abol-Enein et al. 1997).

### 1.1.1 Neoadjuvant Treatment for MIBC

Neoadjuvant chemotherapy has been shown to provide a small but statistically significant overall survival (OS) advantage. The advantage of neoadjuvant chemotherapy is that it facilitates an assessment of the response of the primary cancer to chemotherapy as well as providing an indication as to the likelihood of long-term remission or survival. The disadvantage of neoadjuvant chemotherapy is that definitive surgery management with a radical cystectomy is potentially delayed for those patients who do not have a major response to the neoadjuvant treatment. In addition, certain low-risk (e.g., cT2N0) patients may be overtreated with neoadjuvant chemotherapy because it is difficult to identify low-risk patients reliably before cystectomy (Meeks et al. 2012). It has been reported that $<20\%$ of patients who undergo radical cystectomy have received neoadjuvant chemotherapy prior to surgery (David et al. 2007; Miles et al. 2010; Porter et al. 2011; Raj et al. 2011).

A meta-analysis of data from 11 randomized trials has demonstrated that MIBC is most sensitive to cisplatin-based neoadjuvant chemotherapy, with a 5% net benefit in 5-year OS (Advanced Bladder Cancer Meta-analysis Collaboration 2003). Commonly used cisplatin-based neoadjuvant chemotherapy regimens include MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin), CMV (methotrexate, vinblastine, and cisplatin), and GC (gemcitabine and cisplatin). European Society of Medical Oncology (ESMO), European Association of Urology (EAU) and National Cancer Clinical Network (NCCN) clinical practice guidelines recommend cisplatin-based neoadjuvant chemotherapy prior to cystectomy for MIBC patients (Bellmunt et al. 2014; Witjes et al. 2014). Patients with MIBC who achieve a pathologic complete response (pCR; $pT_0N_0M_0$ stage) or who are down-staged to non-muscle-invasive disease after neoadjuvant chemotherapy

demonstrate longer OS than those who fail to achieve pCR or are not down-staged (Grossman et al. 2003; Petrelli et al. 2014). For patients with residual muscle-invasive disease (pT2–4a) or lymph node-positive disease (pN+) at cystectomy, the median survival is only 3.4 and 2.4 years, respectively (Sonpavde et al. 2009). There is currently no standard active treatment for those patients in the adjuvant setting.

### 1.1.2 Adjuvant Treatment for MIBC

Many patients with MIBC choose to undergo definitive surgery (i.e., radical cystectomy) first and defer neoadjuvant chemotherapy; patients at a high risk for recurrence based on pathologic staging could consider adjuvant chemotherapy given its potential to eradicate micrometastatic disease. However, unlike the benefits that have been shown with neoadjuvant chemotherapy, results from prospective studies of cisplatin-based adjuvant chemotherapy in patients with MIBC after a radical cystectomy are mixed. Two clinical trials have shown a survival benefit (Skinner et al. 1991; Stöckle et al. 1992); however, these trials enrolled less than 100 patients and the small datasets impact the interpretability of the results. A meta-analysis conducted in 2005 (Vale 2005) with data from 491 individual patients obtained from six adjuvant chemotherapy trials was inconclusive because of its small number and heterogeneity among the trials included. Meeks et al. (2012) performed a systematic review, which found no evidence that adjuvant chemotherapy improved survival outcomes, even in the highest-risk patients with pathologic extravesical and/or node-positive disease. Four recent trials (by US Intergroup [Stadler et al. 2011], Italian Multicenter [Cognetti et al. 2012], SOGUG [Paz-Ares et al. 2010], and EORTC [Sternberg et al. 2015]), which were not included in the above mentioned meta-analysis, failed to meet their original accrual goals and were prematurely terminated. As one of the largest randomized trials ever reported for adjuvant chemotherapy in patients with MIBC, the EORTC trial was closed after recruitment of 284 of the planned 660 patients. In that study, 284 patients with pT3–pT4 or N+ M0 MIBC were randomized to receive either immediate versus deferred cisplatin-based combination chemotherapy after cystectomy. Immediate treatment significantly prolonged progression-free survival compared with deferred treatment (HR 0.54; 95% CI: 0.4–0.73; $p < 0.0001$). However, no significant improvement in OS was noted with immediate treatment when compared with deferred treatment (HR 0.78; 95% CI: 0.56–1.08; $p = 0.13$). Thus, the benefit and usefulness of cisplatin-based adjuvant chemotherapy remains highly controversial.

Only approximately 50% of patients are eligible for cisplatin-based adjuvant chemotherapy; factors rendering patients ineligible for cisplatin therapy include an Eastern Cooperative Oncology Group (ECOG) performance status of 2, impaired renal function, hearing loss, and neuropathy (Dash et al. 2006). On the basis of current clinical guidelines, there is no standard adjuvant chemotherapy for patients who are ineligible for cisplatin-based therapy. There is no evidence that non-cisplatin-based adjuvant regimens (e.g., carboplatin-based adjuvant chemotherapy) are as effective as cisplatin-based adjuvant chemotherapy.

Key adjuvant randomized trials are listed in Table 1.

**Table 1 Adjuvant Chemotherapy: Randomized Trials**

| Institution | No. of Patients | Regimen | Survival Benefit | Completed Accrual |
|---|---|---|---|---|
| University of Southern California (Skinner et al. 1991) | 91 | CISCA | Yes [a] | Yes |
| University of Mainz, Germany (Stöckle et al. 1995 | 49 | MVAC/MVEC | Yes | Yes |
| Swiss Group for Clinical Cancer Research, Switzerland (Studer et al. 1994) | 77 | Cisplatin | No | Yes |
| Stanford University (Freiha et al. 1996) | 55 | CMV | No | Yes |
| US Intergroup (Stadler et al. 2011) | 114 | MVAC | No | No |
| Italian multicenter (Cognetti et al. 2012) | 194 | GC | No | No |
| SOGUG (Paz-Ares et al. 2010) | 142 | PCG | Yes [b] | No |
| EORTC Trial (NCT00028756; Sternberg et al. 2015) | 248 | MVAC, GC, DD-MVAC | No | No |

CISCA = cisplatin, doxorubicin; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; MVEC = methotrexate, vinblastine, epirubicin, cisplatin; CMV = cisplatin, methotrexate, vinblastine; GC = gemcitabine, cisplatin; PCG = paclitaxel, gemcitabine, cisplatin; SOGUG = Spanish Oncology Genitourinary Group; EORTC = European Organization for Research and Treatment of Cancer; DD-MVAC = double dense MVAC.

Note: Adapted from Meeks et al. 2012.

[a] Median survival time = chemotherapy – 4.3 yrs; observation – 2.4 yrs ($p = 0.0062$).

[b] PCG: mOS not reported, 5 yr OS 60%; observation mOS 26 months, 5 yr OS 31% ($p < 0.0009$).

## 1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (MPDL3280A) is a humanized immunoglobulin (Ig) G1 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 programmed death-ligand 1 (PD-L1) and inhibits its interaction with its receptors, programmed death-1 (PD-1) and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells.

### 1.2.1 Summary of Nonclinical Studies

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were thus undertaken with atezolizumab.

The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway and supported entry into clinical trials in patients.

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

### 1.2.2 Clinical Experience with Atezolizumab

#### 1.2.2.1 Ongoing Clinical Studies

Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as monotherapy and in combination with several anticancer therapies (see the Atezolizumab Investigator's Brochure for study descriptions). The majority of the safety and efficacy data summarized below are from the following two studies:
1) Study PCD4989g, a Phase Ia, multicenter, first-in-human, open-label, dose-escalation trial evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion every 3 weeks (q3w) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies; and
2) Study IMvigor210, a single-arm Phase II study evaluating single-agent atezolizumab (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 (see Section 4.1.1 for definition of cisplatin-ineligibility). 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.

For the PCD4989g and IMvigor210 studies, an immunohistochemistry (IHC)-based scoring criteria has been formulated to represent PD-L1 expression in tumor-infiltrating immune cells (IC) (see Appendix 3). Any cutoff references are to a single IC score

(e.g., IC2), whereas patient population references include all IC subgroups within a particular cutoff (e.g., IC2/3 population from a selection at the IC2 cutoff).

#### 1.2.2.2 Clinical Safety

The safety data for atezolizumab have been derived mainly from the treatment of patients in Study PCD4989g and Study IMvigor210. As of 10 May 2014, the clinical database contained preliminary safety data from 412 patients in Study PCD4989g who have received any amount of atezolizumab at doses between 0.01 and 20 mg/kg across multiple tumor types. No dose-limiting toxicities (DLTs) have been observed at any dose level and no maximum tolerated dose (MTD) was established.

As 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 (as of 10 May 2014), where 79 safety-evaluable patients with UC from all lines of therapy received atezolizumab monotherapy.

Refer to the Atezolizumab Investigator's Brochure for further updated details on clinical safety.

##### Adverse Events

Of the 412 treated patients, 97% reported an adverse event regardless of attribution to atezolizumab. Of these adverse events, 48.8% were Grade 1 or 2 in maximum severity based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). The most frequently observed adverse events (occurring in $\geq$10% of treated patients) included fatigue, nausea, decreased appetite, pyrexia, dyspnea, diarrhea, constipation, cough, headache, back pain, vomiting, anemia, arthralgia, rash, insomnia, asthenia, abdominal pain, chills, pruritus, generalized pain, and peripheral edema. Treatment-related adverse events (per investigator assessment of causality) were reported in 72% of patients.

##### PCD4989g: Adverse Events in Patients with 1L+ mUC

A total of 79 patients with bladder cancer received atezolizumab in Study PCD4989g as of the 10 May 2014 datacut. Of these, 75 (94.9%) reported at least one adverse event. Grade $\geq$3 adverse events occurred in 45.6% of patients. Seven bladder cancer patients (8.9%) experienced Grade 3–5 treatment-related adverse events. The events included thrombocytopenia, asthenia, alanine aminotransferase increase, aspartate aminotransferase increased, blood creatinine increased, blood phosphorus decreased, and gamma-glutamyltransferase increased.

Table 2 summarizes adverse events regardless of attribution that occurred in ≥ 10% of the bladder cancer patients and the investigator's assessment of relatedness for these events.

**Table 2 Adverse Events Occurring in ≥ 10% of Urothelial Carcinoma Patients (n = 79) in Study PCD4989g**

| Preferred Term | Adverse Event Regardless of Attribution n (%) | Related Adverse Events n (%) |
|---|---|---|
| Anemia | 19 (24.1) | 2 (2.5) |
| Nausea | 12 (15.2) | 8 (10.1) |
| Constipation | 11 (13.9) | 0 (0.0) |
| Abdominal pain | 10 (12.7) | 1 (1.3) |
| Vomiting | 9 (11.4) | 2 (2.5) |
| Fatigue | 18 (22.8) | 11 (13.9) |
| Pyrexia | 15 (19.0) | 8 (10.1) |
| Edema peripheral | 8 (10.1) | 0 (0.0) |
| Pain | 8 (10.1) | 2 (2.5) |
| Urinary tract infection | 16 (20.3) | 0 (0.0) |
| Blood creatinine increased | 18 (22.8) | 1 (1.3) |
| Blood alkaline phosphatase | 8 (10.1) | 1 (1.3) |
| Decreased appetite | 16 (20.3) | 8 (10.1) |
| Back pain | 10 (12.7) | 0 (0.0) |
| Cough | 10 (12.7) | 0 (0.0) |
| Dyspnea | 8 (10.1) | 0 (0.0) |

### IMvigor210 Cohort 1: Adverse Events in Patients with 1L Cisplatin-Ineligible mUC

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 (27.0%), nausea (21.8%), and diarrhea (21.0%).

**Table 3 Safety Profiles for Study IMvigor210: Safety-Evaluable Population**

| Parameter | Cohort 1 [a, b] (n = 119) | Cohort 2 [a, c] (n = 310) |
|---|---|---|
| Any AE | 114 (95.8%) | 302 (97.4%) |
| Related AE | 79 (66.4%) | 218 (70.3%) |
| Grade 3–4 | 53 (44.5%) | 177 (57.1%) |
| Related Grade 3–4 | 18 (15.1%) | 51 (16.5%) |
| Grade 5 | 4 (3.4%) | 3 (1.0%) |
| Related Grade 5 | 1 (0.8%) | 0 |
| SAE | 43 (36.1%) | 143 (46.1%) |
| Related SAE | 10 (8.4%) | 36 (11.6%) |
| AEs leading to withdrawal from study treatment | 7 (5.9%) | 9 (2.9%) |

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

[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.

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 increases (3.4% each), 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 Cohort 1 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. 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.

Cardiac arrest, myocardial infarction, autoimmune colitis, diarrhea, hypersensitivity, sepsis, and respiratory failure were the adverse events that led to 7 Cohort 1 patients (5.9%) terminating atezolizumab.

### IMvigor210 Cohort 2: Adverse Events in Patients with 2L+ mUC

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 Cohort 2 patients (57.1%) reported a Grade 3–4 adverse event (see Table 3), with the most common (≥2.3%) 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 Cohort 2 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). 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).

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 hemorrhage, posterior reversible encephalopathy syndrome, subileus, fatigue, acute kidney injury and pruritus.

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

Guidelines for the management of potential immune-mediated adverse events are described in Section 5.1.4.

#### 1.2.2.3 Clinical Activity

Anti-tumor activity, including Response Evaluation Criteria in Solid Tumors (RECIST)–based responses (i.e., RECIST [Version 1.1] responses), have been observed in patients with different tumor types, including non–small cell lung cancer (NSCLC), renal cell carcinoma (RCC), melanoma, gastric cancer, bladder cancer, colorectal cancer, head and neck cancer, breast cancer, and sarcoma treated with atezolizumab monotherapy in Study PCD4989g.

Among 345 evaluable patients treated by 21 October 2013 (data cutoff of 21 April 2014) with a median of 30.4 weeks of follow-up, 62 patients experienced objective responses per RECIST v1.1 with an objective response rate (ORR) of 18% (95% CI: 14.1%, 22.3%). Objective responses with atezolizumab monotherapy were observed in a broad range of malignancies, including NSCLC, RCC, melanoma, bladder cancer, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. The median duration of response (DOR) was 77.6 weeks (range: 6.4+ to 97.9+ weeks, where "+" denotes a censored value). The majority of these responses have been durable, with 72.6% of responses (45 of 62 patients) ongoing as of the clinical cutoff date.

Refer to the Atezolizumab Investigator's Brochure for details on clinical activity in all patients treated to date, regardless of tumor type.

#### PCD4989g: Clinical Activity in Patients with 1L+ mUC

As of the clinical cutoff of 21 April 2014, efficacy analyses were performed on the 70 patients with locally advanced or metastatic UC in Study PCD4989g who received atezolizumab treatment by 27 January 2014. The median age of this population was 65 years (range: 36–89 years), and the group represented a heavily pre-treated patient population, with 44.3% of patients having received more than two prior systemic therapies (1L+). The median duration on study treatment was 106 days (range: 1–331 days).

Preliminary data show that patients with UC with a high level of PD-L1 expression in tumor-infiltrating immune cells (IC) per immunohistochemistry (IHC) demonstrated a greater response rate after treatment with atezolizumab compared with patients with a low level of PD-L1 expression. When a diagnostic threshold of ≥ 5% PD-L1–stained tumor-infiltrating immune cells (IHC score of IC2 or IC3) was used, IC2/3 patients (n = 33) had an ORR per investigator assessment of 51.5% (95% CI: 33.8%, 69.2%) (see Table 4). When a higher diagnostic threshold of ≥ 10% PD-L1–stained tumor-infiltrating immune cells (IHC score of IC3) was used, IC3 patients (n = 10) had an ORR of 60.0% (95% CI: 26.7%, 85.0%). In responding PD-L1 IC2/3 patients (n = 17), the median time to first response was 43.0 days (range: 38.0–248.0 days) and the median DOR has not been reached (range: 0.1+ to 42.3+ weeks).

For patients with a PD-L1 IHC score of IC0 or IC1, the ORR per investigator assessment was 13.9% (95% CI: 5.6%, 27.9%). In responding patients (n = 5), the median time to first response was 83.0 days (range: 38.0–85.0 days) and the median DOR has not been reached (range: 6.1+ to 19.1+ weeks).

**Table 4 Objective Response Rate (per Investigator Assessment using RECIST v1.1) by PD-L1 Tumor Expression in Efficacy-Evaluable UC Patients in Study PCD4989g**

| IHC Score | Objective Response Rate (CR or PR [a]) | ORR (CR or PR) of Combined IHC Groups |
|---|---|---|
| IC3 (IC ≥ 10%) | 60.0% (6 of 10)<br>(95% CI: 26.7%, 85.0%) | 51.5% (17 of 33)<br>(95% CI: 33.8%, 69.2%) |
| IC2 (10% > IC ≥ 5%) | 47.8% (11 of 23)<br>(95% CI: 26.8%, 68.3%) | |
| IC1 (5% > IC ≥ 1%) | 16.7% (4 of 24)<br>(95% CI: 5.9%, 36.6%) | 13.9% (5 of 36)<br>(95% CI: 5.6%, 27.9%) |
| IC0 (IC < 1%) | 8.3% (1 of 12)<br>(95% CI: 0.4%, 34.9%) | |

CR = complete response; Dx = diagnostic; IC = tumor-infiltrating immune cell; IHC = immunohistochemistry; ORR = overall response rate; PD-L1 = programmed death–ligand 1; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; UC = urothelial carcinoma.

Note: There is 1 UC efficacy-evaluable patient with unknown IHC score.

[a] As of 21 April 2014, 18 of the 22 responses have been confirmed per RECIST v1.1.

### 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 (see Table 5) after first-line treatment with atezolizumab in all PD–L1 IC subgroups: IC0/1 patients had an ORR of 21.8% 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 (Figure 1).

**Table 5 IRF-Assessed ORR and DOR per RECIST v1.1 in 1L Patients with mUC: Efficacy-Evaluable Population in IMvigor210 Cohort 1**

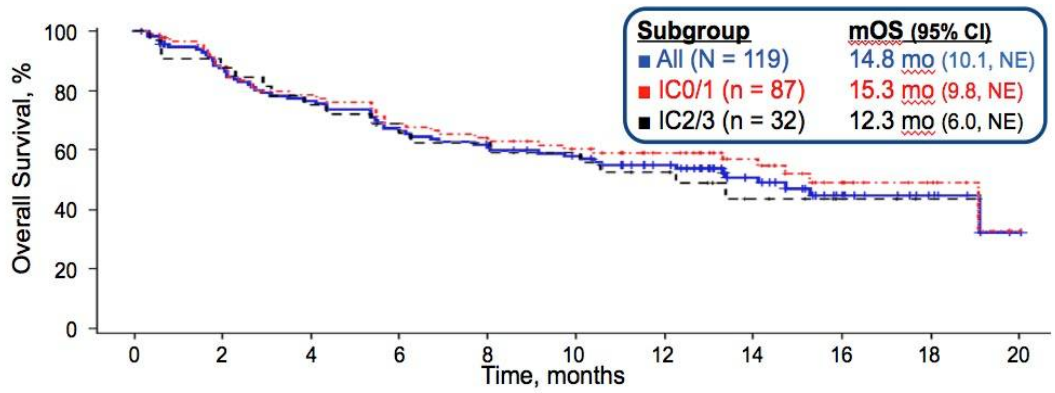
| | IC0/1 (n = 87) | IC2/3 (n = 32) | All Patients (n = 119) |
|---|---|---|---|
| ORR (%) | 19 (21.8) | 9 (28.1) | 28 (23.5) |
| 95% CI | (13.7, 32.0) | (13.8, 46.8) | (16.2, 32.2) |
| Complete response | 6 | 2 | 8 |
| Partial response | 13 | 7 | 20 |
| Median DOR (months) | NE | NE | NE |
| 95% CI | (12.8, NE) | (11.1, NE) | (12.8, NE) |
| Patients with event (%) | 4 (21.1) | 3 (33..3) | 7 (25.0) |

DOR = duration of response; IC = tumor-infiltrating immune cell; IRF = independent review facility; 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.

The clinical cutoff date was 14 March 2016.

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




- With a median follow-up of 14.4 months,[a] the event rate is 47%

[a] Range, 0.2 to 20.1 mo. Data cutoff: March 14, 2016.

## 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) (see Table 6). 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 2).

**Table 6 IRF-Assessed ORR and DOR per RECIST v1.1 in 2L+ Patients with mUC: Efficacy-Evaluable Population in IMvigor210 Cohort 2**

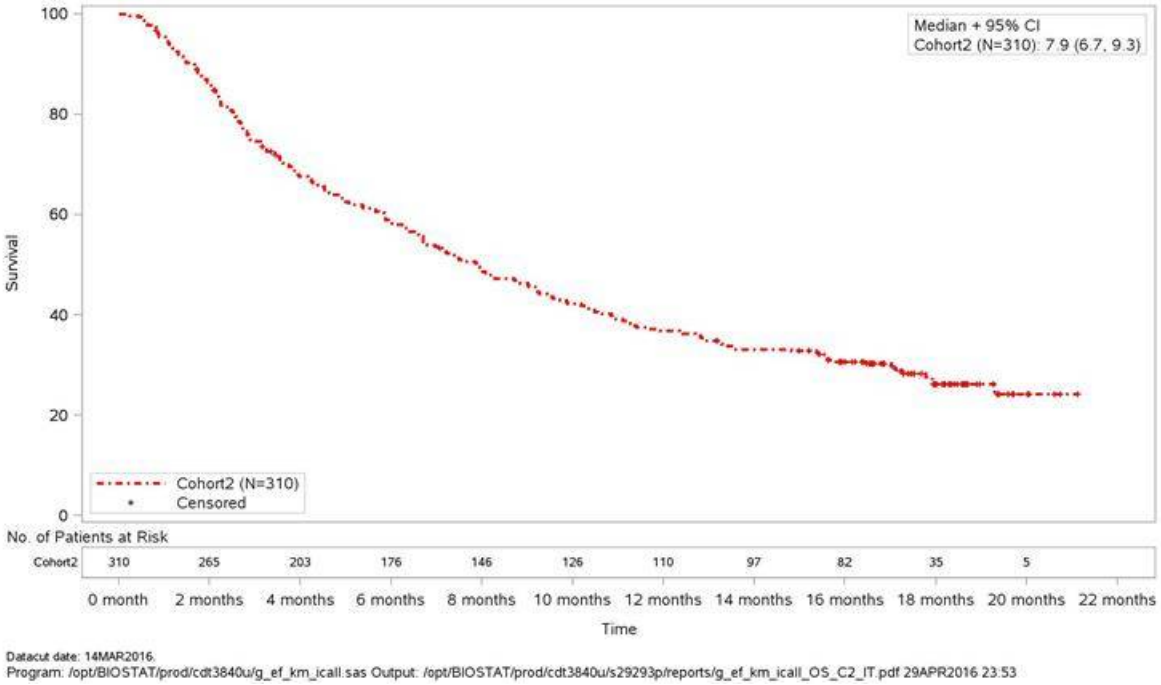
| | IC0/1 (n = 210) | IC2/3 (n = 100) | All Patients (n = 310) |
|---|---|---|---|
| ORR (%) | 21 (10.0) | 28 (28.0) | 49 (15.8) |
| 95% CI | (6.4, 14.9) | (19.5, 37.9) | (11.9, 20.3) |
| Complete response | 6 | 15 | 21 |
| Partial response | 16 | 13 | 28 |
| Median DOR (months) | NE | NE | NE |
| 95% CI | (10.6, NE) | NE | NE |
| Patients with event (%) | 6 (28.6) | 8 (28.6) | 14 (28.6) |

DOR = duration of response; IC = tumor-infiltrating immune cell; IRF = independent review facility; 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.

The clinical cutoff date was 14 March 2016.

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




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

#### 1.2.2.4 Clinical Pharmacokinetics and Immunogenicity

On the basis of available preliminary PK data (0.03–20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses ≥ 1 mg/kg. For the 1 mg/kg and 20 mg/kg dose groups, the mean apparent clearance (CL) and the mean volume of distribution at steady state ($V_{ss}$) had a range of 3.20 to 4.43 mL/day/kg and 48.1 to 64.1 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

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

### 1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Encouraging clinical data emerging in the field of tumor 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).

PD-L1 is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors 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).

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).

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed or refused standard-of-care therapies. In Study PCD4989g, a Phase Ia dose-escalation and expansion study, objective responses with atezolizumab monotherapy were observed in a broad range of malignancies including urothelial carcinoma (see Section 1.2.2.3). More recent data from a pivotal Phase II IMvigor210 study demonstrated clinically meaningful response rates and a noteworthy median overall survival in both 1L, cisplatin-ineligible, and 2L+ mUC patients treated with atezolizumab (see Section 1.2.2.3).

Atezolizumab has been generally well tolerated (see Section 1.2.2.2). Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, hypothyroidism, hepatitis/transaminitis, colitis, and myasthenia gravis, have been observed in Study PCD4989g. To date, these events have been manageable with treatment.

Given the evidence of the clinical activity of atezolizumab in advanced and metastatic UC, treatment with atezolizumab offers the potential for clinical benefit in patients with high risk muscle-invasive UC of the bladder and upper tract. Because most atezolizumab-related toxicities observed to date have been mild and transient in nature, it is anticipated that adjuvant treatment with atezolizumab will have a manageable safety profile and has an acceptable benefit-risk assessment for the conduct of the study.

# 2. OBJECTIVES

## 2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of adjuvant atezolizumab treatment in patients with muscle-invasive urothelial carcinoma (UC) as measured by disease-free survival (DFS)

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of adjuvant atezolizumab treatment, as measured by overall survival (OS)
- To evaluate the efficacy of adjuvant atezolizumab treatment, as measured by disease-specific survival (DSS)
- To evaluate the efficacy of adjuvant atezolizumab treatment, as measured by distant metastasis-free survival (DMFS)
- To evaluate the efficacy of adjuvant atezolizumab treatment, as measured by non-urinary tract recurrence-free survival (NURFS)

## 2.2 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab in the adjuvant setting
- To evaluate the incidence of anti-therapeutic antibodies (ATAs) against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

## 2.3 PHARMACOKINETIC OBJECTIVE

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

- To characterize the pharmacokinetics of atezolizumab

## 2.4 PATIENT-REPORTED OUTCOME OBJECTIVE

The PRO objective for this study is as follows:

- To assess health status as measured by the EuroQol 5-dimension, 5-level version (EQ-5D-5L) questionnaire

## 2.5 EXPLORATORY OBJECTIVE

The exploratory objective for this study is as follows:

- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease recurrence

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF STUDY

Study WO29636 is a global Phase III, open-label, randomized, controlled trial designed to evaluate the efficacy and safety of adjuvant treatment with atezolizumab compared with observation in patients with muscle-invasive UC, who are at high risk for recurrence following resection.

Male and female patients aged ≥ 18 years with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 who have histologically confirmed muscle-invasive UC (also termed TCC) of the bladder or upper urinary tract (i.e., renal pelvis or ureters) are eligible. Patients with upper urinary tract urothelial carcinoma (UTUC) will be limited to no more than approximately 10% of the study population.

Patients with bladder as the site of primary involvement must have undergone radical cystectomy with lymph node dissection. Patients with UTUC as the site of primary involvement must have undergone radical nephroureterectomy (RNU) with excision of the bladder cuff regardless of the location of the tumor in the upper urinary tract. RNU must include lymph node dissection.

Patients who have received prior neoadjuvant chemotherapy are eligible, but must have tumor staging of ypT2–4a or ypN+ (ypT2-4 or ypN+ for patients with UTUC) and M0 at pathological examination of the surgical resection specimen. Patients who have not received prior neoadjuvant chemotherapy must be ineligible for or declined treatment with cisplatin-based adjuvant chemotherapy and have tumor staging of pT3–4a or pN+ (pT3-4 or pN+ for patients with muscle-invasive UTUC) and M0.

Tumor specimens from surgical resection (i.e., radical cystectomy, RNU, or lymph node dissection) from patients who have signed the Informed Consent Form will be evaluated for PD-L1 expression by IHC (see Appendix 3). Only patients whose tumors have sufficient amounts of viable tumor and are evaluable for PD-L1 expression as confirmed by a central pathology laboratory prior to enrollment of the patient in the study will be eligible.

Figure 3 shows the study schema.

Approximately 800 patients globally will be randomized to one of the following arms in a 1:1 ratio:

- Arm A (experimental arm): Atezolizumab 1200 mg q3w
- Arm B (control arm): Observation

Randomization will be stratified by the following factors:

- Number of lymph nodes resected ($<10$ vs. $\geq 10$)
- Nodal status (positive vs. negative)
- Tumor stage after surgical resection ($\leq$pT2 vs. pT3/pT4)
- PD-L1 IHC status (IHC score of IC0/1 vs. IHC score of IC2/3)
- Prior neoadjuvant chemotherapy (yes vs. no)

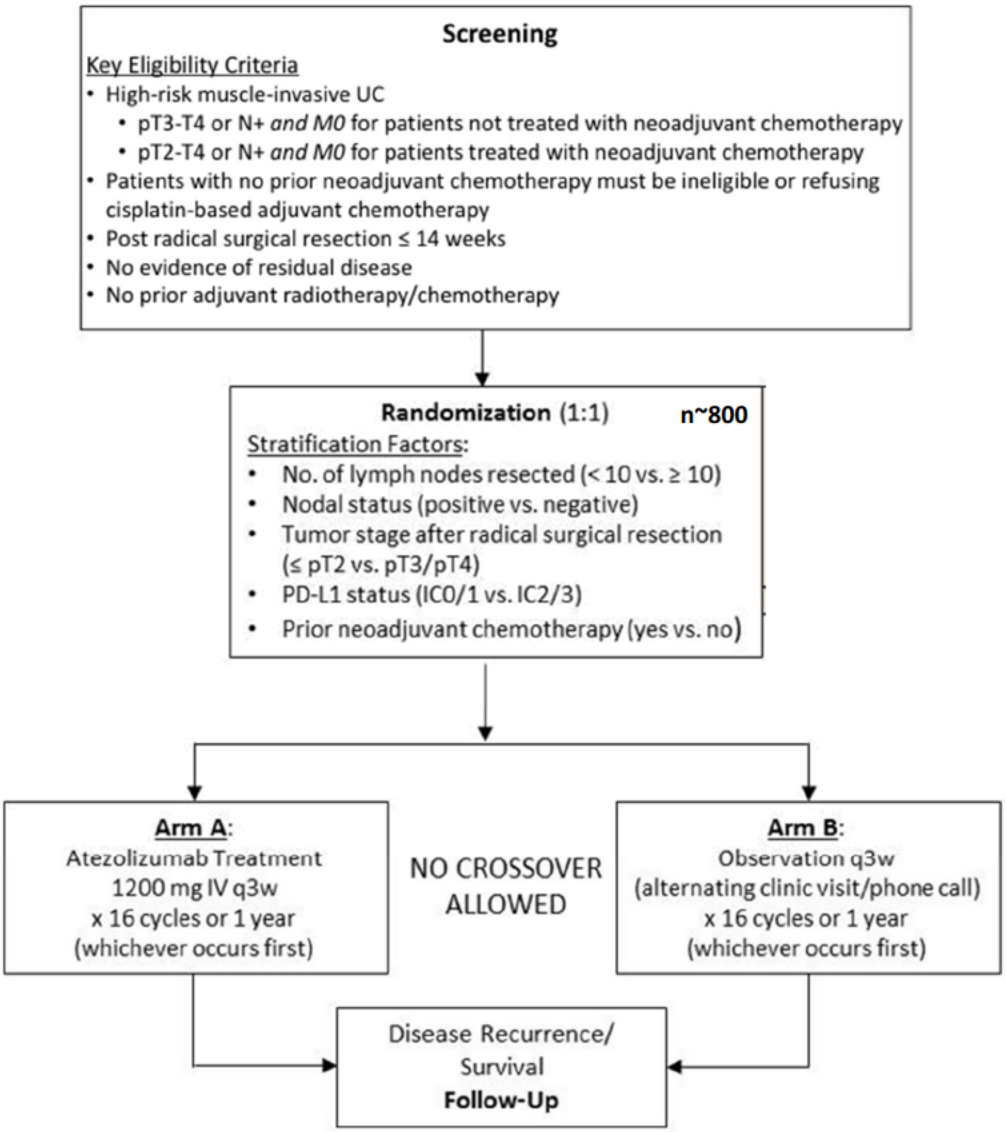
Randomization must occur within 14 weeks after surgical resection of the primary tumor, and study drug administration should begin within 7 calendar days after randomization.

For patients in Arm A, atezolizumab will be administered intravenously (IV) on Day 1 of each 21-day cycle for 16 cycles (up to 1 year). In Arm B, patients will continually undergo observation starting on Day 1 of each 21-day cycle for 16 cycles (up to 1 year). Treatment/observation will be discontinued in the event of disease recurrence, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor.

To ensure the same frequency of study assessments between the treatment arms, including assessments for disease recurrence and safety, patients in Arm B will be required to undergo q3w medical contacts for assessments during the first year, which will consist of formal clinic visits alternating with clinical contacts (either via telephone call or formal outpatient clinic visit) for symptom and adverse event assessment.

Patients in the control arm will not be allowed to cross over to receive atezolizumab treatment within this study.

**Figure 3 Study Schema**




UC = urothelial carcinoma.

All patients will undergo scheduled assessments for tumor recurrence at baseline and every 12 weeks (approximately every 4 cycles) in the first year following randomization. Upon completion of the treatment/observation period, surveillance for tumor recurrence will be performed every 12 weeks for Years 2–3; every 24 weeks for Years 4–5; and at Year 6 (approximately 48 weeks after the last assessment in Year 5). *After the primary analysis, patients in Years 2–3 of the study may be assessed for tumor recurrence every 24 weeks.* In the absence of a DFS event (see definition in Section 3.4.1.1), surveillance for tumor recurrence should continue regardless of whether patients start new anticancer therapy, until withdrawal of consent, loss to follow-up, or study termination by the Sponsor, whichever occurs first. For patients with muscle-invasive bladder cancer

(MIBC), surveillance for tumor recurrence will include physical examination, laboratory evaluation, and imaging studies of the chest, abdomen, upper urinary tracts, and pelvis. Disease recurrence will be determined by the investigator based on radiographic evidence (visual appearance of UC with histological confirmation is acceptable for recurrence in bladder). For patients with UTUC, surveillance for tumor recurrence must include physical examination, cystoscopy, urine cytology and imaging studies of the chest, abdomen, and pelvis. A confirmatory tumor biopsy is mandatory at the time of disease recurrence (see Section 4.5.5). Cases for which biopsy results definitively rule out recurrence of UC will not be considered as disease recurrence for this study. *After the primary analysis, a confirmatory tumor biopsy is optional at the time of disease recurrence.*

Safety assessments will include the incidence, nature, and severity of adverse events, changes in vital signs, and laboratory abnormalities graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0. Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of ATAs to atezolizumab. A sample of archived tumor tissues, as well as serum and plasma samples, will be collected for future exploratory biomarker assessments.

An external independent Data Monitoring Committee (iDMC) will evaluate safety data according to policies and procedures detailed in an iDMC Charter (see Section 3.1.1).

A schedule of assessments is provided in Appendix 1.

### 3.1.1 Independent Data Monitoring Committee

An iDMC will be convened to evaluate safety data until the analysis of the primary endpoint (DFS), after which iDMC review of the study data will be discontinued. The iDMC will evaluate study safety data on a periodic basis, approximately every 6 months after enrollment of the first patient. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. The Sponsor will remain blinded to the results until the analysis of the primary endpoint of DFS.

All summaries and analyses by treatment arm for the iDMC review will be prepared by an external independent data coordinating center (iDCC). The safety data will include demographic data, adverse events, serious adverse events, and relevant laboratory data. Following their data review, the iDMC will provide a recommendation as to whether the study may continue, whether amendment(s) to the protocol should be implemented, or whether the study should be stopped; the final decision will rest with the Sponsor.

## 3.2 END OF STUDY

The end of the study as planned will occur when the required number of events for the final analysis of OS has occurred (projected to be approximately Month 95 from FPI;

see Section 6.1.3). However, the Sponsor may decide to terminate the study at any time (see Section 4.7.3).

## 3.3 RATIONALE FOR STUDY DESIGN

### 3.3.1 Rationale for Primary and Secondary Endpoints

Improvement in DFS represents clinically meaningful benefit to MIBC patients. Up to 65% of MIBC patients who relapsed after cystectomy had symptoms associated with disease recurrence (Volkmer et al. 2009). The most frequent symptoms were pain, ileus, acute urinary retention, hydronephrosis with flank pain, hematuria, and neurological symptoms. After relapse, the current standard chemotherapy regimens given in the locally advanced and metastatic UC setting are associated with significant toxicity (e.g., anemia, thrombocytopenia, neutropenia, and mucositis). An improvement in DFS would delay symptoms associated with recurrence and the initiation of toxic therapy and therefore reflects direct benefit to patients. Further, DFS is not confounded by subsequent therapies. Given the development of multiple agents (including atezolizumab) in the relapsed and metastatic settings, it is likely that the analysis of OS will be confounded in this patient population.

For MIBC, distant metastases or local recurrence typically develop in the first 2 years after cystectomy (Volkmer et al. 2009). Retrospective analysis showed that DFS at 2 or 3 years correlates with 5-year OS of MIBC patients post-cystectomy. In 2724 selected MIBC patients with negative surgical margin, high agreement rates were observed between DFS at 2 and 3 years after cystectomy with OS at 5 years (79% and 81%, respectively; Sonpavde et al. 2011). A strong correlation was observed in a separate study that revealed even higher overall agreements between DFS at 2 years (86.5%) and 3 years (90.1%) and OS at 5 years. In addition to the previous findings, this association was demonstrated in patients with different tumor stages and both negative and positive surgical margins (Nuhn et al. 2012).

OS is included as an important secondary endpoint; since subsequent treatments after disease recurrence are evolving, the impact of adjuvant treatment on OS may be confounded.

Additionally, DSS (also known as cancer-specific survival) is a secondary endpoint because non-bladder cancer mortality in this frail and elderly population can be quite significant and may be a competing cause of mortality. After 20 years of post-operative follow-up, the probability of non-tumor-related death was 42% in patients with Stage pT2a/b disease, 40% in pT3a/b, 25% in pT4a/b, and 12% in pTall pN+ (Hautmann et al. 2012), and improvement in DSS in this population may not be reflected in an analysis of OS.

NURFS is included as a secondary endpoint because the impact of urinary tract recurrence on patient survival may be different from non-urinary tract recurrence. Most urinary tract recurrence could be managed by surgical resection (e.g., the majority

of MIBC patients who develop upper urinary tract recurrence can achieve prolonged disease-free survival when treated with radical nephroureterectomy) (Sanderson et al. 2007).

DMFS is also included as a secondary endpoint because distant recurrence is considered to be a major threat to patient survival. Furthermore, this endpoint will be informative as to how atezolizumab adjuvant treatment might affect patterns of recurrence. For MIBC patients post-cystectomy, distant recurrences have been observed to occur more frequently than locoregional recurrences (approximately 20%–50% vs. 5%–15% of cases) (Stein et al. 2001; Shariat et al. 2006).

### 3.3.2 Rationale for Inclusion of All Patients (All Levels of PD-L1 Expression by IHC) in the Study

This study will enroll patients with muscle-invasive UC of the bladder and upper tract whose tumor specimens are evaluable for PD-L1 expression by IHC as determined by a central laboratory (see Appendix 3).

Recent data from the metastatic UC setting demonstrated a median overall survival in all PD-L1 IC subgroups that was noteworthy when compared to historical controls. The median OS of 14.8 (95% CI: 10.1, NE) months suggests that there may be a benefit that is independent of PD-L1 status in patients treated with atezolizumab (see Section 1.2.2.3). The inclusion of patients with all levels of PD-L1 expression by IHC in this study will enable a robust evaluation of DFS in the overall population with atezolizumab treatment relative to observation treatment irrespective of PD-L1 status. It will also allow assessment of whether high level of PD-L1 expression is predictive for atezolizumab treatment or whether PD-L1 expression is prognostic for disease outcome in the adjuvant setting.

### 3.3.3 Rationale for Patient Population

The majority of urothelial tumors arise in the bladder, with TCC (also called UC) being the most common histologic subtype. TCC accounts for 90% of all MIBC cases in the industrialized world (Chalasani et al. 2009). For patients undergoing radical cystectomy alone, recurrence-free survival (RFS) and OS in male and female patients is reported as 66–68% and 58–66% at 5 years and 60–73% and 43–49% at 10 years, respectively (Stein et al. 2001; Hautmann et al. 2003; Madersbacher et al. 2003). In node-positive patients, 10-year DSS and OS rates decrease to 27.7% and 20.9%, respectively (Gschwend et al. 2002).

ESMO, EAU, and NCCN clinical practice guidelines recommend cisplatin-based neoadjuvant chemotherapy prior to cystectomy for MIBC patients based on a meta-analysis which showed a 5% net benefit in 5-year OS (Sternberg et al. 2006). Patients with pT0 or $<$pT2N0 disease at cystectomy following neoadjuvant chemotherapy were associated with better median survival (13.6 and 12.5 years, respectively). However, median survival (3.4 and 2.4 years, respectively) was very poor for patients with residual

muscle-invasive disease (pT2–4a) or lymph node-positive disease (pN+) following neoadjuvant chemotherapy; there is currently no standard of care for these patients (Sonpavde et al. 2009). Study WO29636 includes MIBC patients with pathological staging of ypT2–4a or ypN+ at cystectomy following neoadjuvant chemotherapy in this trial because this segment of the MIBC patient population has a high unmet medical need.

Despite existing guidelines, the majority of MIBC patients do not receive neoadjuvant chemotherapy before cystectomy. A recent study showed that neoadjuvant chemotherapy is used in only 12% of the approximately 5000 MIBC patients undergoing cystectomy annually in Europe who are being considered for neoadjuvant chemotherapy (Burger et al. 2012). Post cystectomy, adjuvant chemotherapy for MIBC patients is advised only within clinical trials according to current EAU guidelines. However, a recent meta-analysis indicated that cisplatin-based adjuvant chemotherapy is supported specifically in high-risk patients with extravesical or node-positive disease (Leow et al. 2014). Unfortunately, only approximately 50% of patients are eligible for cisplatin-based adjuvant chemotherapy, and factors rendering patients ineligible for cisplatin therapy include ECOG performance status of 2, impaired renal function, hearing loss, and neuropathy (Dash et al. 2006). On the basis of current clinical guidelines, there is no standard adjuvant chemotherapy for patients who are ineligible for cisplatin-based therapy. With radical cystectomy alone, patients with extravesical (pT3–T4a) or lymph node-positive (pN+) disease are at high risk for relapse (40%–67%) and associated with poor 5-year OS (25%–30%) (Gschwend et al. 2002; Shariat et al. 2006). Thus, this population of MIBC patients (with pT3–4a or pN+ disease; who did not receive prior neoadjuvant chemotherapy and have declined or are ineligible for cisplatin-based adjuvant chemotherapy) represents another area of high unmet medical need and are included in this trial.

UTUC are less common and account for only 5–10% of urothelial tumors. Given that UTUC have the same histology as UC of the bladder, the NCCN guidelines recommend that neoadjuvant and adjuvant chemotherapy be considered for selected patients with extensive UTUC based on extrapolation of data from bladder cancer series. Thus, Study WO29636 includes high-risk patients of UTUC with similar staging to MIBC.

### 3.3.4 Rationale for Observation Control Arm

Study WO29636 has an observation control arm. There is no standard of care after surgical resection for patients with muscle-invasive UC of the bladder or upper tract who have declined or are ineligible for cisplatin-based adjuvant chemotherapy. According to EAU guidelines (2014), there is no evidence that non-cisplatin-based adjuvant regimens (e.g., carboplatin-based adjuvant chemotherapy) are as effective as cisplatin-based adjuvant chemotherapy. Use of adjuvant chemotherapy for cisplatin-ineligible patients is not listed in current EU and US guidelines.

For patients who have been treated with neoadjuvant chemotherapy and fail to achieve a pCR or downgrading to pT0-1, there is currently no standard active treatment for these patients in the adjuvant setting.

Given the concerns of giving mock infusion q3w intravenously for up to 1 year to patients in the control arm, this study will not employ a placebo-controlled design.

### 3.3.5 Rationale for Stratification Factors

In order to balance the disease-related risk factors between the treatment arms, patients will be stratified at study entry. A stratified permuted-block randomization scheme will be used to obtain a balanced assignment to each treatment within levels of the stratification factors.

- Nodal involvement is considered to be a major prognostic factor for predicting disease recurrence and OS after cystectomy (Stein et al. 2001; Karakiewicz et al. 2006; Hautmann et al. 2012). The number of lymph nodes removed during cystectomy is prognostic as well (Herr et al. 2004).
- Pathological tumor stage is the most important independent prognostic variable for recurrence and OS for invasive bladder cancer. Comprehensive pathologic staging could be performed after cystectomy (with lymphadenectomy) (Stein et al. 2001; Shariat et al. 2006).
- Neoadjuvant chemotherapy has been added as a stratification factor to control for the potential differences in local standard care in major regions and for any differences in outcomes based upon the receipt of prior neoadjuvant chemotherapy.
- The level of PD-L1 expression by IHC has been shown to correlate with recurrence or OS in patients with UC (McDaniel et al. 2016; Bellmunt et al. 2015).

### 3.3.6 Rationale for Atezolizumab Dose and Schedule

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

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 was also informed by available clinical activity, safety, PK, and immunogenicity data. Anti-tumor activity has been observed across doses from 1–20 mg/kg in Study PCD4989g (see Section 1.2.2.3). In Study PCD4989g, the MTD of atezolizumab was not reached, and no DLTs were observed at any dose levels.

Available preliminary PK data (0.03–20 mg/kg) suggests that for doses ≥ 1 mg/kg, atezolizumab generally exhibits pharmacokinetics that are both linear and consistent with typical IgG1 antibodies (see Section 1.2.2.4). Detectable ATAs were observed in patients at all dose levels but were associated with changes in pharmacokinetics for some patients in the lower dose cohorts only (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 the development of detectable ATAs does not appear to have a significant impact on pharmacokinetics for doses from 10–20 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 minimize the potential of both interpatient variability and possible effect of ATAs leading 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 using the methodology of Bai et al. (2012) do not suggest any clinically meaningful differences in exposure for atezolizumab following a fixed dose or dose adjusted for weight. On the basis of this analysis, a fixed dose of 1200 mg (equivalent to a body weight–based dose of 15 mg/kg) was selected for ongoing and future studies of atezolizumab.

A 1-year period of adjuvant treatment has been selected because this is believed to balance the risks and tolerability of therapy with the expected benefit in the adjuvant setting on the basis of an assessment of benefit versus risk observed in the metastatic setting.

### 3.3.7 Rationale for Collection of Archival and/or Pre-Treatment Tumor Specimens

In this study, surgical resection or lymph node dissection tumor specimens from patients will be prospectively tested for PD-L1 expression by a central laboratory during the screening period and PD-L1 status (IHC score of IC0/1 vs. IC2/3) will be used as one of the stratification factors. In addition to the assessment of PD-L1 status, other exploratory markers, such as potential predictive and prognostic markers related to the clinical benefit of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may also be analyzed.

Patients with additional pre-study tumor tissue samples (i.e., beyond those required to meet eligibility requirements) from procedures performed at different times during the course of their UC will be requested (but not required) to also submit these samples for central testing. Tissue samples obtained at multiple times from individual patients will greatly contribute to an improved understanding of the dynamics of PD-L1 expression and relationship with intervening anti-cancer therapy.

### 3.3.8 Rationale for Blood Sampling for Biomarkers and for Optional Collection of Tumor Specimens

Changes in different blood biomarkers may provide evidence for biologic activity of atezolizumab in humans and may allow for the development of a blood-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 samples.

In addition, potential correlations of these pharmacodynamic markers with the dose, safety, and anti-tumor activity of atezolizumab will be explored.

For this study, a confirmatory tumor biopsy is mandatory at the time of disease recurrence. Analysis of biomarkers in the tumor samples may explain why UC recurs and help develop further treatment. However, it is optional for patients to agree for their biopsy samples to be placed in the Roche Clinical Repository (RCR; see Section 4.5.12). *After the primary analysis, a confirmatory tumor biopsy is optional at the time of disease recurrence.*

## 3.4 OUTCOME MEASURES

### 3.4.1 Efficacy Outcome Measures

#### 3.4.1.1 Primary Efficacy Outcome Measure

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

- Investigator-assessed DFS, defined as the time from randomization to the time of first occurrence of a DFS event, defined as any of the following:

  Local (pelvic) recurrence of UC (including soft tissue and regional lymph nodes)

  Urinary tract recurrence of UC (including all pathological stages and grades)

  Distant metastasis of UC

  Death from any cause

#### 3.4.1.2 Secondary Efficacy Outcome Measures

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

- OS, defined as the time from randomization to the date of death from any cause
- DSS, defined as the time from randomization to the date of death from UC per investigator assessment of cause of death
- DMFS, defined as the time from randomization to the date of diagnosis of distant (i.e., non-locoregional) metastases or death from any cause

- NURFS, defined as the time from randomization to the time of first occurrence of a NURFS event, defined as any of the following:

  Local (pelvic) recurrence of UC (including soft tissue and regional lymph nodes)

  Distant metastasis of UC

  Death from any cause

### 3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events graded according to NCI CTCAE v4.0
- Changes in vital signs and clinical laboratory results
- Incidence of ATA response to atezolizumab and potential correlation with PK, pharmacodynamic, safety, and efficacy parameters

### 3.4.3 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Maximum observed serum atezolizumab concentration ($C_{max}$) after infusion on Day 1 of Cycle 1
- Minimum observed serum atezolizumab concentration ($C_{min}$) prior to infusion on Day 1 of Cycles 1, 2, 3, and 4; every 8 cycles starting on Cycle 8; at treatment discontinuation; and at 120 days ($\pm$30 days) after the last dose of atezolizumab

### 3.4.4 Patient-Reported Outcome Measure

The PRO outcome measure for this study is as follows:

- EQ-5D-5L as a measure of patient-reported health status

### 3.4.5 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Status of tumor immune-related or disease type−related exploratory biomarkers in archival and/or freshly obtained tumor tissues and association with disease recurrence
- Status of exploratory biomarkers in plasma, whole blood, or serum (including but not limited to cytokines such as IL-6) collected before or during treatment with atezolizumab or at recurrence and association with disease recurrence

## 4. MATERIALS AND METHODS

## 4.1 PATIENTS

### 4.1.1 Inclusion Criteria

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

- Histologically confirmed muscle-invasive UC (also termed TCC) of the bladder or upper urinary tract (i.e., renal pelvis, or ureters)

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

- TNM classification (UICC/AJCC 7th edition) at pathological examination of surgical resection specimen as follows:

  For patients treated with prior neoadjuvant chemotherapy: tumor stage of ypT2–4a or ypN+ (ypT2-4 or ypN+ for patients with UTUC) and M0

  For patients who have not received prior neoadjuvant chemotherapy: tumor stage of pT3–4a or pN+ (pT3-4 or pN+ for patients with UTUC) and M0

- Surgical resection of muscle-invasive UC of the bladder, or UTUC upper tract

  For patients with MIBC, radical cystectomy may be performed by the open, laparoscopic, or robotic approach. Cystectomy must include bilateral lymph node dissection, the extent of which will be at the discretion of the treating surgeon but optimally should extend at a minimum from the mid common iliac artery proximally to Cooper's ligament distally, laterally to the genitofemoral nerve, and inferiorly to the obturator nerve. The method of urinary diversion for patients undergoing cystectomy will be at the discretion of the surgeon and choice of the patient.

  Patients with a negative surgical margin (i.e., R0 resection) or with carcinoma in situ (CIS) at the distal ureteral or urethral margin will be eligible.

  Patients with a positive R2 margin (which is defined as a tumor identified at the inked perivesical fat margin surrounding the cystectomy specimen) or R1 margin (which is defined as evidence of microscopic disease identified at the tumor margin), except for CIS at distal ureteral or urethral margin, will be excluded.

  For patients with UTUC, RNU, with excision of the bladder cuff is required and may be performed by the open or laparoscopic approach. RNU must include lymph node dissection (LND), the extent of which will be at the discretion of the treating surgeon but optimally should include the para-aortic, paracaval or interaortocaval nodes from the renal hilum to the inferior mesenteric artery in renal pelvis and proximally ureteral tumors, or nodes from the renal hilum to the bifurcation of the common iliac artery and ipsilateral pelvic nodes in mid and lower ureteral tumors, respectively.

  Patients must have a negative surgical margin (i.e., R0 resection). Patients with a positive R1 or R2 surgical margin will be excluded.

- Patients who have not received prior platinum-based neoadjuvant chemotherapy, have refused or are ineligible (“unfit”) for cisplatin-based adjuvant chemotherapy

  Patients who have received at least two cycles of a platinum-containing regimen will be considered as those who have received prior neoadjuvant chemotherapy.

Cisplatin ineligibility is defined by any one of the following criteria:

Impaired renal function (glomerular filtration rate [GFR]< 60 mL/min); GFR should be assessed by direct measurement (i.e., creatinine clearance or ethyldediaminetetra-acetate) or, if not available, by calculation from serum/plasma creatinine (Cockcroft-Gault formula)

A hearing loss (measured by audiometry) of 25 dB at two contiguous frequencies

Grade 2 or greater peripheral neuropathy (i.e., sensory alteration or parasthesis including tingling)

ECOG performance status of 2 (see Appendix 7)

- Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens from surgical resection (i.e., radical cystectomy, nephroureterectomy, or lymph node dissection) in paraffin blocks (blocks preferred) or at least 15 unstained slides, with an associated pathology report, for central testing and determined to be evaluable for tumor PD-L1 expression prior to study enrollment

  Patients with fewer than 15 unstained slides available at baseline (but no fewer than 10) may be eligible following discussion with Medical Monitor.

  Tumor tissue of bladder or upper tract should be of good quality based on total and viable tumor content and must contain a muscle invasive component (i.e., T2 or greater) of the tumor as verified by local pathology review. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.

  Patients having additional tissue samples from procedures performed at different times during the course of their muscle-invasive UC (e.g., a specimen from a prior transurethral resection of bladder tumor [TURBT]) or having lymph node involvement identified at lymph node dissection will be requested (but not required) to also submit these samples for central testing. Tissue samples obtained at multiple times or anatomical sites for individual patients will greatly contribute to an improved understanding of the dynamics of PD-L1 expression and relationship with intervening anti-cancer therapy.

  In situations where multiple specimens were received from different sites or at different times, the score from the surgical resection of the primary tumor or lymph node dissection specimen will be used for both primary and secondary analyses.

- Muscle-invasive UC with PD-L1 expression per IHC (see Appendix 3) prospectively determined on the surgical resection or lymph node dissection tumor specimens by a central laboratory

- Absence of residual disease and absence of metastasis, as confirmed by a negative baseline computed tomography (CT) or magnetic resonance imaging (MRI) scan of the pelvis, abdomen, and chest no more than 4 weeks prior to randomization.

  For patients with MIBC, imaging of the upper urinary tracts must include one or more of the following: intravenous pyelogram (IVP), CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy or MRI urogram, and must be completed no more than 4 weeks prior to randomization.

  For patients with UTUC, cystoscopy and urine cytology must be completed no more than 4 weeks prior to randomization, however upper tract imaging is not needed.

  Other examinations should be performed as clinically indicated.

  For patients with both primary MIBC and primary UTUC, imaging of the upper urinary tracts, cystoscopy, and urine cytology is not required.
- Full recovery from cystectomy or nephroureterectomy within 14 weeks following surgery
- ECOG performance status of $\leq 2$ (see Appendix 7)
- Life expectancy $\geq 12$ weeks
- Adequate hematologic and end-organ function, as defined by the following laboratory results obtained within 14 days prior to the first study treatment:

  ANC $\geq 1500$ cells/$\mu$L (without granulocyte colony–stimulating factor support within 2 weeks prior to Cycle 1, Day 1)

  WBC counts $> 2500/\mu L$

  Lymphocyte count $\geq 300/\mu L$

  Platelet count $\geq 100{,}000/\mu L$ (without transfusion within 2 weeks prior to Cycle 1, Day 1)

  Hemoglobin $\geq 9.0$ g/dL

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

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

  Serum bilirubin $\leq 1.0 \times$ ULN

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

  PTT/PT $\leq 1.5 \times$ ULN or INR $< 1.7 \times$ ULN

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

  Calculated creatinine clearance $\geq$ 20 mL/min (Cockcroft-Gault formula)

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 5 months after the last dose of atezolizumab, and agreement to 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 trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

### 4.1.2 Exclusion Criteria

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

#### Cancer-Specific Exclusion Criteria

- Any approved anti-cancer therapy, including chemotherapy, or hormonal therapy within 3 weeks prior to initiation of study treatment

  Hormone-replacement therapy or oral contraceptives are allowed.

- Adjuvant chemotherapy or radiation therapy for UC following surgical resection

  Patients who have received primary chemoradiation for bladder preservation before cystectomy are eligible and will be treated as the same as patients who have received prior neoadjuvant chemotherapy.

  Post-surgical intrapelvic/intravesical chemotherapy or BCG is not allowed for patients with UTUC.

- Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days or five half-lives of the drug, whichever is longer, prior to enrollment

- Malignancies other than UC within 5 years prior to Cycle 1, Day 1:

  Patients with high risk UTUC (defined as tumor stage ypT2–4a or ypN+) within 5 years prior to Cycle 1 Day 1 will be ineligible after the UTUC limit of approximately 10% has been met.

Patients with localized low risk prostate cancer (defined as Stage ≤T2b, Gleason score ≤7, and PSA at prostate cancer diagnosis ≤20 ng/mL [if measured]) treated with curative intent and without prostate-specific antigen (PSA) recurrence are eligible.

Patients with low risk prostate cancer (defined as Stage T1/T2a, Gleason score ≤7 and PSA ≤10 ng/mL) who are treatment-naive and undergoing active surveillance are eligible.

Patients with malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death <5% at 5 years) are eligible provided they meet all of the following criteria:

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

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

### General Medical Exclusion Criteria

- Pregnancy or breastfeeding
- 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 or any component 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 antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 5 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.

  Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen may be eligible for this study.
- 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

- Patients with active hepatitis B virus (HBV; chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

    Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBc Ab] and absence of HBsAg) are eligible. HBV DNA must be obtained in these patients prior to Cycle 1, Day 1.

    Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Active tuberculosis
- Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1
- Receipt of therapeutic oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1

    Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent 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

    Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction $<$ 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
- Major surgical procedure other than for diagnosis within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study
- Prior allogeneic stem cell or solid organ transplant
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 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 through May in the Northern Hemisphere and approximately 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 randomization, during treatment or within 5 months following the last dose of atezolizumab (for patients randomized to atezolizumab).
- Any other disease, 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

### Medication-Related Exclusion Criteria

- Prior treatment with CD137 agonists or immune checkpoint–blockade therapies, including anti-CD40, anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including but not limited to interferons, IL-2) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to Cycle 1, Day 1
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1, or anticipated requirement for systemic immunosuppressive medications during the trial

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea, multiple doses for contrast allergy) may be enrolled in the study.

  The use of inhaled or low-dose (e.g., ≤ 10 mg/day prednisone) corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, mineralocorticoids (e.g., fludrocortisone for adrenal insufficiency) and low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

## 4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study. The investigator and patient will not be blinded to treatment assignment.

After written informed consent has been obtained and eligibility has been established, the study site will obtain the patient's identification number and treatment assignment from the Interactive Voice/Web Response System (IxRS).

Patients will be randomized to one of the following two treatment arms in a 1:1 ratio:

- Arm A (experimental arm): Atezolizumab 1200 mg q3w for 16 cycles or 1 year (whichever occurs first)
- Arm B (control arm): Observation q3w for 16 cycles or 1 year (whichever occurs first)

Randomization will be stratified by the following factors:

- Number of lymph nodes resected (< 10 vs. ≥ 10)
- Nodal status (positive vs. negative)
- Tumor stage after surgical resection (≤ pT2 vs. pT3/pT4)
- PD-L1 status (IC0/1 vs. IC2/3)
- Prior neoadjuvant chemotherapy (yes vs. no)

A stratified permuted-block randomization method will be implemented in order to obtain a balanced assignment to each treatment within levels of the stratification factors.

## 4.3 STUDY TREATMENT

Atezolizumab is considered the investigational medicinal product (IMP) in this study.

### 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.

### 4.3.2 Dosage, Administration, and Compliance

#### 4.3.2.1 Atezolizumab

The dose level of atezolizumab to be tested in this study is 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) administered by IV infusion q3w (21 [±3] days) × 16 cycles or 1 year (whichever occurs first).

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. For further details, see the Atezolizumab Pharmacy Manual and Investigator’s Brochure.

Atezolizumab infusions will be administered per the instructions outlined in Table 7.

**Table 7 Administration of First and Subsequent Infusions of Atezolizumab**

| First Infusion | Subsequent Infusions |
|---|---|
| • No pre-medication is allowed.<br>• Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion.<br>• Infuse atezolizumab (one vial in 250 mL NaCl) over 60 (±15) minutes.<br>• Record patient's vital signs during the infusion and/or 30 minutes (± 10) after the infusion if clinically indicated.<br>• Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. | • If patient experienced infusion-related reaction during any previous infusion, pre-medication with antihistamines may be administered for Cycles ≥2 at the discretion of the treating physician.<br>• If the patient tolerated the first infusion well without infusion-associated adverse events, the second infusion may be delivered over 30 (±10 minutes) minutes.<br>• If the patient had an infusion-related reaction during the previous infusion, the subsequent infusion must be delivered over 60 (±15) minutes.<br>• If clinically indicated or patient experienced symptoms during the previous infusion, record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion, during the infusion and/or 30 minutes (± 10) after the infusion.<br>• If no reaction occurs, continue subsequent infusions over 30 (±10) minutes with same schedule for recording vital signs. |

NaCl = sodium chloride.

For anaphylaxis precautions, see Appendix 6.

Guidelines for dosage modification and treatment interruption or discontinuation and the management of specific adverse events are provided in Sections 5.1.3, 5.1.4 and Appendix 9.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF (see Section 5.3.5.12).

See the Atezolizumab Investigator's Brochure and Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

### 4.3.3 Investigational Medicinal Product Accountability

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer, small-cell lung cancer, and triple-negative breast cancer. The investigational medicinal product (IMP) required for completion of this study, atezolizumab, will be

provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

### 4.3.4 Post-Trial Access to 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 with Atezolizumab

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to written informed consent until the treatment/observation discontinuation visit. All such medications should be reported to the investigator.

Premedication with antihistamines may be administered for any atezolizumab infusions after Cycle 1.

The following therapies should continue while patients are in the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as low–molecular weight heparin or warfarin at a stable dose level)
- Inactive influenza vaccinations during influenza season ONLY
- Megestrol administered as an appetite stimulant
- Inhaled or low-dose corticosteroids for COPD, or asthma
- Mineralocorticoids (e.g., fludrocortisone)

- Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, as per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and $\beta_2$-adrenergic agonists; see Appendix 6.

All medications must be recorded on the Concomitant Medications eCRF.

### 4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

Systemic corticosteroids and TNF-$\alpha$ inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations where systemic corticosteroids or TNF-$\alpha$ inhibitors would be routinely administered, alternatives (including antihistamines) should be considered first by the treating physician. If the alternatives are not feasible, systemic corticosteroids and TNF-$\alpha$ inhibitors may be administered at the discretion of the treating physician, including use of corticosteroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance).

Systemic corticosteroids are recommended and permitted for management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, potential pancreatic or eye toxicity and other immune-mediated adverse events when associated with atezolizumab therapy, at the discretion of the treating physician (see the Atezolizumab Investigator's Brochure for details; see Appendix 6 for precautions for anaphylaxis).

The concomitant use of herbal therapies is not recommended as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, their use for patients on study is allowed at the discretion of the investigator.

### 4.4.3 Prohibited Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment (depending on the anticancer agent; see Section 4.1.2) and during study treatment until disease recurrence is documented and patient has discontinued study treatment. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, intravesical therapy, or investigational agents

  UTUC patients with bladder recurrence of papillary urothelial neoplasm of low malignant potential (PUNLMP) or low-grade papillary urothelial carcinoma (pTa), requiring local resection may still be eligible to continue study treatment, at the discretion of the investigator.

The following medications are prohibited for patients randomized to atezolizumab during study treatment, unless otherwise noted:

- Any live, attenuated vaccine (e.g., FluMist®) within 28 days prior to randomization, during treatment or within 5 months following the last dose of atezolizumab (for patients randomized to atezolizumab)
- Immunomodulatory agents, including but not limited to interferons or IL-2, during the entire study; these agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab

## 4.5 STUDY ASSESSMENTS

Refer to Appendix 1 for the schedule 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; 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 preclude the visit, the visit should be scheduled on the nearest following feasible date.

### 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.

Prior to signing the main consent form for the study, patients may specifically allow for the collection and testing of archival or fresh tumor tissue by signing the prescreening Informed Consent Form.

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

### 4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, 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 written informed consent.

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

### 4.5.3 Physical Examinations

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

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

### 4.5.4 Vital Signs

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

For patients assigned to atezolizumab treatment (Arm A), at first infusion, vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before the infusion. Additional vital signs will be recorded at the first or following infusions only if clinically indicated (see Table 7). Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Vital signs will be performed as standard of care if clinically indicated for patients randomized to the observation arm (Arm B).

### 4.5.5 Surveillance for UC Recurrence

Patients will be assessed for tumor recurrence every 12 weeks for Years 1–3, every 24 weeks for Years 4–5, and at Year 6 (approximately 48 weeks after the last assessment in Year 5) until occurrence of a DFS event, loss to follow-up, withdrawal of consent, or study termination, whichever occurs first, regardless of length of treatment/observation. *After the primary analysis, patients in Years 1–3 of the study may be assessed for tumor recurrence every 24 weeks.*

For patients with MIBC, surveillance for tumor recurrence must include physical examination, and imaging studies of the chest, abdomen, upper urinary tracts, and pelvis. Imaging of the upper urinary tracts is required and may include one or more of the following: IVP, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram. However, separate imaging of the upper urinary tracts during surveillance via one of these modalities is not required if the upper tracts are covered in the imaging of the abdomen and pelvis. Other examinations such as laboratory evaluation (e.g., to monitor tumor recurrence in liver or bone), urine cytology or bone scan should be performed as clinically indicated.

For patients with UTUC, surveillance for tumor recurrence must include physical examination, cystoscopy, urine cytology and imaging studies of the chest, abdomen, and pelvis, however upper tract imaging is not needed. Other examinations such as laboratory evaluation (e.g., to monitor tumor recurrence in liver or bone) or bone scans should be performed as clinically indicated.

For patients with primary MIBC and primary UTUC, imaging of the upper urinary tracts, cystoscopy, and urine cytology are not required.

All eligible patients will undergo a contrast-enhanced CT or MRI of the chest, abdomen, and pelvis at screening (no more than 4 weeks prior to randomization). In patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance), MRIs of the abdomen and pelvis with a non-contrast CT scan of the chest may be used. For MIBC patients with renal impairment or contrast allergy, upper tract imaging is still required. For patients with renal impairment, CT urography with a reduced contrast agent or a non-contrasted MRI is recommended. For patients with a contrast allergy, non-contrasted MRI urogram or ureteroscopy is recommended.

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

Surveillance imaging studies should use the same imaging modality that was used at screening and be performed at the timepoints specified in Appendix 1, regardless of drug delays or interruptions.

If recurrent disease or occurrence of a new primary tumor is suspected on clinical grounds, imaging studies must be performed expeditiously, even if not mandated in the schedule of assessments.

All patients who present with findings suspicious for disease recurrence must undergo a confirmatory biopsy for histopathologic confirmation. Biopsy can only be waived for patients who have no lesions amenable for biopsy at disease recurrence, following discussion with and approval by the Medical Monitor. *After the primary analysis, a confirmatory tumor biopsy is optional at the time of disease recurrence.*

Disease recurrence will be determined by the investigator based on radiographic evidence. For patients with UTUC, disease recurrence determined by visual appearance of UC in bladder is acceptable with histopathologic confirmation. Cases for which biopsy results definitively rule out recurrence of UC will not be considered as disease recurrence for this study. *After the primary analysis, a confirmatory tumor biopsy is optional at the time of disease recurrence.*

### 4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for hematology, serum chemistries, coagulation, urinalysis, and the pregnancy test will be analyzed at the study site's local laboratory. 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 pharmacodynamic biomarkers, ATA assays, and auto-antibody testing. Instruction manuals and supply kits will be provided for all central laboratory assessments.

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 (aPTT and INR)
- Serum pregnancy test during screening and serum or urine pregnancy tests during the study (for women of childbearing potential, including women who have had a tubal ligation)
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)
- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4)

- All patients will be tested for HIV prior to the inclusion into the study, and HIV-positive patients will be excluded from the clinical trial.
- HBV serology (HBsAg, antibody to HBsAg [anti-HBs], anti-HBc)

  HBV DNA is required on or before Cycle 1, Day 1 if patient has negative serology for HBsAg and positive serology for anti-HBc.
- HCV serology (anti-HCV)

Instruction manuals and supply kits will be provided for all central laboratory assessments. The following assessments will be performed at a central laboratory or by the Sponsor:

- ATA assays (patients assigned to atezolizumab only)

  Serum samples will be assayed for the presence of ATAs to atezolizumab with use of validated immunoassays.
- PK assays (patients assigned to atezolizumab only)

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

  Residual PK and ATA samples will be retained for further method development, validation and characterization. Samples will be stored for 5 years after the study results have been reported.
- Auto-antibody testing (patients assigned to atezolizumab only); baseline sample to be collected on Cycle 1, Day 1 prior to the first dose of study drug. For patients who show evidence of immune-mediated toxicity, additional samples may be collected and all samples will be analyzed centrally.

  Anti-nuclear antibody

  Anti–double-stranded DNA

  Circulating anti-neutrophil cytoplasmic antibody

  Perinuclear anti-neutrophil cytoplasmic antibody
- Biomarker assays

  Blood 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 2. Samples will be processed to obtain plasma and serum 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).

### 4.5.7 Resected Tumor Tissue Samples

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

See the Laboratory Manual for additional details on tissue sample handling.

#### 4.5.7.1 Resected Tumor Tissues for Screening

Representative FFPE tumor specimens in paraffin blocks (blocks preferred) or at least 15 unstained slides, with an associated pathology report, must be submitted for central testing for determination of sufficient viable tumor content prior to study enrollment; tumor specimens will be evaluated for PD-L1 expression.

Tumor tissue 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). Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.

Patients having additional tissue samples from procedures performed at different times during the course of their UC will be requested (but not required) to also submit these samples for central testing. Tissue samples obtained at multiple times for individual patients will greatly contribute to an improved understanding of the dynamics of PD-L1 expression and relationship with intervening anti-cancer therapy.

The status of immune-related and tumor type–related and other exploratory biomarkers (including but not limited to T-cell markers and tumor mutation status) in archival and fresh tumor tissue samples of enrolled patients may be evaluated.

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.

#### 4.5.7.2 Tumor Biopsy at the Time of Disease Recurrence

Biopsy at the time of first radiographic confirmation of disease recurrence is mandatory for all randomized patients (in both Arms A and B). Biopsy can only be waived for patients who have no lesions amenable for biopsy at disease recurrence, following discussion with and approval by the Medical Monitor. *After the primary analysis, a confirmatory tumor biopsy is optional at the time of disease recurrence.*

Acceptable samples include resections; core needle biopsies for deep tumor tissue or lymph nodes; or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. For core needle biopsy specimens, at least three cores should be submitted for evaluation.

The status of immune-related and tumor type–related, and other exploratory biomarkers (including but not limited to T-cell markers and tumor mutation status) in tumor tissue samples of enrolled patients may be evaluated.

Next-Generation Sequencing (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 recurrence in the form of an NGS report, which is available upon request directly from Foundation Medicine. The investigator may share and discuss the results with the patient, unless the patient chooses otherwise.
The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions.

#### 4.5.7.3 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.

### 4.5.8 Anti-Therapeutic Antibody Testing (Atezolizumab-Treated Patients Only)

Atezolizumab may elicit an immune response. Patients with signs of any potential immune response to atezolizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect ATAs at multiple timepoints before, during, and after treatment with atezolizumab (see Appendix 2 for the schedule).
The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Rosenberg et al. 2004; Koren et al. 2008) to characterize ATA responses to atezolizumab in support of the clinical development program. This tiered strategy will include an assessment of whether ATA responses correlate with relevant clinical endpoints. Implementation of ATA characterization assays will depend on the safety profile and clinical immunogenicity data.

### 4.5.9 Electrocardiograms

A twelve-lead ECG is required at screening and when clinically indicated during study. ECGs for each patient should be obtained from the same machine wherever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

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

### 4.5.10 Patient-Reported Outcomes

The EQ-5D-5L is a generic preference-based HRQoL questionnaire that provides a single index value for health status (see Appendix 8) and is used to inform pharmacoeconomic evaluations and to measure general health status. The EQ-5D-5L consists of two parts; the first part, health state classification, contains five dimensions of

health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. From these five items, a utility measure is obtained for each patient. The second part, consisting of a visual analog scale (VAS), allows the patient to indicate, on a scale of 0–100, how his or her health is on the day of assessment, with 100 being the "best imaginable health state" and 0 being the "worst imaginable health state." The VAS score will be used as a measure of overall health status.

The EQ-5D-5L will be administered every 6 weeks during study treatment/observation. After discontinuation of the treatment/observation period, for patients who have not experienced disease recurrence, the EQ-5D-5L will be administered at the same schedule as the assessments for disease recurrence (see Section 4.5.5). The EQ-5D-5L will also be recorded (in both study arms) at 6, 12, and 24 weeks after occurrence of a DFS event. *After the primary analysis, the EQ-5D-5L assessments are no longer required for patients who are in disease recurrence follow-up or who have had a DFS event.*

During study treatment/observation, the EQ-5D-5L will be administered at the study sites. The PRO questionnaires, translated as required in the local language, will be distributed by the investigator's staff and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires filled out at the study sites should be self-administered at the investigational site prior to the completion of other study assessments and the administration of study treatment. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. Hard copy originals of the questionnaires must be maintained as part of the patient's medical record at the site for source data verification. These originals should have the respondent's initials on each page in compliance with good clinical practices.

Assessments of the EQ-5D-5L at 6, 12, and 24 weeks after a DFS event will be administered by telephone. Interviews will be conducted by trained site staff and in compliance with best practices and recommendations by EuroQol. Study personnel will record patient responses on a paper copy of the EQ-5D-5L during the telephone interview as record of source documentation. *After the primary analysis, the EQ-5D-5L assessments are no longer required for patients who have had a DFS event.*

### 4.5.11 Age-Adjusted Charlson Comorbidity Index (ACCI)

ACCI (see Appendix 4) is a significant independent predictor for OS and for cancer-specific mortality following radical cystectomy in multivariate analysis that included other clinicopathologic features (Koppie et al. 2008; Mayr et al. 2012). A baseline ACCI should be determined for every patient.

### 4.5.12 Optional Biopsies and Samples for Roche Clinical Repository (Optional Future Research)

#### 4.5.12.1 Overview of the Roche Clinical Repository

The 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, 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 recurrence
- 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 (Section 4.5.12) will not be applicable at that site.

#### 4.5.12.3 Sample Collection

The following samples will be collected for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers:

- Remaining blood derivatives (serum, plasma, PBMCs and their 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
- Optional tissue samples collected for biopsy during the study (preferably at the time of disease recurrence)

The following samples will be collected for research purposes, including but not limited to research on genetic (inherited) biomarkers:

- Whole blood sample for DNA isolation

This sample will be collected from patients who have consented to optional RCR sampling at baseline as shown in the schedule of assessments in Appendix 1. If, however, the RCR genetic blood sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study. Collection of whole blood will enable the evaluation of single nucleotide polymorphisms in genes associated with immune biology including but not restricted to the target and pathway associated genes such as PD-L1, PD-1, and B7.1 as well as IL-8, IL-6, and related cytokines. The sample may be processed using techniques such as kinetic PCR and DNA sequencing.

For all samples, dates of consent 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).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

#### 4.5.12.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "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.

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.

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 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.

#### 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 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 trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RCR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from Study WO29636 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 WO29636.

#### 4.5.12.7 Monitoring and Oversight

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

### 4.5.13 Timing of Study Assessments

Flowcharts of scheduled study assessments are provided in Appendix 1 and Appendix 2. 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; 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.

#### 4.5.13.1 Screening and Pre-Treatment Assessments

Prior to signing the main consent form for the study, patients may specifically allow for the collection and testing of archival or fresh tumor tissue by signing the pre-screening consent form. Written informed consent for participation in the study (on the main study Informed Consent Form) 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.

Screening tests and evaluations will be performed within 28 days prior to randomization, unless otherwise specified. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days (or as otherwise specified) prior to randomization may be used; such tests do not need to be repeated for screening. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

See Appendix 1 for the schedule of screening and pre-treatment assessments.

#### 4.5.13.2 Assessments during Treatment/Observation

All visits must occur within ±3 days from the scheduled date unless otherwise noted (see Appendix 1). All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study

treatment infusion unless otherwise noted. Local laboratory assessments from each cycle must be reviewed prior to study treatment administration for each cycle.

See the table provided in Appendix 1 for the schedule of treatment/observation period assessments.

The following assessments may be performed ≤96 hours before Day 1 of each cycle: ECOG performance status, limited physical examination, local/central laboratory tests, adverse event evaluation, and concomitant medication evaluation.

For patients in Arm A, if scheduled dosing is precluded because of a holiday, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule. If treatment was postponed for fewer than 2 days, the patient can resume the original schedule. For patients in both arms, if scheduled study assessments cannot be obtained because of a holiday, these assessments should then be obtained at the soonest following date, provided that the soonest following date is not within 2 days of other regularly scheduled study assessments.

Assessments for disease recurrence should continue to occur as specified in Section 4.5.5, regardless of treatment delays.

After five cycles have been completed, one cycle may be delayed by 1 week (i.e., 28 days instead of 21 days for one cycle) for one time to allow for vacations.

Blood samples for pharmacodynamic biomarker analysis and pharmacokinetics will be obtained for patients in Arm A according to the schedule in Appendix 2.

#### 4.5.13.3 Assessments at Treatment/Observation Discontinuation Visit

Atezolizumab-treated patients (in Arm A) who discontinue early from treatment or who complete the study treatment in full (16 cycles or 1 year, whichever occurs first) will be asked to return to the clinic not more than 30 days after the last treatment for a treatment discontinuation visit. The visit at which the decision is made to discontinue treatment (e.g., disease recurrence is determined or confirmed) may be used as the treatment discontinuation visit.

Patients randomized to observation (in Arm B) and who discontinue early from the observation period or who complete observation in full (16 cycles or 1 year, whichever occurs first) will also be asked to return to the clinic not more than 30 days after the last cycle visit for an observation discontinuation visit. The visit at which the decision is made to discontinue patient from the observation period (e.g., disease recurrence is determined or confirmed) may be used as the observation discontinuation visit.

See Appendix 1 and Appendix 2 for the schedule of assessments performed at the treatment/observation discontinuation visit.

## 4.6 FOLLOW-UP ASSESSMENTS

### 4.6.1 Ongoing Imaging Assessments for Disease Recurrence

Patients assigned to atezolizumab (Arm A) who complete the treatment phase (16 cycles or 1 year, whichever occurs first) will discontinue treatment with atezolizumab. Patients without recurrence will continue to undergo imaging assessments for recurrence (disease recurrence follow-up phase) every 12 weeks for 2 years (i.e., during Years 2 and 3); every 24 weeks for another 2 years (i.e., during Years 4 and 5); and at Year 6, until DFS event, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. *After the primary analysis, patients in Years 2–3 of the study may be assessed for tumor recurrence every 24 weeks.* Investigators may perform additional scans or more frequent assessments if clinically indicated. Patients who discontinue study drug for reasons other than disease recurrence (e.g., toxicity) should continue to undergo scheduled imaging assessments for recurrence until DFS event, loss to follow-up, consent withdrawal, or study termination by the Sponsor whichever occurs first.

Patients assigned to observation (Arm B) who complete the initial observation period (16 cycles or 1 year, whichever occurs first) will also continue to undergo imaging assessments as specified above for Arm A patients. Investigators may perform additional scans or more frequent assessments if clinically indicated.

### 4.6.2 Adverse Events

All adverse events, regardless of attribution, will be recorded until 30 days after the last dose of study drug (for patients in Arm A) or 30 days after the last day of the observation period (for patients in Arm B), or the initiation of another anticancer therapy, whichever occurs first. Serious adverse events (see Section 5.2.2) and protocol defined adverse events of special interest (see Section 5.2.3) will be recorded until 90 days after the last dose of study drug or until the initiation of another anti-cancer therapy, whichever occurs first (for patients in Arm A).

After the treatment/observation discontinuation visit, adverse events should be followed as outlined in Section 5.6.

### 4.6.3 Anti-Therapeutic Antibody and Pharmacokinetic Assessments

For patients assigned to atezolizumab only, a post-treatment ATA and PK sample should be collected 120 days (±30 days) after the last dose of study drug unless the patient withdraws consent or the study closes.

See the schedules of assessments provided in Appendix 1 and Appendix 2 for specified follow-up assessments.

### 4.6.4 Survival and Subsequent Anti-Cancer Therapy

Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months *from the completion or discontinuation of the treatment/observation period* until death, loss to follow-up, or study termination by the Sponsor. All patients will be followed for survival and all new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up (this request must be documented in the source documents and signed by the investigator) or the study is terminated by the Sponsor. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Patients who have completed the treatment or observation phase and continue in disease recurrence follow-up should have survival follow-up *in parallel* approximately every 3 months. All patients must still be followed for new anti-cancer therapy.

Before considering a patient lost to follow-up, at least three different documented attempts to contact them should be made. If local regulations permit, the attempts should include but not be limited to:

- A written contact (e.g., letter by certified mail or email with read receipt)
- Contact with the patient's primary care physician (where the patient has consented to this type of contact)

## 4.7 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

### 4.7.1 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. Patients who withdraw their consent to be followed for the primary study endpoint (DFS) will be asked to continue follow-up for OS. 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.

### 4.7.2 Discontinuation from Study Drug

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

- Pregnancy
- Disease recurrence (local recurrence, urinary tract recurrence, or distant metastasis of UC), as determined by the investigator, documented by radiographic evidence. For patients with UTUC, disease recurrence determined by visual appearance of UC in bladder is acceptable with histopathologic confirmation. For UTUC patients with bladder recurrence of PUNLMP or low-grade pTa, continuation of study treatment is allowed after local resection.

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

### 4.7.3 Study and Site Discontinuation

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

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

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

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

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

## 5. ASSESSMENT OF SAFETY

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer, small-cell lung cancer, and triple-negative breast cancer. Safety studies are currently ongoing and the entire safety profile is not known at this time. The following information is based on results from nonclinical and clinical studies and published data on similar molecules.

## 5.1 SAFETY PLAN

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2) and close monitoring (as indicated below and in Section 4.5). An iDMC has also been incorporated into the trial design to periodically review aggregate safety data (see the iDMC Charter for a detailed monitoring plan).

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. All adverse events and serious adverse events will be recorded during the trial. Serious adverse events and adverse events of special interest will be recorded until 90 days after the last dose of study drug or until the initiation of another anti-cancer therapy (whichever occurs first) and all other adverse events will be recorded until 30 days after the last dose of study drug or until the initiation of another anti-cancer therapy, whichever occurs first. After this period, investigators should report any serious adverse events that are believed to be related to prior treatment with study drug. The potential safety issues anticipated in this trial, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections and management of atezolizumab-specific adverse events are outlined in Appendix 9.

### 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 9 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab (see Appendix 6 for precautions for anaphylaxis).

### 5.1.2 General Plan to Manage Safety Concerns

#### 5.1.2.1 Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this trial. 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 4 weeks of randomization are excluded from the study (see Section 4.1.2 for additional details).

#### 5.1.2.2 Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events defined and graded according to NCI CTCAE v4.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Laboratory values must be reviewed prior to each infusion.

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).

During the study, patients will be closely monitored for the development of any adverse events, including signs or symptoms of autoimmune conditions and infection.

All serious adverse events (see Section 5.2.2) and protocol-defined events of special interest (see Section 5.2.3) will be reported in an expedited fashion (see Section 5.4.2). In addition, the iDMC will review safety data as described in Section 3.1.1.

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.

For patients in Arm A who have an ongoing study drug–related adverse event upon treatment completion or at discontinuation from study treatment 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.

### 5.1.3 Atezolizumab Dose Modification

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment for up to 42 days beyond the last dose if they experience adverse events that require a dose to be held. If atezolizumab is held because of adverse events for $>$42 days beyond the last dose, then the patient will be discontinued from atezolizumab and will be followed for safety and efficacy.

If, in the judgment of the investigator, the patient is likely to derive clinical benefit from atezolizumab after a hold of $>$42 days, 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 42 days 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 an agreement between the investigator and the Medical Monitor.

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.

### 5.1.4 Management of Atezolizumab-Specific Adverse Events

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine 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 primary approach to Grade 1–2 immune-mediated adverse events is supportive and symptomatic care with continued treatment with atezolizumab; for higher grade immune-mediated adverse events, atezolizumab should be held and oral/parenteral steroids administered. Recurrent Grade 2 immune-mediated adverse events may also mandate withholding atezolizumab or the use of steroids. Consideration for benefit–risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening immune-mediated adverse events.

See Appendix 9 for details on management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, pancreatic, eye, neurologic, or renal toxicity, and other immune-mediated adverse events. See Section 5.3.5.2 for guidelines for the recording and reporting of infusion-related reactions (see Appendix 6 for precautions for anaphylaxis).

## 5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

### 5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, regardless of causal attribution. For patients in the observation arm, an adverse event is any untoward medical occurrence. An adverse event can 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 it is considered related to the medicinal product or not
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)
- Late complications related to surgery (e.g., urinary infection, intestinal obstruction, wound dehiscence, anastomotic leak or stricture)

### 5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 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 (Arm A Only; Immediately Reportable to the Sponsor)

For patients in the atezolizumab treatment arm (Arm A), 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:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study 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, hypothyroidism and hypophysitis
- Hepatitis, including AST or ALT $>$ 10 $\times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barre syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis
- Nephritis

- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, and systemic inflammatory response syndrome
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade $\geq$ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

## 5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

### 5.3.1 Adverse Event Reporting Period

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

**After informed consent** has been obtained **but prior to initiation of study drug** for patients in Arm A or prior to the Cycle 1, Day 1 visit for patients in Arm B, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

For patients in Arm A, after initiation of study drug, all serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or until the initiation of another anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or until the initiation of another anti-cancer therapy, whichever occurs first.

For patients in Arm B, all adverse events occurring from the date of the Cycle 1, Day 1 visit until 30 days after the last day of the observation period or until the start of an anti-cancer therapy (whichever occurs first) will be reported.

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

### 5.3.2 Eliciting Adverse Event Information

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

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

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

### 5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity. Table 8 will be used for assessing the severity for adverse events that are not specifically listed in the NCI CTCAE.

**Table 8 Adverse Event Severity Grading Scale**

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

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

Note: On the basis of the NCI CTCAE (Version 4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5 × 11.pdf

[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:

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

### 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 Infusion-Related Reactions

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

#### 5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

#### 5.3.5.4 Persistent or Recurrent Adverse Events

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

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

#### 5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating 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 5.3.5.4 for details on recording persistent adverse events).

#### 5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

#### 5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$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).

#### 5.3.5.8 Deaths

For this protocol, mortality is a secondary efficacy endpoint. All deaths must be recorded on the Study Completion/Discontinuation eCRF.

Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to recurrence of UC are not considered an adverse event and should not be recorded on the Adverse Event eCRF. Rather, these deaths should be recorded on the Study Completion/Discontinuation eCRF.

All other deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent DSMB will monitor the frequency of deaths from all causes.

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

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

#### 5.3.5.9 Preexisting Medical Conditions

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

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

#### 5.3.5.10 Recurrence of Urothelial Carcinoma (UC)

Events that are clearly consistent with the expected pattern of disease recurrence should **not** be recorded as adverse events. These data will be captured as efficacy assessment data only. However in situations in which there is no confirmation of disease recurrence, the underlying symptoms should be captured as adverse events and assessed accordingly for seriousness, severity, and causality until a diagnosis or cause for such events is established or until confirmation of UC recurrence. If the symptoms are later confirmed to be due to recurrence of disease, then symptoms reported as adverse events should be retracted.

#### 5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

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

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

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

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

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

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

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

#### 5.3.5.13 Patient-Reported Outcome Data

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

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

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

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

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

### 5.4.1 Emergency Medical Contacts

**Medical Monitor Contact Information**

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

**Back-up Medical Monitor Contact Information**

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

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, as well as Medical Monitor contact information, will be distributed to all investigators.

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

#### 5.4.2.1 Events That Occur prior to Study Drug Initiation

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

#### 5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug or until they receive another anti-cancer therapy, whichever comes first. All adverse events, regardless of attribution, will be reported until 30 days after the last dose of study drug (for patients in Arm A) or 30 days after the last day of the observation period (for patients in Arm B), or the initiation of another anti-cancer therapy, whichever occurs first. Investigators should record all case details for serious adverse events and adverse events of special interest that can be gathered immediately (i.e., within 24 hours after

learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

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

### 5.4.3 Reporting Requirements for Pregnancies

#### 5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy 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 pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

#### 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 immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no

more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

#### 5.4.3.3 Congenital Anomalies/Birth Defects

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

## 5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

### 5.5.1 Investigator Follow-Up

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

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

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.

### 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 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. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its

designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- Atezolizumab Investigator's Brochure

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

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

An iDMC will monitor the incidence of these expected events during the study.
An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

## 6.1 DETERMINATION OF SAMPLE SIZE

Approximately 800 patients will be randomized in this study.

### 6.1.1 Type I Error Control

The type I error (alpha) for this study is 0.05 (two-sided). Type I error will be controlled for the primary endpoint of DFS and the key secondary endpoint of OS. To control the Type I error at alpha = 0.05 (two-sided) for DFS and OS endpoints, the treatment arms will be compared in a hierarchical fashion as follows: If the DFS analysis results (as defined for United States registrational purposes; see Section 6.4.1) are statistically significant at alpha = 0.05 (two-sided), then the analysis of OS will be performed at alpha = 0.05 (two-sided) and the interim analysis boundaries for OS (see Section 6.9.2) will be calculated according to alpha = 0.05 (two-sided).

### 6.1.2 Primary Endpoint: Disease-Free Survival

The analysis of the primary endpoint of DFS will take place when approximately 377 DFS events have occurred and at least 12 months after the last patient is enrolled have elapsed. The estimated number of events required for the analysis is based on the following assumptions:

- Two-sided log-rank test at the 0.05 significance level (two-sided)
- 80% power
- 1:1 randomization ratio
- Median DFS for the control (observation) arm of 20 months and estimated median DFS in the atezolizumab arm of 26.7 months (corresponding to a HR of 0.75)
- No interim analysis of DFS

Accrual of the planned 800 patients is projected to occur over 32 months, assuming a ramp-up period of 13 months to a projected accrual rate of 35 patients per month. On the basis of these assumptions, and the projected probability of loss to follow-up for DFS of approximately 32% over 24 months after enrollment, the required number of DFS events is projected to occur at Month 50 from the time the first patient is randomized. Also on the basis of these assumptions, it is projected that an observed HR of 0.82 or lower will result in a statistically significant difference between treatment arms (i.e., an HR of 0.82 will be the minimally detectable difference at the analysis; this corresponds to an improvement of 4.5 months in median DFS, from 20 months in the control [observation] arm to 24. 5 months in the atezolizumab arm).

### 6.1.3 Secondary Endpoint: Overall Survival

The final analysis of the secondary endpoint of OS will take place when approximately 428 deaths have occurred on the basis of the following assumptions:

- Two-sided log-rank test at the 0.05 significance level (two-sided)
- 80% power
- 1:1 randomization ratio
- Median OS for the control (observation) arm of 34 months and estimated median OS in the atezolizumab arm of 44.7 months (corresponding to HR of 0.76)
- Two interim analyses of OS

On the basis of these assumptions, the projected probability of loss to follow-up for OS of approximately 24% over 24 months after enrollment, and projected accrual, the required number of OS events for the final analysis of OS is projected to occur 95 months from the time the first patient is randomized. It is projected that an observed HR of 0.82 or lower will result in a statistically significant difference between treatment arms (i.e., an HR of 0.82 will be the minimally detectable difference at the analysis; this corresponds to an improvement of 7.4 months in median OS, from 34 months in the control [observation] arm to 41.4 months in the atezolizumab arm).

Two interim analyses of OS are planned; see Section 6.9 for details.

## 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 treatment arm for the ITT population. Study treatment administration and reasons for discontinuation from the study treatment will be summarized by treatment arm for all treated patients.

## 6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables such as age, sex, race/ethnicity, stratification factors (nodal status, number of lymph nodes resected, tumor stage, PD-L1 status, and prior neoadjuvant chemotherapy), baseline and disease characteristics (e.g., ACCI, time since initial diagnosis, time since surgery, surgery-related information, type of urinary diversion, and ECOG Performance Status) will be summarized by treatment arm for all randomized patients. Continuous variables will be summarized using means, standard deviations, 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.

## 6.4 EFFICACY ANALYSES

The efficacy analyses will include all randomized patients based on the ITT principle, with patients grouped according to the treatment assigned at randomization.

### 6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is investigator-assessed DFS, defined as the time from randomization to the time of first occurrence of a DFS event, defined as any of the following: local (pelvic) recurrence of UC; urinary tract recurrence of UC; distant metastasis of UC; or death from any cause. Data for patients without a DFS event will be censored at the last date the patient was assessed to be alive and recurrence free as determined with radiographic evidence. Data for patients with no post-baseline disease assessment will be censored at the randomization date.

For United States registrational purposes, the primary efficacy endpoint of DFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with a DFS event who missed two or more scheduled assessments immediately prior to the DFS event will be censored at the last tumor assessment as determined with radiographic evidence prior to the missed visits. Type I error control (see Section 6.1.1) will be applied to this analysis of DFS.

DFS will be analyzed in the ITT population. The following analyses will be performed for both DFS endpoints described above. DFS will be compared between treatment arms using the stratified log-rank test. The hazard ratio (HR) for recurrence or death will be estimated using a stratified Cox proportional hazards model and the 95% CI for the HR will be provided. The stratification factors will be the same as the randomization stratification factors (see Section 4.2); however, stratification factors may be combined for analysis purposes if necessary to minimize small stratum cell sizes. Combination of stratification factors, if any, would be specified in the Statistical Analysis Plan (SAP) prior to analysis. The stratification factors will be obtained from the IxRS at the time of randomization. Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate median DFS for each treatment arm; Kaplan-Meier curves will be produced. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median DFS for each treatment arm. The DFS rate at various timepoints (i.e., every 6 months after randomization) will be estimated by Kaplan-Meier methodology for each treatment arm, and the 95% CI will be calculated using Greenwood's formula.

The following additional analyses will be performed for both DFS endpoints described above:

- Analyses at landmark timepoints, described in Section 6.8.1
- Subgroup analyses, described in Section 6.8.2

### 6.4.2 Secondary Efficacy Endpoints

#### 6.4.2.1 Overall Survival

OS is defined as the time from randomization to the date of death from any cause, regardless of whether the death occurs during study treatment or following treatment discontinuation. Data for patients who have not died will be censored at the last date they were known to be alive. Methods for comparison of OS between treatment arms will be the same as the methods for treatment comparison for the primary efficacy endpoint of DFS.

Three analyses of OS are planned (two interim analyses and one final analysis; see Section 6.9 for details). The first interim analysis of OS will occur at the time that the primary endpoint of DFS is analyzed. The type I error control for the secondary endpoint of OS is described in Section 6.1.1.

#### 6.4.2.2 Disease-Specific Survival

DSS is defined as the time from randomization until the date of death from UC. Data for patients who have not died will be censored at the last date they were known to be alive. Data for patients who died from causes other than UC will be censored at the date of death. Methods for comparison of DSS between treatment arms will be the same as the methods for treatment comparison for the secondary efficacy endpoint of OS.

For the purposes of evaluating DSS, for each patient death, the cause of death will be assessed as related or not related to UC by the investigator.

#### 6.4.2.3 Distant Metastasis-Free Survival

DMFS is defined as the time from randomization to the date of a DMFS event, defined as diagnosis of distant (i.e., non-locoregional) metastasis or death from any cause. Data for patients without a DMFS event will be censored at the last date the patient was assessed to be alive and free of distant metastasis. Data for patients with no post-baseline disease assessment will be censored at the randomization date. Methods for comparison of DMFS between treatment arms will be the same as the methods for treatment comparison for the primary efficacy endpoint of DFS.

#### 6.4.2.4 Non-urinary Tract Recurrence-Free Survival

NURFS is defined as the time from randomization to the date of a NURFS event, defined as diagnosis of non-urinary tract recurrence (i.e., pelvic soft tissue or regional lymph node recurrence, or distant metastasis) or death from any cause. Data for patients without a NURFS event will be censored at the last date the patient was assessed to be alive and free of non-urinary tract recurrence. Data for patients with no post-baseline disease assessment will be censored at the randomization date. Methods for comparison of NURFS between treatment arms will be the same as the methods for treatment comparison for the primary efficacy endpoint of DFS.

### 6.4.3 Handling of Missing Data

For DFS, data for patients without a DFS event will be censored at the last date the patient was assessed to be alive and recurrence free. Data for patients with no post-baseline disease assessment will be censored at the randomization date. In the analysis of DFS for United States registrational purposes, data for patients with a DFS event who missed two or more scheduled assessments immediately prior to the DFS event will be censored at the last tumor assessment with radiographic evidence prior to the missed visits (see Section 6.4.1).

For OS, data for patients not reported as having died will be censored on the date last known to be alive.

For DSS, data for patients without a DSS event will be censored at the last date the patients were assessed to be alive and free of UC.

For DMFS, data for patients without a DMFS event will be censored at the last date the patients were assessed to be alive and free of distant metastasis.

For NURFS, data for patients without a NURFS event will be censored at the last date the patients were assessed to be alive and free of non-urinary tract recurrence.

## 6.5 SAFETY ANALYSES

Safety analyses will include all patients who received at least one dose of study treatment (atezolizumab) and all patients randomized to the observation arm with at least one safety assessment. Exposure to atezolizumab treatment and length of safety follow-up will be summarized by arm.

Verbatim descriptions of adverse events will be mapped to MedDRA terms. Treatment-emergent events (defined as events occurring on or after the first dose of atezolizumab, or, for patients in the observation arm, after the date of randomization) will be summarized by MedDRA term, appropriate MedDRA levels, and NCI CTCAE v4.0 grade. For each patient, the maximum severity reported will be used in the summaries. Adverse events will be summarized regardless of relationship to study drug as assessed by the investigator. All adverse events, adverse events leading to withdrawal of study drug, adverse events leading to dose reduction or interruption, Grade $\geq 3$ adverse events, serious adverse events, and adverse events of special interest will be summarized. Deaths and cause of death will be summarized.

Changes in NCI CTCAE grade for selected laboratory tests will be tabulated by arm. Changes in selected vital signs will be summarized. ATA results will be summarized and listed by patient for patients in Arm A only.

## 6.6 PHARMACOKINETIC ANALYSES

Atezolizumab serum concentration data ($C_{min}$ and $C_{max}$) will be tabulated and summarized for each cycle at which pharmacokinetics are to be measured ($C_{max}$ will be reported for Cycle 1 only; $C_{min}$ will be evaluated at Cycles 1, 2, 3, and 4; every 8 cycles starting on Cycle 8; and both at treatment discontinuation and at 120 days [$\pm 30$ days] after the last dose of atezolizumab). Descriptive statistics will include means, medians, ranges, and SDs, as appropriate.

Additional PK and pharmacodynamic analyses will be conducted as appropriate.

## 6.7 PATIENT-REPORTED OUTCOME ANALYSES

Results from the EQ-5D-5L (VAS) will be summarized descriptively for each timepoint as mean and median values, as well as mean and median change from baseline.

The first five questions of the EQ-5D-5L will be used to build utilities for health economic modeling and will be summarized in a separate report.

## 6.8 EXPLORATORY ANALYSES

### 6.8.1 Analyses at Landmark Timepoints

The rates of DFS, OS, DSS, and DMFS at various timepoints (i.e., every 6 months after randomization) will be estimated by the Kaplan-Meier methodology for each arm and the 95% CI will be calculated using Greenwood's formula. The 95% CIs for the difference in

OS rates between the two arms will be estimated using the normal approximation method. The difference in Kaplan-Meier rates between the two arms will be tested at annual landmark timepoints using z-statistics and the normal approximation.

### 6.8.2 Subgroup Analyses

To assess the consistency of study results in subgroups defined by demographic and baseline characteristics, efficacy outcomes of DFS, OS, DSS and DMFS in these subgroups will be examined. Summaries of these endpoints, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of the median will be produced separately for each level of the categorical variables.

The subgroups to be considered include, but are not limited to, the following:

- Age at randomization ($<65$ years, $\geq 65$ years)
- Race (non-White, White)
- Sex (female, male)
- Region (North America, Europe, Asia, Australia)
- PD-L1 status (IC0/1, IC2/3)
- Number of lymph nodes resected ($<10$, $\geq 10$)
- Nodal status (positive, negative)
- Tumor stage after resection ($\leq$pT2, pT3/pT4)
- Prior neoadjuvant chemotherapy (yes, no)
- ACCI (0–1, 2–3, $\geq 4$)
- ECOG performance status at randomization (0, 1–2)
- Primary disease (MIBC, UTUC)
- Type of urinary diversion (ileal conduit, orthotopic, other)

### 6.8.3 Biomarker Analyses

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with study drug response, including efficacy and/or adverse events. Biomarker analyses may be reported in a separate report.

## 6.9 INTERIM ANALYSES

### 6.9.1 Disease-Free Survival

No interim efficacy analyses of DFS are planned for this study.

### 6.9.2 Overall Survival

A total of three analyses of OS will be performed by the Sponsor (two interim analyses and one final analysis). The final analysis of OS will be performed when approximately 428 deaths (54% of 800 patients) have occurred in the ITT population (see also Section 6.1.3). On the basis of accrual projections and projected median OS for each

treatment arm (see Section 6.1.3), the final analysis of OS is projected to occur 95 months from the time the first patient is randomized. The interim analysis boundaries for statistical significance at each interim analysis will be determined on the basis of the Lan-DeMets implementation of the O'Brien-Fleming use function.

The first interim analysis of OS will be performed at the time of the DFS analysis. On the basis of the projected median OS for each treatment arm and the projected time of the final analysis of DFS, it is projected that approximately 280 deaths (35% of 800 patients) will have occurred at the first interim analysis of OS, which corresponds to approximately 65% of the 428 deaths required for the final analysis of OS. It is projected that an observed HR of 0.74 or lower will result in a statistically significant difference between treatment arms at this analysis.

The second interim analysis of OS will be performed when approximately 342 deaths (43% of 800 patients) have occurred, which corresponds to 80% of the 428 deaths required for the final analysis of OS. The required number of OS events for the second interim analysis of OS is projected to occur 63 months from the time the first patient is randomized. It is projected that an observed HR of 0.78 or lower will result in a statistically significant difference between treatment arms at this analysis.

The interim analyses of OS will be performed by the Sponsor. The boundary for statistical significance at each interim analysis and the final analysis will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming use function Lan and DeMets 1983). For example, with $\alpha = 0.05$ (two-sided) and using the two-sided log-rank test, if 280 deaths have occurred at the time of the first OS interim analysis, statistical significance will be declared $p \leq 0.011$; if 342 deaths have occurred at the time of the second OS interim analysis, statistical significance will be declared if $p \leq 0.021$; and if 428 deaths have occurred at the time of the final OS analysis, statistical significance will be declared if $p \leq 0.042$.

An iDMC will be convened to evaluate safety results approximately every 6 months after enrollment of the first patient until the analysis of the primary endpoint (DFS) (see Section 3.1.1).

### 6.9.3 Optional Interim Analysis

In addition to the planned interim analyses of OS, one additional interim analysis of OS may be performed at the discretion of the Sponsor. The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis will be documented in the SAP, and the SAP will be submitted to relevant health authorities prior to the conduct of the interim analyses.

# 7. DATA COLLECTION AND MANAGEMENT

## 7.1 DATA QUALITY ASSURANCE

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

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, with use of the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures. Data from paper PRO questionnaires will be entered into the EDC system by site staff.

## 7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

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

## 7.4 USE OF COMPUTERIZED SYSTEMS

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

## 7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO 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 study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

# 8. ETHICAL CONSIDERATIONS

## 8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

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

## 8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

## 8.4 CONFIDENTIALITY

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

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

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

Data generated by this study must be available for inspection upon request by representatives of the U.S. 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.

## 9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

### 9.1 STUDY DOCUMENTATION

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

### 9.2 PROTOCOL DEVIATIONS

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

### 9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will

permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

## 9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann-La Roche Ltd. Approximately 200 sites globally will participate in the study and approximately 800 patients will be randomized.

## 9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, 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:

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

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

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

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

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

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

## 9.6 PROTOCOL AMENDMENTS

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

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

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# Appendix 1
# Schedule of Assessments

| | Both Arms | Arm A (Atezolizumab) | | Arm B (Observation) | | | Both Arms |
|---|---|---|---|---|---|---|---|
| | Screening for Randomization | All Cycles | Discon-tinuation [a] | Cycles 1, 3, 5, 7, 9, 11, 13, and 15 | Cycles 2, 4, 6, 8, 10, 12, 14, and 16 | Discon-tinuation [a] | |
| Study Procedures | Days –28 to –1 | Day 1 (±3 Days for Cycles ≥2) [b] | ≤30 Days after Last Dose | Day 1 (±3 Days for Cycles ≥2) [b] | Day 1 (±3 Days) [b] | ≤30 Days after Last Visit | Follow-Up |
| Signed Informed Consent Form(s) [c] | x | | | | | | |
| Review of eligibility criteria | x | | | | | | |
| Medical, surgical, and cancer histories, including demographic information [d] | x | | | | | | |
| Pregnancy test [e] | x | x | x | | | | |
| ECOG performance status | x | x [f] | x | x [f] | | x | |
| Age-adjusted Charlson comorbidity index (ACCI) | x | | | | | | |
| Complete physical examination [g] | x | | x | | | x | |
| Limited physical examination [g] | | x [f] | | x [f] | | | |
| Weight | x | x | x | x | | x | |
| Height | x | | | | | | |
| Vital signs [h] | x | x | x | x | | x | |
| 12-lead electrocardiogram [i] | x | x | x | | | | |
| HIV, HCV serology [j] | x | | | | | | |
| Hematology [k] | x | x [f] | x | x [f] | | x | |
| Serum chemistry [l] | x | x [f] | x | x [f] | | x | |
| Coagulation panel (aPTT, INR) | x | | x | | | x | |

# Appendix 1
# Schedule of Assessments (cont.)

| | Both Arms | Arm A (Atezolizumab) | | Arm B (Observation) | | | Both Arms |
|---|---|---|---|---|---|---|---|
| | Screening for Randomization | All Cycles | Discon-tinuation [a] | Cycles 1, 3, 5, 7, 9, 11, 13, and 15 | Cycles 2, 4, 6, 8, 10, 12, 14, and 16 | Discon-tinuation [a] | |
| Study Procedures | Days –28 to –1 | Day 1 (±3 Days for Cycles ≥2) [b] | ≤30 Days after Last Dose | Day 1 (±3 Days for Cycles ≥2) [b] | Day 1 (±3 Days) [b] | ≤30 Days after Last Visit | Follow-Up |
| Urinalysis [m] | x | x [n,f] | x | x [n] | | x | |
| TSH, free T3, free T4 | x | x [o,f] | x | | | | |
| Auto-antibody testing [p] | | x | x | | | | |
| Serum sample for ATA assessment | | See Appendix 2 | | | | | |
| Serum sample for PK sampling | | See Appendix 2 | | | | | |
| Blood samples for biomarkers | | See Appendix 2 | | | | | |
| Optional whole blood sample for RCR [q] | | x [q] | | x [q] | | | |
| Study drug infusion [r] | | x | | | | | |
| Archival/screening FFPE tumor tissue specimen or 15 unstained slides [s] | x | | | | | | |
| Fresh biopsy (mandatory sample [t] and optional RCR sample [u]) | | At the time of radiographic confirmation of disease recurrence [t,u] | | | | | |
| Assessments for UC recurrence [v] | x | Every 12 weeks following randomization (± 7 days; at approximately every four cycles) in first 3 years; every 24 weeks (±10 days) for Years 4 and 5; and at Year 6 (± 10 days), until death, disease recurrence, loss to follow-up, end of Year 6, or withdrawal of consent. *After the primary analysis, patients in the first 3 years of the study may be assessed for tumor recurrence every 24 weeks.* | | | | | |
| Concomitant medications [w] | x | x | x | x | x | x | |

# Appendix 1
# Schedule of Assessments (cont.)

| | Both Arms | Arm A (Atezolizumab) | | Arm B (Observation) | | | Both Arms |
|---|---|---|---|---|---|---|---|
| | Screening for Randomization | All Cycles | Discon-tinuation [a] | Cycles 1, 3, 5, 7, 9, 11, 13, and 15 | Cycles 2, 4, 6, 8, 10, 12, 14, and 16 | Discon-tinuation [a] | |
| Study Procedures | Days –28 to –1 | Day 1 (±3 Days for Cycles ≥2) [b] | ≤30 Days after Last Dose | Day 1 (±3 Days for Cycles ≥2) [b] | Day 1 (±3 Days) [b] | ≤30 Days after Last Visit | Follow-Up |
| Adverse events [x] | x | x | x | x | x | x | |
| Telephone contact [y] | | | | | x | | |
| Survival and anticancer therapy follow-up [z] | | | | | | | x |
| Patient-reported outcomes [aa] | | x [bb] | x | x | | x | x |

Note: For Arm A, assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

[a] Patients will be asked to return to the clinic for a discontinuation visit not more than 30 days after the decision to discontinue treatment/observation early, or after the end of the one-year treatment/observation period.

[b] After five cycles have been completed, one cycle may be delayed by 1 week (i.e., 28 days instead of 21 days for one cycle) for one time to allow for vacations.

[c] Written informed consent is required for performing any study-specific tests or procedures. Written informed consent (on the main study Informed Consent Form) can be obtained outside the 28 days screening period prior to randomization. Prior to signing the main consent form for the study, patients may specifically allow for the collection and testing of archival or fresh tumor tissue by signing the pre-screening consent form. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to randomization (except where otherwise specified) may be used for screening assessments rather than repeating such tests.

[d] Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Demographic information includes sex, age, and self-reported race/ethnicity.

[e] 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. Starting from Cycle 3, either serum or urine pregnancy test (positive urine test results will be confirmed with a serum pregnancy test) must be performed every two cycles during the study treatment, and as clinically indicated thereafter.

[f] ECOG performance status, limited physical examination and local/central lab assessments may be obtained ≤ 96 hours before Day 1 of each cycle.

# Appendix 1
# Schedule of Assessments (cont.)

[g] Complete and limited physical examinations are defined in Section 4.5.3.

[h] Vital signs include heart rate, respiratory rate, blood pressures, and temperature and will be performed as standard of care if clinically indicated for patients randomized to the observation arm. For patients randomized to the atezolizumab treatment arm, for the first infusions of study drug, the patient's vital signs should be determined up to 60 minutes before the start of infusion, and if clinically indicated, during and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be recorded if clinically indicated or if symptoms occurred in the prior infusion.

[i] ECG recordings will be obtained during screening and when clinically indicated during study. ECGs for each patient should be obtained from the same machine wherever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

[j] See Section 4.5.6 for serology tests. 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 HBc.

[k] Blood samples collected to monitor safety will be collected in patients randomized to both arms. Hematology consists of CBC, including 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. Refer to Section 4.1.1 for a list of laboratory results to be obtained within 14 days prior to the first dose of study treatment.

[l] Serum chemistry includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin. Refer to Section 4.1.1 for a list of laboratory results to be obtained within 14 days prior to the first dose of study treatment.

[m] Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood).

[n] On Day 1 of Cycle 3 and every two cycles thereafter.

[o] On Day 1 of Cycle 5 and every four cycles thereafter.

[p] Baseline sample to be collected on Cycle 1, Day 1 prior to the first dose of study treatment. For patients who show evidence of immune mediated toxicity, additional samples will be collected, and all samples will be analyzed centrally. Includes anti-nuclear antibody, anti-double stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti neutrophil cytoplasmic antibody.

[q] Whole blood for DNA isolation will be collected from patients who have consented to optional RCR sampling at baseline (pre-dose C1D1). If, however, the RCR genetic blood sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study.

# Appendix 1
# Schedule of Assessments (cont.)

[r] Patients in Arm A will receive their first dose of study drug the day of randomization if possible. If this is not possible, the first dose should occur no later than 7 days after randomization. The initial dose of atezolizumab treatment will be delivered over 60 (±15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. Atezolizumab treatment may be continued for a maximum of 16 cycles (or 12 months, whichever occurs first) until disease recurrence, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor.

[s] Tumor tissue from radical surgical resection 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). Prior to signing the main consent form for the study, patients may specifically allow for the collection and testing of archival or fresh tumor tissue by signing the prescreening Informed Consent Form. After signing of the Informed Consent Form, retrieval and submission of archival tumor sample can occur outside the 28-day screening period.

[t] All patients will undergo a mandatory tumor biopsy sample collection at the time of radiographic confirmation of disease recurrence (see Section 4.5.5). Acceptable samples include resections; core needle biopsies for deep tumor tissue or lymph nodes; or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. For core needle biopsy specimens, at least three cores should be submitted for evaluation. *After the primary analysis, a confirmatory tumor biopsy is optional at the time of disease recurrence.*

[u] For patients who have consented to collection of optional biopsies on the Optional Collection of Samples for RCR Informed Consent Form, optional tumor biopsy samples may be collected by core needle or excisional/punch biopsy per investigator discretion. Optional biopsy tissue will be stored in the RCR. Not applicable for sites that have not been granted approval for RCR sampling.

[v] Surveillance for tumor recurrence must include physical examination and imaging studies of the chest, abdomen, upper urinary tracts, and pelvis. Other examinations such as laboratory or urine cytology should be performed as clinically indicated. Recurrence assessment at Year 6 will be performed at approximately 48 weeks after the last one in Year 5. *Patients in Years 1–3 of the study may be assessed for tumor recurrence every 24 weeks.* See Section 4.5.5 for details of assessment requirements.

[w] 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 written informed consent should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

# Appendix 1
# Schedule of Assessments (cont.)

[x] After informed consent has been obtained but prior to randomization, only serious adverse events caused by a protocol-mandated intervention should be reported. Upon randomization into study, patients who experience a serious adverse event or protocol-defined adverse 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 reported for patients until 30 days after the last dose of study treatment (for Arm A) or the last day in the observation period (approximately Day 365 for Arm B), or until initiation of another anti-cancer therapy, whichever occurs first. After this period, investigators should ensure any deaths, serious adverse events, or other adverse events of concern are reported if they are later assessed to be related to atezolizumab treatment. 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 atezolizumab treatment or trial-related procedures until a final outcome can be reported.

[y] This clinic contact can be either via telephone call or formal clinic visit.

[z] Survival follow-up information will be recorded via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 7 days) *from the completion or discontinuation of the treatment/observation period* until death, loss to follow-up, or study termination by Roche. All patients (irrespective of which arm they are randomized to) will be followed for survival and new anticancer therapy information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. Patients who have completed the treatment or observation phase and continue in disease recurrence follow-up should have survival follow-up *in parallel* approximately every 3 months. All patients must still be followed for new anti-cancer therapy.

[aa] The PRO questionnaire EQ-5D-5L will be completed by the patients at the investigational site. All PRO questionnaires are required to be administered prior to administration of study treatment (Arm A) and/or prior to any other study assessment(s) to ensure that the validity of the instrument is not compromised and to ensure that data quality meets regulatory requirements. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site, and the hard copy originals of the questionnaires must be maintained as part of the patient's medical record when relevant at the site for source data verification. After discontinuation of the treatment/observation period, for patients who have not experienced disease recurrence, the EQ-5D-5L will be administered at the same schedule as the assessments for disease recurrence (see Section 4.5.5). The EQ-5D-5L will also be recorded at 6, 12, and 24 weeks after disease recurrence per telephone interview by trained site staff and in compliance with best practices and recommendations by EuroQol. Study personnel will record patient responses on a paper copy of the EQ-5D-5L during the telephone interview as record of source documentation. *After the primary analysis, the EQ-5D-5L assessments are no longer required for patients who are in disease recurrence follow-up or who have had a DFS event.*

[bb] Odd-numbered cycles only (i.e., Cycles 1, 3, 5, 7, 9, 11, 13, and 15).

# Appendix 2
# Schedule of Pharmacodynamic and Pharmacokinetic Assessments

| Study Visit | Time | Sample | Arm A | Arm B |
|---|---|---|---|---|
| Cycle 1, Day 1 | Predose | Serum atezolizumab ATAs | x | |
| | | Serum atezolizumab PK | x | |
| | | PD biomarker [a] | x | x |
| | 30 min (±10 min) after end of atezolizumab infusion | Serum atezolizumab PK | x | |
| Cycles 2, 3, and 4, Day 1 | Predose | Serum atezolizumab ATAs | x | |
| | | Serum atezolizumab PK | x | |
| | | PD biomarker (Cycle 3, Day 1 only) [a] | x | x |
| Cycles ≥8, Day 1, every 8 cycles starting Cycle 8 | Predose | Serum atezolizumab ATAs | x | |
| | | Serum atezolizumab PK | x | |
| At time of fresh biopsy (e.g., at the time of first radiographic confirmation of disease recurrence) | | PD biomarker [a] | x | x |
| Treatment discontinuation visit | At visit | Serum atezolizumab ATAs | x | |
| | | Serum atezolizumab PK | x | |
| | | PD biomarker[a] | x | |
| 120 days (±30 days) after last dose of atezolizumab [b] | At visit | Serum atezolizumab ATAs | x | |
| | | Serum atezolizumab PK | x | |

ATAs = anti-therapeutic antibodies; PD=pharmacodynamics; PK=pharmacokinetics.

[a] Pharmacodynamic samples may include plasma, serum, and whole blood (see laboratory manual for details on sample collection).

[b] To be collected unless the patient withdraws consent or the study closes.

# Appendix 3
# Criteria for PD-L1 Diagnostic Assessment in Study WO29636

| Description of IHC Scoring Algorithm | IHC IC score |
|---|---|
| Absence of any discernible PD-L1 staining<br>OR<br>Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells (IC) covering $<1\%$ of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma | IHC IC0<br>($IC<1\%$) |
| Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering between $\geq 1$ % to $<5\%$ of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma | IHC IC1<br>($5\% > IC \geq 1\%$) |
| Presence of discernible PD-L1 staining of any intensity in tumor infiltrating immune cells covering between $\geq 5$ % to $<10\%$ of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma | IHC IC2<br>($10\% > IC \geq 5\%$) |
| Presence of discernible PD-L1 staining of any intensity in tumor infiltrating immune cells covering $\geq 10\%$ of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma | IHC IC3<br>($IC \geq 10\%$) |

# Appendix 4
# Age-Adjusted Charlson Comorbidity Index (ACCI) Worksheet

| Weight | Comorbidity |
|---|---|
| 1 | Myocardial infarction |
| | Congestive heart failure |
| | Peripheral vascular disease or bypass |
| | Cerebrovascular disease or transient ischemic disease |
| | Dementia or Alzheimer's |
| | Chronic obstructive pulmonary disease |
| | Rheumatic or connective tissue disease |
| | Gastric or peptic ulcer |
| | Diabetes without end-organ damage |
| | Warfarin |
| | Depression |
| | Hypertension |
| 2 | Hemiplegia |
| | Mild liver disease |
| | Renal disease |
| | Diabetes with end-organ damage |
| | Any solid tumor, leukemia or lymphoma |
| | Skin ulcers/cellulitis |
| 3 | Severe liver disease |
| 6 | Metastatic solid tumor |
| | HIV or AIDS |
| 1 | For each decade over age 40 |

ACCI scores will be calculated by the method previously reported by Charlson et al. (1987), in which comorbid conditions are weighted and scored, with additional points added for age.

**REFERENCE**

Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-383.

# Appendix 4
# Age-Adjusted Charlson Comorbidity Index (ACCI) Worksheet (cont.)

| Patient Number: | Patient Age: |
|---|---|

| Condition | Weight | Calculate Score | Notes |
|---|---|---|---|
| 1. Myocardial infarction | 1 | | |
| 2. Congestive heart failure | 1 | | |
| 3. Peripheral vascular disease or bypass | 1 | | |
| 4. Cerebrovascular disease or transient ischemic disease | 1 | | CVA only |
| 5. Hemiplegia | 2 | | If hemiplegia, do not count CVA separately |
| 6. Pulmonary disease/ asthma | 1 | | |
| 7. Diabetes | 1 | | Diabetes only |
| 7a. Diabetes with end organ damage | 2 | | If end organ damage, do not count Diabetes separately |
| 8. Renal disease | 2 | | |
| 9. Mild liver disease | 2 | | |
| 9a. Severe liver disease | 3 | | |
| 10. Gastric or peptic ulcer | 1 | | |
| 11. Cancer (lymphoma, leukemia, solid tumor) | 2 | | Non-metastatic cancer only (other than UC) |
| 11a. Metastatic solid tumor | 6 | | If Metastatic, do not count cancer separately |
| 12. Dementia or Alzheimer's | 1 | | |
| 13. Rheumatic or connective tissue disease | 1 | | |
| 14. HIV or AIDS | 6 | | |
| 15. Hypertension | 1 | | |
| 16. Skin ulcers/ cellulitis | 2 | | |
| 17. Depression | 1 | | |
| 18. Warfarin | 1 | | |

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

| TOTAL Score | |
|---|---|

ACCI scores will be calculated by the method previously reported by Charlson et al. (1987), in which comorbid conditions are weighted and scored, with additional points added for age.

## REFERENCE

Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-383.

# Appendix 5
# Preexisting Autoimmune Diseases

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). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

| | | |
|---|---|---|
| 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 | Morphea | Vitiligo |
| demyelinating polyneuropathy Churg-Strauss syndrome | Multiple sclerosis | Vogt-Kovanagi-Harada disease |
| Crohn's disease | Myasthenia gravis | Wegener's granulomatosis |
| Dermatomyositis | Neuromyotonia | |
| | Opsoclonus myoclonus syndrome | |
| | Optic neuritis | |

# Appendix 6
# Anaphylaxis Precautions

## EQUIPMENT NEEDED

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

## PROCEDURES

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

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

# Appendix 7
# Eastern Cooperative Oncology Group
# Performance Status Scale

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

# Appendix 8
# Patient-Reported Outcomes Instrument


**Health Questionnaire**

**English version for the USA**

# Appendix 8
# Patient-Reported Outcomes Instrument (cont.)

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

**MOBILITY**

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

**SELF-CARE**

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

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

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

**PAIN / DISCOMFORT**

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

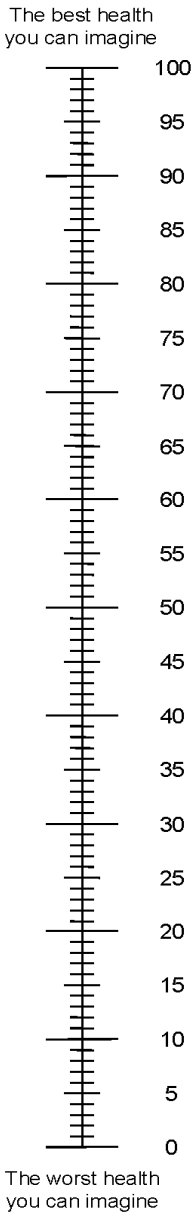
**ANXIETY / DEPRESSION**

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

# Appendix 8
# Patient-Reported Outcomes Instrument (cont.)

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

YOUR HEALTH TODAY = ☐



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

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

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

## PULMONARY EVENTS

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

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

# Appendix 9
# Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

## Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

| Event | Management |
|---|---|
| Pulmonary event, Grade 1 | • Continue atezolizumab and monitor closely.<br>• Re-evaluate on serial imaging.<br>• Consider patient referral to pulmonary specialist. |
| Pulmonary event, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL.<br>• Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]<br>• 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]<br>• Bronchoscopy or BAL is recommended.<br>• Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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 9
# 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.<br>• Monitor LFTs until values resolve to within normal limits. |
| Hepatic event, Grade 2 | **All events:**<br>• Monitor LFTs more frequently until return to baseline values.<br>**Events of > 5 days' duration:**<br>• Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• 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 9
# Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

## Table 2 Management Guidelines for Hepatic Events (cont.)

| Event | Management |
|---|---|
| Hepatic event, Grade 3 or 4 | • Permanently discontinue atezolizumab and contact Medical Monitor. [c]<br>• Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury.<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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 9
# Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

| Event | Management |
|---|---|
| Diarrhea or colitis, Grade 1 | • Continue atezolizumab.<br>• Initiate symptomatic treatment.<br>• Endoscopy is recommended if symptoms persist for >7 days.<br>• Monitor closely. |
| Diarrhea or colitis, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Initiate symptomatic treatment.<br>• Patient referral to GI specialist is recommended.<br>• For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• 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]<br>• Refer patient to GI specialist for evaluation and confirmatory biopsy.<br>• 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.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• 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 9
# Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

| Event | Management |
|---|---|
| Diarrhea or colitis, Grade 4 | • Permanently discontinue atezolizumab and contact Medical Monitor. [c]<br>• Refer patient to GI specialist for evaluation and confirmation biopsy.<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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 9
# 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.<br>• Initiate treatment with thyroid replacement hormone.<br>• Monitor TSH weekly. |
| Symptomatic hypothyroidism | • Withhold atezolizumab.<br>• Initiate treatment with thyroid replacement hormone.<br>• Monitor TSH weekly.<br>• Consider patient referral to endocrinologist.<br>• Resume atezolizumab when symptoms are controlled and thyroid function is improving. |
| Asymptomatic hyperthyroidism | **TSH ≥ 0.1 mU/L and < 0.5 mU/L:**<br>• Continue atezolizumab.<br>• Monitor TSH every 4 weeks.<br>**TSH < 0.1 mU/L:**<br>• Follow guidelines for symptomatic hyperthyroidism. |
| Symptomatic hyperthyroidism | • Withhold atezolizumab.<br>• Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.<br>• Consider patient referral to endocrinologist.<br>• Resume atezolizumab when symptoms are controlled and thyroid function is improving.<br>• 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 9
# Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

## Table 4 Management Guidelines for Endocrine Events (cont.)

| Event | Management |
|---|---|
| Symptomatic adrenal insufficiency, Grade 2–4 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Refer patient to endocrinologist.<br>• Perform appropriate imaging.<br>• 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.<br>• If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b]<br>• 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.<br>• Initiate treatment with insulin if needed.<br>• Monitor for glucose control. |
| Hyperglycemia, Grade 3 or 4 | • Withhold atezolizumab.<br>• Initiate treatment with insulin.<br>• Monitor for glucose control.<br>• 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 9
# Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

## Table 4 Management Guidelines for Endocrine Events (cont.)

| Event | Management |
|---|---|
| Hypophysitis (pan-hypopituitarism), Grade 2 or 3 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Refer patient to endocrinologist.<br>• Perform brain MRI (pituitary protocol).<br>• 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.<br>• Initiate hormone replacement if clinically indicated.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]<br>• For recurrent hypophysitis, treat as a Grade 4 event. |
| Hypophysitis (pan-hypopituitarism), Grade 4 | • Permanently discontinue atezolizumab and contact Medical Monitor. [c]<br>• Refer patient to endocrinologist.<br>• Perform brain MRI (pituitary protocol).<br>• 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.<br>• 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 9
# 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.<br>• Patient referral to ophthalmologist is strongly recommended.<br>• Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.<br>• If symptoms persist, treat as a Grade 2 event. |
| Ocular event, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Patient referral to ophthalmologist is strongly recommended.<br>• Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• 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]<br>• Refer patient to ophthalmologist.<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• 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 9
# 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 GI illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

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

# Appendix 9
# Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

## Table 6 Management Guidelines for Immune-Mediated Myocarditis

| Event | Management |
|---|---|
| Immune-mediated myocarditis, Grade 1 | • Refer patient to cardiologist.<br>• 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.<br>• Refer patient to cardiologist.<br>• Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate.<br>• Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.[a]<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• 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]<br>• Refer patient to cardiologist.<br>• Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. [a,b]<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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 9
# 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. For subsequent cycles, IRRs should be managed according to institutional guidelines.

# Appendix 9
# 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]<br>*Fever* [b] *with or without constitutional symptoms* | • *Immediately interrupt infusion.*<br>• *Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.*<br>• *If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate.*<br>• *If symptoms recur, discontinue infusion of this dose.*<br>• *Administer symptomatic treatment,* [c] *including maintenance of IV fluids for hydration.*<br>• *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.*<br>• *For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.* |
| *Grade 2* [a]<br>*Fever* [b] *with hypotension not requiring vasopressors*<br>***and/or***<br>*Hypoxia requiring low-flow oxygen* [d] *by nasal cannula or blow-by* | • *Immediately interrupt infusion.*<br>• *Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.*<br>• *If symptoms recur, discontinue infusion of this dose.*<br>• *Administer symptomatic treatment.* [c]<br>• *For hypotension, administer IV fluid bolus as needed.*<br>• *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.*<br>• *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.*<br>• *Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).*<br>• *Consider anti-cytokine therapy.* [e]<br>• *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.*<br>• *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.*<br>• *If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.* |

# Appendix 9
# 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.)*

| *Event* | *Management* |
|---|---|
| *Grade 3* [a]<br>*Fever* [b] *with hypotension requiring a vasopressor (with or without vasopressin)*<br>***and/or***<br>*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]<br>• *Administer symptomatic treatment.* [c]<br>• *For hypotension, administer IV fluid bolus and vasopressor as needed.*<br>• *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.*<br>• *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.*<br>• *Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).*<br>• *Consider anti-cytokine therapy.* [e]<br>• *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]<br>*Fever* [b] *with hypotension requiring multiple vasopressors (excluding vasopressin)*<br>***and/or***<br>*Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)* | • *Permanently discontinue atezolizumab and contact Medical Monitor.* [f]<br>• *Administer symptomatic treatment.* [c]<br>• *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.*<br>• *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.*<br>• *Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).*<br>• *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.*<br>• *Hospitalize patient until complete resolution of symptoms.* |

# Appendix 9
# Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (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 (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.*

[b] *Fever is defined as temperature ≥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 9
# Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

## PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

### Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

| Event | Management |
|---|---|
| Amylase and/or lipase elevation, Grade 2 | • Continue atezolizumab.<br>• Monitor amylase and lipase weekly.<br>• 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]<br>• Refer patient to GI specialist.<br>• Monitor amylase and lipase every other day.<br>• If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]<br>• 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 9
# Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

## Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

| Event | Management |
|---|---|
| Immune-mediated pancreatitis, Grade 2 or 3 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Refer patient to GI specialist.<br>• 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.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]<br>• For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c] |
| Immune-mediated pancreatitis, Grade 4 | • Permanently discontinue atezolizumab and contact Medical Monitor. [c]<br>• Refer patient to GI specialist.<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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 9
# Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

## DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

### Table 9 Management Guidelines for Dermatologic Events

| Event | Management |
|---|---|
| Dermatologic event, Grade 1 | • Continue atezolizumab.<br>• Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines). |
| Dermatologic event, Grade 2 | • Continue atezolizumab.<br>• Consider patient referral to dermatologist.<br>• Initiate treatment with topical corticosteroids.<br>• 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]<br>• Refer patient to dermatologist.<br>• 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.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• 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 $\leq 10$ 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 $\geq 1$ month to $\leq 10$ 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 9
# Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

## NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup 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.<br>• Investigate etiology. |
| Immune-mediated neuropathy, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Investigate etiology.<br>• Initiate treatment as per institutional guidelines.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• 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]<br>• Initiate treatment as per institutional guidelines. |
| Myasthenia gravis and Guillain-Barré syndrome (any grade) | • Permanently discontinue atezolizumab and contact Medical Monitor. [c]<br>• Refer patient to neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• 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.

# Appendix 9
# Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

## 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]<br>• Refer patient to neurologist.<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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.<br>• 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]<br>• Refer patient to renal specialist.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• 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.<br>• Refer patient to renal specialist and consider renal biopsy.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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 9
# 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.<br>• Refer patient to rheumatologist or neurologist.<br>• 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.<br>• Refer patient to rheumatologist or neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• 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.<br>• If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• 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 $\leq 10$ 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 $\geq 1$ month to the equivalent of $\leq 10$ mg/day oral prednisone before atezolizumab can be resumed.

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

# Appendix 9
# Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

## Table 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.<br>• Refer patient to rheumatologist or neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• Respiratory support may be required in more severe cases.<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]<br>• For recurrent events, treat as a Grade 4 event. |
| Immune-mediated myositis, Grade 4 | • Permanently discontinue atezolizumab and contact Medical Monitor. [c]<br>• Refer patient to rheumatologist or neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• Respiratory support may be required in more severe cases.<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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 9
# 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 $\geq 38.5$°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin $< 90$ g/L (9 g/dL) ($< 100$ g/L [10 g/dL] for infants $< 4$ weeks old)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides $> 2.992$ mmol/L (265 mg/dL) and/or fibrinogen $< 1.5$ g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin $> 500$ mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated $\geq 2$ standard deviations above age-adjusted laboratory-specific norms

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

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

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

# Appendix 9
# 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.<br>• Consider patient referral to hematologist.<br>• Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines.<br>• Consider initiation of IV corticosteroids and/or an immunosuppressive agent.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over $\geq$1 month. |

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

## REFERENCES

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