Official Title: A Phase III, Multicenter, Randomized, Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) as Monotherapy and in Combination With Platinum-Based Chemotherapy in Patients With Untreated Locally Advanced or Metastatic Urothelial Carcinoma

NCT Number: NCT02807636

Document Date: Protocol Version 11: 17-December-2022

PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) AS MONOTHERAPY AND IN COMBINATION WITH PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH UNTREATED LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA**
PROTOCOL NUMBER:	WO30070
VERSION NUMBER:	11
EUDRACT NUMBER:	2016-000250-35
IND NUMBER:	120827
NCT NUMBER	NCT02807636
TEST PRODUCTS:	Atezolizumab (RO5541267), gemcitabine, carboplatin, cisplatin
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL:	See electronic signature and date stamp on the final page of the document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
11	See electronic signature and date stamp on the final page of the document
10	10 January 2022.
9	9 March 2021
8	12 December 2019
7	29 November 2018
6	30 April 2018
5	20 November 2017
4	27 June 2017
3	21 September 2016
2	27 May 2016
1	20 February 2016

PROTOCOL AMENDMENT, VERSION 11: RATIONALE

Protocol WO30070 has been amended to include recent safety information as per the Investigator's Brochure Version 19, including Addendums 1 and 2 to the Atezolizumab Investigator's Brochure, Version 19, update the end of the study definition, define the overall survival (OS) monitoring period and clarify that after the final OS analysis the following activities will be stopped: completion of the patient reported outcome (PRO) questionnaire, collection of tumor, pharmacokinetic, immunogenicity, and biomarker samples.

Changes to the protocol, along with a rationale for each change, are summarized below:

- To clarify the definition for the end of the study (Section 3.2).
- To reduce the collection of PROs to only the first 4 survival follow-up visits and to stop collecting PROs after the final OS analysis (Section 4.5.6 and Appendix 1).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.10.6).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 19, including Addendums 1 and 2 to the Atezolizumab Investigator's Brochure, Version 19 (Section 5.1.5).
- The list of identified risks for atezolizumab has been revised to include pericardial disorders, myelitis and facial paresis (Section 5.1.1).
- Hemophagocytic lymphohistiocytosis has been updated from a potential risk to an identified risk associated with atezolizumab and language has been revised accordingly (Section 5.1.1).
- The list of adverse events of special interest has been revised to include myelitis, facial paresis, vasculitis, autoimmune hemolytic anemia, and severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis) (Section 5.2.3).
- The medical term "Wegener granulomatosis" has been replaced by the term "granulomatosis with polyangiitis" to align with the updated preferred term in MedDRA (Appendix 8 [Preexisting Autoimmune Diseases and Immune Deficiencies]).
- Appendix 8 has been revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a pericardial disorder while receiving another immunostimulatory anti-cancer agent.
- Appendix 8 has been revised to include autoimmune myelitis.
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section 8.4).
- To stop the collection of serum atezolizumab ATA, serum atezolizumab pharmacokinetics, plasma PD biomarker, serum PD biomarker, whole blood PBMC, fresh biopsy at the time of radiographic progression, optional RBR tumor biopsy and

whole blood samples and PROs after the final OS analysis (Appendix 1 and Appendix 2).

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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) AS MONOTHERAPY AND IN COMBINATION WITH PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH UNTREATED LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA**
PROTOCOL NUMBER:	WO30070
VERSION NUMBER:	11
EUDRACT NUMBER:	2016-000250-35
IND NUMBER:	120827
NCT NUMBER	NCT02807636
TEST PRODUCTS:	Atezolizumab (RO5541267), gemcitabine, carboplatin, cisplatin
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) AS MONOTHERAPY AND IN COMBINATION WITH PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH UNTREATED LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA**
PROTOCOL NUMBER:	WO30070
VERSION NUMBER:	11
EUDRACT NUMBER:	2016-000250-35
IND NUMBER:	120827
NCT NUMBER	NCT02807636
TEST PRODUCTS:	Atezolizumab (RO5541267), gemcitabine, carboplatin, cisplatin
PHASE:	Phase III
INDICATION:	Urothelial cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This is a Phase III, multicenter, randomized, placebo-controlled, partially blind study designed to evaluate the efficacy of atezolizumab given as monotherapy or in combination with platinum-based chemotherapy versus placebo in combination with platinum-based chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who have not received prior systemic therapy.

EFFICACY OBJECTIVES

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus platinum-based chemotherapy compared with placebo plus platinum-based chemotherapy on the basis of the following endpoints:

- Co-primary endpoints of progression-free survival (PFS) and overall survival (OS)

  PFS is defined as the time from randomization to the first documented disease progression as determined by the investigator with use of Response Evaluation Criteria in Solid Tumors Version 1 (RECIST v1.1), or death due to any cause, whichever occurs first.

  OS is defined as the time from randomization to death due to any cause.

In addition, a primary efficacy objective is to evaluate the efficacy of atezolizumab monotherapy compared with placebo plus platinum-based chemotherapy on the basis of OS, as defined above.

The secondary efficacy objectives for this study are to evaluate the efficacy of atezolizumab given as either monotherapy or in combination with platinum-based chemotherapy compared with placebo in combination with platinum-based chemotherapy on the basis of the following endpoints:

- Objective response rate (ORR), defined as the proportion of patients with a confirmed objective response, either complete response (CR) or partial response (PR), observed on two assessments ≥28 days apart per RECIST v1.1, based on investigator assessment
- Duration of response (DOR), defined for patients with an objective response as the time from the first documented objective response to documented disease progression per RECIST v1.1, based on investigator assessment, or death due to any cause, whichever occurs first
- Independent review facility PFS (IRF-PFS), defined as the time from randomization to the first documented disease progression as determined by blinded independent central review with use of RECIST v1.1, or death due to any cause, whichever occurs first
- Investigator-assessed PFS (INV-PFS) in patients treated with atezolizumab monotherapy compared with patients treated with placebo plus platinum-based chemotherapy
- OS rate at 1 year
- PFS rate at 1 year
- Time to deterioration in global health status as measured by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30
- Time to deterioration in physical function as measured by the QLQ-C30

EXPLORATORY EFFICACY OBJECTIVES

The exploratory efficacy objectives for this study are to evaluate the efficacy of atezolizumab given as either monotherapy or in combination with platinum-based chemotherapy compared with placebo in combination with platinum-based chemotherapy on the basis of the following endpoints:

- Disease control rate (DCR), defined as the proportion of patients with confirmed CR or PR as best response, or stable disease maintained for ≥ 6 months, per RECIST v1.1
- Relationship between tumor tissue programmed death–ligand 1 (PD-L1) expression and measures of efficacy
- Predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status and/or response to study treatment
- Disease and treatment burden as measured by the symptom (e.g., pain, fatigue) and function scores from the QLQ-C30

HEALTH ECONOMICS OBJECTIVE

Health status will be measured using the EuroQol EQ-5D-5L questionnaire to be included in health economic modeling. As such, data from the EQ-ED-5L will not be reported in the Clinical Study Report.

SAFETY OBJECTIVES

The safety objectives for this study are to evaluate the safety and tolerability of atezolizumab given as either monotherapy or in combination with platinum-based chemotherapy compared with placebo plus platinum-based chemotherapy on the basis of the following:

- Incidence, nature, and severity of adverse events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0
- Changes in vital signs, and clinical laboratory results

PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is to characterize the pharmacokinetics of atezolizumab when administered as monotherapy or in combination with platinum-based chemotherapy in patients who are treatment-naive:

- PK parameters for atezolizumab include maximum serum concentration and minimum serum concentration when appropriate, as data allow.

IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab as monotherapy and in combination with platinum-based chemotherapy on the basis of the following endpoint:

- Incidence of anti-therapeutic antibodies (ATAs) during the study relative to the prevalence of ATAs at baseline

The exploratory immunogenicity objective for this study is to evaluate potential effects of detectable ATAs on the basis of the following endpoint:

- Correlation between ATA status and efficacy, safety, and PK endpoints

STUDY DESIGN

DESCRIPTION OF STUDY

This is a Phase III, multicenter, randomized, placebo-controlled, partially blind study (IMvigor130) designed to evaluate the safety and efficacy of atezolizumab given as monotherapy or in combination with platinum-based chemotherapy versus placebo in combination with platinum-based chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who have not received prior systemic therapy.

Treatment with platinum-based chemotherapy can continue until progressive disease (PD) per RECIST v1.1 or unacceptable toxicity per investigator discretion. In the case of CR, only two more cycles of platinum-based chemotherapy will be administered after the response confirmation. In specific circumstances, treatment may continue beyond disease progression.

No crossover will be allowed from the control arm to either experimental arm (Arms A and B).

Patients should be considered eligible to receive treatment with platinum-based chemotherapy (either gemcitabine with cisplatin or gemcitabine with carboplatin) and have measurable disease, defined by RECIST v1.1.

Note, the study was initially implemented with randomization to two treatment arms (carboplatin plus gemcitabine with or without atezolizumab) in patients who were ineligible for cisplatin-based chemotherapy. In Protocol WO30070, Version 3, a third treatment arm was added (open-label atezolizumab monotherapy). In addition, the eligibility criteria were expanded to also allow patients who are eligible for cisplatin-based chemotherapy to enter the study. Protocol WO30070, Version 3 was implemented while recruitment was ongoing. Patients recruited into the study prior to Version 3 will be included in the final analysis.

Tumor specimens from eligible patients will be prospectively tested for PD-L1 immunohistochemistry (IHC) expression by a central laboratory prior to randomization. The IHC scores will have three categories (tumor-infiltrating immune cell [IC]0, IC1, IC2/3). Sponsor, patients, and investigators will be blinded to the PD-L1 expression status, but the Sponsor will be able to view aggregate PD-L1 expression data. An exception is the case for any new patients enrolled in Arm B, in which PD-L1 status will be unblinded to the patient and investigator at the time of randomization. However, the Sponsor will not be able to review these scores (see below for further information regarding Protocol Version 6 update based on iDMC recommendation). The study will enroll all eligible patients whose tissue is evaluable for expression testing, regardless of PD-L1 expression status.

This study will enroll approximately 1200 patients at approximately 229 sites globally.

Following implementation of Protocol WO30070, Version 3, patients will be randomized in a 1:1:1 ratio to receive one of the following:

- Arm A (experimental arm): blinded atezolizumab in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin)
- Arm B (experimental arm): open-label atezolizumab monotherapy
- Arm C (control arm): blinded placebo in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin)

Based on an ad-hoc review of survival data of all patients randomized in the study up to 12 March 2018, the study iDMC recommended closure of Arm B (atezolizumab monotherapy) to further accrual of all patients with a PD-L1 expression status of IC0 or IC1. The iDMC did not recommend a change in therapy for patients already randomized to monotherapy on study.

The iDMC recommendation also stated that patients with a PD-L1 expression status of IC2/3 can continue to be randomized to Arm A, B, or C and that Arms A and C should remain unchanged (open to all patients regardless of PD-L1 status).

Randomization to the three arms in a 1:1:1 ratio will continue regardless of PD-L1 status.

Prior to randomization, all patients will be informed per the consent form that if randomized to Arm B (atezolizumab monotherapy) and are determined to have a tumor PD-L1 expression status of IC0 or IC1, they will receive chemotherapy combined with atezolizumab instead of atezolizumab monotherapy. The consent will also inform patients who are randomized to Arm B, are found to have with a tumor PD-L1 expression status of IC0 or IC1, and who are not willing to undergo treatment with atezolizumab with chemotherapy should consider treatment outside of the trial rather than proceeding with trial enrollment.

<u>For all new patients randomized to Arm B (open-label atezolizumab monotherapy) after approval of Protocol WO30070, Version 6:</u>

- The PD-L1 status will be unblinded to the investigator and patient at the time of randomization.
- Patients whose PD-L1 expression status of IC2/3 will receive atezolizumab monotherapy.
- Patients with a PD-L1 expression status of IC0 or IC1 will receive open-label atezolizumab plus platinum (carboplatin or cisplatin) and gemcitabine chemotherapy instead of atezolizumab monotherapy.

  If a patient with a PD-L1 expression status of IC0 or IC1 subsequently wished to receive standard-of-care chemotherapy instead of atezolizumab plus platinum and gemcitabine, chemotherapy will be able to receive standard-of-care chemotherapy of their choice (to be provided outside of the protocol) and continue on survival follow-up.

<u>For all patients in Arm B who are currently being treated with open-label atezolizumab monotherapy at the time of approval of Protocol WO30070, Version 6:</u>

- Patients will be informed that the iDMC has not recommended any changes to therapy for those already randomized to atezolizumab monotherapy.
- PD-L1 status may be unblinded to the patient and the investigator upon request.
- Patients with PD-L1 expression status of IC2/3 will continue receiving atezolizumab monotherapy.
- Patients with PD-L1 expression status of IC0 or IC1 are recommended to continue with atezolizumab monotherapy, as the iDMC did not recommend a change in therapy for patients already randomized to monotherapy on study.

  However, if the patient after discussion of benefit-risk with the treating physician determines that continuation of atezolizumab monotherapy is not considered beneficial, a treatment alternative of atezolizumab plus platinum (cisplatin or carboplatin) and gemcitabine chemotherapy will be provided. These patients should then be treated the same as patients in Arms A and C.

  If the decision is made to unblind the patient and add platinum (cisplatin or carboplatin) and gemcitabine chemotherapy to the regimen, it must be added before the patient has known progressive disease. Chemotherapy cannot be added to patients in Arm B with documented progressive disease within the study.
- Patients will also have the option to stop study therapy and receive standard-of-care treatment outside of the study by their physician.
- All patients (including those who choose to stop atezolizumab monotherapy) are requested to continue in the study for survival follow up.

Prior to randomization, the investigator will select which chemotherapy the patient should receive (gemcitabine and carboplatin vs. gemcitabine and cisplatin) if the patient is randomized to Arm A or Arm C. The Galsky criteria should be used to guide determination of cisplatin ineligibility. The criteria to determine ineligibility for cisplatin should be the same as the criteria used in the initial implementation of the study.

Randomization will be stratified by the following factors:

- PD-L1 status (IC0 vs. IC1 vs. IC2/3)
- Bajorin model risk factor score/liver metastasis (0 vs. 1 vs. 2 or patients with liver metastasis)
- Investigator-determined chemotherapy (gemcitabine and carboplatin vs. gemcitabine and cisplatin)

Gemcitabine will be administered at a dose of 1000 mg/m^2 by intravenous (IV) infusion on Day 1 and Day 8 of each 21-day cycle.

Carboplatin will be administered at area under the concentration–time curve (AUC) 4.5 by IV infusion on Day 1 of each 21-day cycle.

Cisplatin will be administered at a dose of 70 mg/m^2 by IV infusion on Day 1 of each 21-day cycle. Split dosing of cisplatin is not permitted.

All visits and infusions may be administered with a window of ± 3 days, except for the Day 8 visit. The Day 8 dose of gemcitabine may be given no earlier than Day 7 but may be given up to Day 11 (–1 to + 3) of a cycle.

Gemcitabine and platinum chemotherapy (carboplatin or cisplatin) will be administered until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity.

For patients who receive chemotherapy and who have a CR, only two more cycles of chemotherapy will be administered after the response confirmation.

For patients who receive chemotherapy and who have a PR or stable disease, chemotherapy administration may be discontinued after completion of six cycles, if necessary, to comply with institutional guidelines.

If the initial protocol doses of chemotherapy agents differ from institutional guidelines or local label, the initial doses may be modified to achieve compliance.

Atezolizumab will be administered at a fixed dose of 1200 mg by IV infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1.

Placebo for atezolizumab (Arm C) will be administered by IV infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1. In specific circumstances, treatment may continue beyond disease progression. No crossover will be allowed from the control arm to either experimental arm (Arms A and B).

Patients will undergo scheduled tumor assessment at baseline and every 9 weeks (from initiation of the first dose) thereafter for 54 weeks after randomization. After 54 weeks, patients will undergo tumor assessment every 12 weeks until disease progression per RECIST v1.1, death, study termination by the Sponsor, or withdrawal of consent, whichever occurs first. Patients must discontinue treatment at the first occurrence of radiographic progression, per RECIST v1.1, with the following exception: Patients who have achieved a PR or CR of target lesions and who develop new lesions (≤ 3) that are amenable to surgery or ablative techniques (e.g., radiotherapy, radiofrequency ablation) may continue to receive study treatment if they demonstrate no further progression of disease at the next imaging assessment and continue to demonstrate clinical benefit per investigator; for these patients, tumor assessments should continue until loss of clinical benefit as determined by the Investigator. Because gemcitabine is not indicated for use in combination with radiation therapy and has been shown to cause excess toxicity (mucositis, pneumonitis) as well as radiation recall when administered in close proximity to radiation therapy, patients who continue treatment with gemcitabine should not receive radiation to ports that include a significant proportion of lung or mucosal surface (esophagus, intestine). In the absence of disease progression, tumor assessments should continue, regardless of whether patients start new anti-cancer therapy, until death, loss of follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. Follow-up data capture, including subsequent anti-cancer therapies (including targeted therapies and

immunotherapies), will continue for each patient until death, loss of follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Patients are required to undergo tumor biopsy sample collection, if clinically feasible as assessed by investigators, at the first evidence of radiographic disease progression. These data will be used to confirm that radiographic findings are consistent with the presence of tumor. In addition, these data will be analyzed for the association between changes in tumor tissue and clinical outcome and to understand further the potential mechanisms of resistance to treatment.

All primary imaging data used for tumor assessment will be collected by the Sponsor to enable a centralized independent review until the analysis of the co-primary endpoint of PFS is completed.

Safety assessments will include the incidence, nature, and severity of adverse events, vital signs and laboratory abnormalities graded per the NCI CTCAE v4.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of antibodies to atezolizumab. Patient samples, including archival tumor tissues, as well as serum, plasma, and blood, 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.

After approximately 1200 patients have been randomized, enrollment in sites will be closed.

NUMBER OF PATIENTS

Approximately 229 sites globally will participate in the study, and approximately 1200 patients will be randomized.

TARGET POPULATION

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Considered to be eligible to receive platinum-based chemotherapy, in the investigator's judgment
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2
- Able to comply with the study protocol, in the investigator's judgment
- Histologically documented, locally advanced (T4b, any N; or any T, N 2–3) or metastatic urothelial carcinoma (M1, Stage IV) (also termed TCC or UCC of the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra)

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

  Locally advanced bladder cancer must be inoperable on the basis of involvement of pelvic sidewall or adjacent viscera (clinical Stage T4b) or bulky nodal metastasis (N2–N3).
- Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens 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.

  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.

  Transurethral Resection of Bladder Tumor (TURBT) specimens must contain a muscle invasive component (i.e., T2 or greater) of the bladder tumor as verified by local pathology review. If the TURBT specimens do not contain a muscle invasive component, then specimens obtained at the time of cystectomy/nephroureterectomy (i.e., pT2 or greater) or metastatic spread (i.e., sample from a metastatic lesion) will be

required prior to randomization. An archival specimen, if available, should also be submitted.

Patients who do not have tissue specimens that meet eligibility requirements may undergo a biopsy during the screening period. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

Patients who have additional tissue samples from procedures performed at different times during the course of their urothelial carcinoma may also submit these samples for central testing. Tissue samples that are obtained at multiple times for individual patients may 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 highest score will be used for stratification and for subsequent analyses.

- No prior chemotherapy for inoperable, locally advanced, or metastatic urothelial carcinoma

  For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for urothelial carcinoma, a treatment-free interval > 12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment naive in the metastatic setting.

  Prior local intravesical chemotherapy or immunotherapy is allowed if completed at least 4 weeks prior to the initiation of study treatment.
- Measurable disease, as defined by RECIST v1.1

  Previously irradiated lesions should not be counted as target lesions unless there has been demonstrated progression in the lesion since radiotherapy and no other lesions are available for selection as target lesions.
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 28 days prior to the first study treatment:

  ANC ≥ 1500 cells/μL (without granulocyte colony-stimulating factor support within 2 weeks prior to Cycle 1, Day 1)

  WBC counts > 2500 cells/μL

  Lymphocyte count ≥ 300 cells/μL

  Platelet count ≥ 100,000 cells/μL (without transfusion within 2 weeks prior to Cycle 1, Day 1)

  Hemoglobin ≥ 9.0 g/dL

  Patients may be transfused to meet this criterion.

  Patients with a solitary kidney or chronic kidney disease with low erythropoietin production may use erythropoietin-stimulating agents.

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

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

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

  Serum bilirubin ≤ 1.5 × ULN

  Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.

  PTT/aPTT ≤ 1.5 × ULN

PT ≤ 1.5 × ULN or INR < 1.7

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

Calculated creatinine clearance ≥ 30 mL/min (Cockcroft-Gault formula)

Serum calcium ≤ 3 mmol/L

For patients with serum albumin < 40 g/L, corrected serum calcium must be ≤ ULN

- 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 6 months after the last dose of carboplatin, cisplatin, or gemcitabine or for 5 months after the last dose of atezolizumab

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

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

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

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 6 months after the last dose of gemcitabine and/or carboplatin, and/or cisplatin. Men must refrain from donating sperm during this same period.

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

<u>Exclusion Criteria</u>

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

Cancer-Specific Exclusions

- Any approved anti-cancer therapy, including chemotherapy or hormonal therapy, within 3 weeks prior to initiation of study treatment; the following exceptions are allowed:

  Palliative radiotherapy for bone metastases or soft tissue lesions should be completed > 7 days prior to baseline imaging.

  Hormone-replacement therapy or oral contraceptives
- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to enrollment
- Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging evaluation during screening and prior radiographic assessments

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

  Evaluable or measurable disease outside the CNS

  No metastases to midbrain, pons, medulla, or within 10 mm of the optic apparatus (optic nerves and chiasm)

No history of intracranial or spinal cord hemorrhage

No ongoing requirement for corticosteroid as therapy for CNS disease; anti-convulsants at a stable dose are allowed

No evidence of significant vasogenic edema

No stereotactic radiation, whole-brain radiation or neurosurgical resection within 4 weeks prior to Cycle 1, Day 1

Radiographic demonstration of interim stability (i.e., no progression) between the completion of CNS-directed therapy and the screening radiographic study

Screening CNS radiographic study ≥4 weeks since completion of radiotherapy or surgical resection and ≥2 weeks since discontinuation of corticosteroids

- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled tumor-related pain

  Patients who require pain medication must be on a stable regimen at study entry.

  Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment.

  Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled hypercalcemia defined as any one or more of the following criteria:

  >1.5 mmol/L ionized calcium

  Serum calcium >3 mmol/L

  Corrected serum calcium >ULN (if serum albumin <40 g/L)

  Symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab

  Patients who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.
- Malignancies other than urothelial carcinoma within 5 years prior to Cycle 1, Day 1

  Patients with localized prostate cancer (defined as Stage ≤pT2c, Gleason score ≤7, and prostate-specific antigen (PSA) at prostate cancer diagnosis ≤20 ng/mL) treated with curative intent and without PSA recurrence are eligible.

  Patients with pre-existing low-risk prostate cancer (defined as Stage cT1/T2a, Gleason score ≤6 and PSA ≤10 ng/mL) who are treatment-naive and undergoing active surveillance are eligible.

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

  Malignancy treated with expected curative intent (e.g., 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 Exclusions

- Life expectancy of <12 weeks

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

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- Serum albumin <25 g/L

Exclusion Criteria Related to Atezolizumab

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy 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, *granulomatosis with polyangiitis*, 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 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis) are permitted provided that they meet the following conditions:

  Rash must cover less than 10% of body surface area (BSA)

  Disease is well controlled at baseline and only requiring low potency topical steroids

  No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
- Patients with prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class III or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina
- Known left ventricular ejection fraction (LVEF) <40%

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF 40%–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. Patients with a history of clinically significant cardiac disease (including anatomic abnormality, coronary disease, congestive heart failure, abnormal LVEF, arrhythmia, or abnormal ECG) will be required to undergo a screening echocardiogram.
- Positive test for HIV
- Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. A negative HBV DNA test must be obtained in these patients prior to Cycle 1, Day 1.

Patients who test 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 randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Therapeutic oral or IV antibiotics within 2 weeks prior to randomization

  Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease [COPD] or for dental extraction) are eligible.
- Major surgical procedure within 4 weeks prior to randomization or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis.
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1

  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 within 28 days prior to initiation of study treatment, during treatment, or within 5 months after the last dose of atezolizumab.
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- Prior treatment with CD137 agonists, anti–CTLA-4, anti–programmed death-1 (PD-1), or anti–PD-L1 therapeutic antibody or pathway-targeting agents
- Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to 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 [TNF] agents) within 2 weeks prior to Cycle 1, Day 1 or anticipated requirement for systemic immunosuppressive medications during the study

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

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

END OF STUDY

The end of this study is defined as the date of the last visit of the last patient in the study/last scheduled procedure shown in the schedule of activities for the last patient in the study globally or the date at which the required number of deaths has been observed for the final analysis of OS in the global (main) study's intent-to-treat (ITT) population whichever occurs later.

Additionally, the Sponsor may decide to terminate the study at any time.

LENGTH OF STUDY

The total length of the global (main) study, from randomization of the first patient to the end of the study, is expected to be approximately 44 months.

INVESTIGATIONAL MEDICINAL PRODUCTS

The investigational medicinal products (IMPs) for this study are atezolizumab, placebo, gemcitabine, carboplatin, and cisplatin.

TEST PRODUCTS (INVESTIGATIONAL DRUGS)

Atezolizumab

The dose level of atezolizumab in this study is 1200 mg administered by IV infusion every 3 weeks (q3w). Administration of atezolizumab and placebo will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

Gemcitabine

Gemcitabine will be administered according to the local prescribing information. The starting dose of gemcitabine will be 1000 mg/m^2, administered by IV infusion on Day 1 and Day 8 of each 21-day cycle. The Day 8 dose of gemcitabine may be given no earlier than Day 7 but may be given up to Day 11 (–1 to + 3) of a cycle. A change of body weight ± 5% compared to previous measured weight requires that the dose be re-calculated.

Carboplatin

Carboplatin will be administered according to the local prescribing information. The starting dose of carboplatin will be calculated to achieve an AUC of 4.5, administered by IV infusion on Day 1 of each 21-day cycle. If institutional guidelines conflict with protocol carboplatin dosing, carboplatin may be administered at a maximum starting AUC of 5.0. A change of body weight ± 5% compared to previous measured weight requires that the dose be re-calculated.

Cisplatin

Cisplatin will be administered according to the local prescribing information. The starting dose of cisplatin will be 70 mg/m^2, administered by IV infusion on Day 1 of each 21-day cycle. Split dosing of cisplatin is not permitted. A change of body weight ± 5% compared to previous measured weight requires that the dose be re-calculated.

Comparator

Placebo

The placebo will be identical in appearance to atezolizumab and comprise the same excipients but without atezolizumab drug product. It should be handled, stored, and used in the same manner as atezolizumab (by IV infusion q3w).

Duration of Chemotherapy Treatment

Gemcitabine and platinum chemotherapy (carboplatin or cisplatin) will be administered until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity.

For patients in the combination arms who receive chemotherapy (Arms A and C) and who have a CR, only two more cycles of chemotherapy will be administered after the response confirmation.

For patients in the combination arms who receive chemotherapy and who have a PR or stable disease, chemotherapy administration may be discontinued after completion of six cycles, if necessary, to comply with institutional guidelines.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

None.

STATISTICAL METHODS

PRIMARY ANALYSIS

The efficacy analyses for PFS and OS will be performed on all randomized patients (ITT population) for the respective treatment arm comparison according to the analysis hierarchy. Patients will be grouped according to the treatment assigned at randomization. Analysis of secondary and exploratory efficacy endpoints will be performed for randomized patients in the ITT population.

Co-Primary Efficacy Endpoints

The co-primary efficacy endpoints are PFS as assessed by the investigator using RECIST v1.1 and OS. Because type I error will be controlled accounting for two co-primary endpoints, the study will be considered a positive study if statistical significance is achieved for either of the co-primary endpoints.

PFS is defined as the time from randomization to the first documented disease progression as assessed by the investigator using RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or death will be censored

at the last tumor assessment. Data for patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

For U.S. registration purposes, the co-primary efficacy endpoint of PFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits.

OS is defined as the time from randomization to death due to any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.

The following analyses will be performed for both PFS and for OS. PFS and OS will be compared between treatment arms with the use of the stratified log-rank test. For the comparisons of Arm A versus Arm C, a possible effect of study stage will be taken into account.

The HR for PFS and OS will be estimated using a stratified Cox regression model. The 95% CI for the HR will be provided. The stratification factors will be the same as the randomization stratification factors, with values as recorded in the IxRS. Results from an unstratified analysis will also be presented. Kaplan-Meier methodology will be used to estimate median PFS and OS for each treatment arm, and Kaplan-Meier plots will be constructed to provide a visual description of the difference between the treatment and control arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS and OS for each treatment arm.

For the primary analysis of OS in the ITT population for Arm B versus Arm C, all available data for these patients (before and after implementation of the iDMC recommendation in Protocol WO30070, Version 6) will be included.

However, if a substantial number of patients with a PD-L1 expression status of IC0 or IC1 randomized to Arm B prior to implementation of Protocol WO30070, Version 6 choose to switch to the combination of atezolizumab and chemotherapy, an additional analysis may be performed to account for treatment switching. A sensitivity analysis will also be performed on patients randomized to Arm B or Arm C prior to implementation of Protocol WO30070, Version 6 that will include their data only up to the time of implementation of the iDMC recommendation.

The analysis of OS in the PD-L1 IC2/3 population for Arm B versus Arm C will use the same methods as that for the ITT population for Arm B versus Arm C, except that PD-L1 status will not be one of the stratification factors. The analysis will include all available data for these patients (before and after implementation of the iDMC recommendation of Protocol WO30070, Version 6).

DETERMINATION OF SAMPLE SIZE

A total of approximately 1200 patients will be randomized to the study (Stage 1 and Stage 2 combined).

Enrollment of approximately 1200 patients is based on the following assumptions: approximately 258 patients are projected to be enrolled in Stage 1 and allocated 2:1 to Arm A (atezolizumab in combination with platinum therapy) or Arm C (placebo in combination with platinum therapy). Approximately 942 patients are projected to be enrolled in Stage 2 and allocated 1:1:1 to Arm A, Arm B (atezolizumab monotherapy), or Arm C.

Simulations were performed to check the expected power of the analyses of co-primary endpoints PFS and OS for this sample size.

INTERIM ANALYSES

There are no interim analyses planned for PFS in this study.

A total of three efficacy analyses of OS are planned (two interim analyses and the final analysis). The final analysis of OS in Arm A versus Arm C will be performed when approximately 667 OS events in Arm A and Arm C of the ITT population have occurred. Based on observed survival up to the final PFS/interim OS analysis, the required number of events is projected to occur at Month 55 from the time the first patient was randomized.

The interim and final analyses of OS in Arms A versus C and Arms B versus C will be performed according to the analysis hierarchy.

The first interim OS analysis will be conducted by the Sponsor at the time of the final PFS analysis.

The second interim OS analysis will take place after approximately 12 months of additional follow-up compared with the clinical cut-off date for the primary analysis, or when at least 579 patients (68%) have died in Arm A and C, whichever is later.

Because the patient populations enrolled during Stage 1 and Stage 2 are considered independent, standard methods of group sequential designs apply.

If the required number of OS events in Arm B versus Arm C has not been reached at the time of the second interim or final OS analysis in Arm A versus Arm C, then two further interim analyses for the comparison of Arm B versus Arm C may be performed at the time of these analyses.

To control type I error for OS, the stopping boundaries for the OS interim and final analyses are to be computed for the appropriate alpha level with use of the Lan-DeMets implementation of the O'Brien-Fleming use function.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
anti-HBc	antibody to hepatitis B core antigen
ATA	anti-therapeutic antibody
AUC	area under the concentration time–curve
BSC	best supportive care
CarboGem	carboplatin and gemcitabine
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CR	complete response
CRP	C-reactive protein
CRS	cytokine-release syndrome
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
EAU	European Association of Urology
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GFR	glomerular filtration rate
GSM	Global Study Manager
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
IC	tumor-infiltrating immune cell
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IFN	interferon
IHC	immunohistochemistry

Abbreviation	Definition
IL	interleukin
IMP	investigational medicinal product
INV-PFS	investigator-assessed progression-free survival
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRR	infusion related reaction
IRF	independent review facility
IRF-PFS	Independent Review Facility progression-free survival
ITT	intent-to-treat
IV	intravenous
IxRS	interactive voice/web response system
LVEF	left ventricular ejection fraction
MDSC	myeloid-derived suppressor cells
M-CAVI	methotrexate, carboplatin, and vincristine
MAS	macrophage activation syndrome
MRI	magnetic resonance imaging
MVAC	methotrexate, vinblastine, doxorubicin, and cisplatin
NaF	sodium fluoride
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD-1	programmed death-1
PD-L1	programmed death–ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen
q3w	every 3 weeks
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan

Abbreviation	Definition
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SEER	Surveillance, Epidemiology and End Results
TC	tumor cell
TC-99m	technetium-99m
TCC	transitional cell carcinoma
TIMC	tumor-infiltrating mononuclear cell
TNF	tumor necrosis factor
TTR	time to response
TURBT	transurethral resection of bladder tumor
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON UROTHELIAL CARCINOMA

Urothelial carcinoma (UC, also termed transitional cell carcinoma [TCC], urothelial bladder cancer or urothelial cell carcinoma [UCC] of the urinary tract) is the most common cancer of the urinary system worldwide with urothelial carcinoma of the bladder being the predominant histologic type and location. Although less common, urothelial carcinoma may originate in the renal pelvis, ureter, or urethra. It was estimated that in 2015, there would be 74,000 new cases and 16,000 deaths from bladder cancer in the United States (American Cancer Society 2015). Similar worldwide data estimate that there were 123,000 deaths from bladder cancer in men and 42,000 in women in 2012 (Ferlay et al. 2015).

The overall 5-year survival rate for metastatic urothelial carcinoma is approximately 5.4% (Surveillance, Epidemiology and End Results [SEER] 2015). Poor prognostic factors for survival in patients with metastatic urothelial carcinoma include advanced stage of disease at the time of initial diagnosis, Karnofsky Performance Status < 80%, and visceral metastasis (i.e., lung, liver, or bone; Bajorin et al. 1999). The presence of these unfavorable features was associated with a median survival of 4 months compared with 18 months in patients without these features (Loehrer et al. 1992).

TCC is the most common histologic subtype associated with bladder cancer and accounts for greater than 90% of all urothelial carcinoma cases in the industrialized world, whereas non-urothelial subtypes, including squamous cell, adenocarcinoma, and small cell carcinoma, are more frequent in other areas of the world (Chalasani et al. 2009).

1.1.1 Metastatic Urothelial Carcinoma

A high unmet need exists for patients with metastatic urothelial carcinoma given the limited therapeutic advances that have been made over the past 30 years. In contrast to 5-year survival improvements observed in other advanced-stage diseases (approximately 20%–40% for breast, colon, melanoma, ovarian, and prostate cancer), there has been no improvement observed for metastatic urothelial carcinoma (SEER 2015). An analysis of the SEER dataset for patients with metastatic urothelial carcinoma who were diagnosed 1990–2010 observed no differences in disease-specific survival between 1990–2000 and 2001–2010 regardless of treatment (Pal et al. 2015). In addition, information is very limited regarding the disease burden and the impact of available treatments or molecules under investigation on symptoms (e.g., back pain, fatigue, weight loss, and frequent urination), patient functionality, and health-related quality of life.

Approximately 5% of patients present with metastatic disease at diagnosis. Despite the low frequency of de novo disease, approximately half of the patients with locally advanced urothelial carcinoma progress to metastatic disease within two years of

cystectomy. Platinum-based combination chemotherapy is the preferred regimen in the first-line setting, and single agent chemotherapy is typically reserved for the second-line setting.

1.1.2 First-Line Treatment of Metastatic Urothelial Carcinoma

Platinum-based chemotherapy is the current standard-of-care for patients with previously untreated metastatic urothelial carcinoma. For medically fit patients with metastatic urothelial carcinoma, cisplatin-based combination chemotherapy is the preferred initial therapy. Common cisplatin-based regimens include methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and gemcitabine and cisplatin. Initial studies with MVAC produced overall response rates greater than 70% with approximately 35% of patients achieving a complete response (CR) (Sternberg et al. 1985; Sternberg et al. 1989), although subsequent studies showed lower response rates (Loehrer et al. 1992). Subsequently, a Phase III study of 405 patients showed that patients who received gemcitabine and cisplatin had a similar overall survival (OS) to patients who were randomized to MVAC (14.0 months for gemcitabine and cisplatin vs. 15.2 months for MVAC; hazard ratio [HR] = 1.09; 95% CI: 0.88, 1.34, p = 0.66) with less Grade 3 or 4 toxicity and, as a result, gemcitabine and cisplatin has largely displaced MVAC as the standard of care (von der Maase et al. 2005). The 1-year landmark OS rate for gemcitabine and cisplatin was 58.4% (95% CI: 51.6, 65.2) and for MVAC was 62.6% (95% CI: 55.9, 69.3). Both regimens are associated with substantial toxicities, such as febrile neutropenia, myelosuppression, nausea, alopecia, nephropathy, and neuropathy, and there is a significant medical need for efficacious and more tolerable regimens.

Despite the observed efficacy of cisplatin-based combination chemotherapy, up to 50% of patients are medically "unfit" or ineligible to receive cisplatin because of baseline comorbidities (Sonpavde et al. 2014; Thompson et al. 2014). A consensus working group has defined cisplatin-ineligibility under specific criteria (Galsky et al. 2011), including performance status, renal function, hearing-loss history, peripheral neuropathy, and cardiac function. For patients who are ineligible to receive cisplatin, treatment options include carboplatin-based or non–platinum based combinations, single-agent regimens, and best supportive care (BSC). The benefit of carboplatin-based chemotherapy in these medically "unfit" or cisplatin-ineligible patients was demonstrated in the European Organisation for Research and Treatment of Cancer (EORTC) Trial 30986. In this study, 238 patients with previously untreated advanced urothelial carcinoma and either a poor performance status (i.e., Eastern Cooperative Oncology Group [ECOG] performance status 2) and/or impaired renal function (glomerular filtration rate [GFR] < 60 but > 30 mL/min) were enrolled to receive carboplatin and gemcitabine (CarboGem) or methotrexate, carboplatin, and vincristine (M-CAVI) (De Santis et al. 2012). Although the confirmed objective response rate (ORR) of CarboGem was 36.1% versus 21.0% for the M-CAVI arm, the study demonstrated no difference in OS (median OS 9.3 vs. 8.1 months; HR = 0.94; 95% CI: 0.72, 1.22;

p=0.64). In the CarboGem arm, 37.0% (44/119) and 13.4% (16/119) of patients were alive 1 year and 2 years after randomization, respectively (M. De Santis, personal communication).

Notably, patients with both impaired renal function and poor performance status had especially poor outcomes and increased acute toxicity with either combination chemotherapy in the study. In addition, a post hoc analysis of OS by Bajorin risk groups showed that as the number of risk factors increased, OS decreased significantly (Bajorin et al. 1999). Guidelines from National Comprehensive Cancer Network (NCCN 2015), European Society for Medical Oncology (Bellmunt et al. 2014), and European Association of Urology (EAU) recommend the use of carboplatin-based regimens or single-agent therapy (taxane or gemcitabine) in this patient population (Bellmunt et al. 2014; Witjes et al. 2014; NCCN 2015).

Two independent retrospective studies of medical claims in the SEER-Medicare database showed that only about 50% of patients receive treatment with chemotherapy for first-line metastatic urothelial carcinoma. Among patients receiving chemotherapy, 50% received carboplatin-based therapy (32% received CarboGem), 36% received cisplatin-based therapy, and the remainder received a variety of other single-agent or non-platinum combination therapies. For the patients that did not receive chemotherapy, the outcomes were extremely poor, with a median OS of only 3 months (Sonpavde et al. 2014; Galsky et al. 2015).

A survival analysis conducted in the SEER Medicare database of 822 previously untreated patients with metastatic urothelial carcinoma who received either non-cisplatin chemotherapy (including doublet and single agent therapy; n=285) or no chemotherapy (n=537) demonstrated overall poor outcomes in this population, including a median OS of 5.2 months and a probability of 1-year survival of 0.3 (Galsky et al. 2015).

1.1.3 Targeted Therapy for Urothelial Carcinoma

Although there is an increasing understanding of the molecular biology and signaling pathways that underlie bladder cancer development and progression (particularly the fibroblast growth factor receptor–, vascular endothelial growth factor–, and epidermal growth factor receptor–/human epidermal growth factor 2–pathways), no targeted agents currently have a role in the treatment of urothelial carcinoma.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (also known as MPDL3280A) is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human 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.

Atezolizumab is being evaluated as a single agent and in combination with other therapies for the treatment of a broad range of tumor types and hematologic malignancies.

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma. Atezolizumab is approved for one or more of these indications in multiple countries globally.

1.2.1 Summary of Nonclinical Studies

The strategy of the atezolizumab nonclinical program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, and to demonstrate an acceptable safety profile. 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 that were observed for atezolizumab supported entry into clinical studies and included the provision of adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of down-modulation of the PD-L1/PD-1 pathway and supported entry into clinical studies in patients.

See 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

Studies of atezolizumab relevant to this combination study include an ongoing Phase Ia monotherapy study, an ongoing combination study with chemotherapy in patients with solid tumors, and Phase II and Phase III monotherapy studies in patients with urothelial carcinoma (see the Atezolizumab Investigator's Brochure for study descriptions as well as additional studies).

Phase Ia Study PCD4989g

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

As of 2 December 2014, efficacy analyses were performed on 87 patients with locally advanced or metastatic urothelial carcinoma who were followed up for a minimum of 12 weeks. Responses were observed in all PD-L1 subgroups (ranging 13.3%–66.7%), with higher ORRs associated with higher PD-L1 expression in tumor-infiltrating immune cells (IC).

Phase Ib Study GP28328

The ongoing Phase Ib Study GP28328 is evaluating the safety and pharmacology of atezolizumab administered with bevacizumab alone (Arm A) or with bevacizumab plus leucovorin, 5-fluorouracil, and oxaliplatin (Arm B) in patients with advanced solid tumors. Additional cohorts have been included to investigate atezolizumab in combination with carboplatin plus paclitaxel (Arm C); in combination with carboplatin plus pemetrexed (Arm D); and in combination with carboplatin plus nab-paclitaxel, (Arm E) in patients with chemotherapy-naive advanced or metastatic non–small cell lung cancer. As of 29 September 2014, efficacy analyses were performed on 30 patients in Arms C–E (atezolizumab plus carboplatin plus either paclitaxel, pemetrexed, or nab-paclitaxel). Responses were observed in each arm independent of PD-L1 expression (range: 60%–75%). The treatment combinations in Study GP28328 have been generally well tolerated, and no DLTs have been reported during the dose escalation stage in any study arm.

Phase II Study GO29293 (IMvigor210)

The ongoing Study GO29293 is a single-arm, open label, Phase II study to assess the clinical benefit of atezolizumab as a single agent in patients with locally advanced or metastatic urothelial carcinoma. Two cohorts of patients were enrolled: Cohort 1 enrolled first-line (1L) patients who were ineligible to receive cisplatin-based chemotherapy, Cohort 2 enrolled a pretreated population that had progressed during or following platinum-based chemotherapy. The co-primary endpoints of the study are Independent Review Facility–assessed ORR according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (both cohorts) and investigator-assessed ORR according to modified RECIST criteria (Cohort 2 only).

Data from Cohort 2 showed that Study GO29293 met its co-primary endpoints in all-comer patients, demonstrating significant improvement over a historical 10% ORR,

and durable responses were observed. Similar to Study PCD4989g, higher PD-L1 IC status was associated with higher ORRs. Atezolizumab was well tolerated with a low rate of treatment-related Grade 3–4 toxicities and no treatment-related Grade 5 adverse events (Hoffman-Censits et al. 2016; Rosenberg et al. 2016).

Data from Cohort 1 showed that durable responses were achieved in 1L cisplatin-ineligible patients with metastatic urothelial carcinoma who received atezolizumab monotherapy. The ORR in all patients was 24%, and responses were seen in all PD L1 IC subgroups. At the clinical data cutoff of 14 March 2016, the median survival in all patients was 14.8 months and the 1-year OS rate was 57%. In this patient population, atezolizumab was well tolerated, with a low rate of treatment-related Grade 3–4 adverse events and discontinuations due to adverse events (Balar et al. 2016).

Phase III Study GO29294 (IMvigor211)

This is an ongoing Phase III, global, multicenter, open-label, two-arm, randomized, controlled study designed to evaluate the efficacy and safety of atezolizumab compared with chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who have progressed during or following a platinum-containing regimen. The study has enrolled 931 patients, who have been randomized (1:1) to receive either atezolizumab or chemotherapy (vinflunine, paclitaxel, or docetaxel). The primary endpoint for the study is OS.

See the Atezolizumab Investigator's Brochure for further details regarding atezolizumab clinical studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 The PD-L1/PD-1 Pathway in Cancer

PD-L1 is a transmembrane protein that down-regulates immune responses primarily in peripheral tissues through binding to its two receptors PD-1 and B7.1. 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 down-regulation of immune responses, including inhibition of T-cell activation and cytokine production (Butte et al. 2007; Yang et al. 2011). PD-L1 expression has been observed in immune cells and malignant cells (Dong et al. 1999). Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity suppressed by the expression of PD-L1 in the tumor microenvironment.

1.3.2 PD-L1 in Urothelial Carcinoma

In bladder cancer, expression of PD-L1 has been associated with poor prognosis. Nakanishi et al. (2007) was one of the first groups to observe an association between expression of PD-L1 (B7-H1) and outcomes in advanced urothelial cancers. In their study, PD-L1 (B7-H1) expression was significantly associated with a high frequency of disease recurrence and poor survival rate. Multivariate analysis also showed PD-L1 (B7-H1) expression to be a more significant prognostic factor than tumor grade (Nakanishi et al. 2007). Zhang et al. (2013) similarly presented data on PD-L1 expression and outcomes in bladder cancer. Results of the study showed PD-L1 expression in 43% of primary bladder cancers with an association between immunohistochemistry (IHC) positivity and intensity with tumor grade and staging (Zhang et al. 2013). Faraj et al. (2015) showed high intratumoral CD8 + T-cell density to be associated with better OS and disease-specific survival in advanced bladder cancer. Bellmunt et al. (2015) reported PD-L1 expression in tumor cells (TCs) and tumor-infiltrating mononuclear cells (TIMCs). Results of the study showed PD-L1 expression in TIMCs to be associated with longer survival but not predictive of survival. The association between PD-L1 expression in TC or IC and clinical benefit with PD-L1/PD-1 pathway inhibitors has been reported in Phase I clinical studies (Brahmer et al. 2010; Topalian et al. 2012; Herbst et al. 2014). Furthermore, targeting the PD-L1 pathway has demonstrated durable activity in patients with advanced urothelial carcinoma whose standard-of-care therapies have failed or who have refused standard-of-care therapies (Powles et al. 2014; Dreicer et al. 2016; Hoffman-Censits et al. 2016).

Treatment with atezolizumab monotherapy in metastatic urothelial carcinoma has shown responses in patients with platinum-refractory cancer as well as in patients with 1L disease who are ineligible to receive cisplatin. Responses achieved with atezolizumab in these patient populations appear to be durable (Balar et al. 2016; Rosenberg et al. 2016). Results from the pivotal multicenter Phase II study, IMvigor210, showed that durable responses were achieved in 1L cisplatin-ineligible patients with metastatic urothelial carcinoma who received atezolizumab monotherapy. The ORR in all patients was 24%, and responses were seen in all PD-L1 IC subgroups. The median survival in all patients was 14.8 months, and the 1-year OS rate was 57% (Balar et al. 2016).

Atezolizumab has been generally well tolerated (see Section 5.1.1); adverse events with potentially immune-mediated causes that are consistent with an immunotherapeutic agent, including rash, hypothyroidism, hepatitis/elevated transaminases, colitis, and myasthenia gravis, have been observed in ongoing studies of atezolizumab. To date, these events have been amenable to monitoring and treatment.

This trial will enroll patients with untreated locally advanced or metastatic urothelial carcinoma. Given the relatively poor prognosis and limited treatment options for these patients, this population is considered appropriate for trials of novel therapeutic

candidates. The benefit–risk ratio for atezolizumab is expected to be acceptable in this setting.

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of SARS-CoV-2 infection.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by cancer immunotherapy.

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

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for SARS-CoV-2–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

The management of risks associated with platinum-based chemotherapy will follow the local prescribing information; however, the understanding of the longer-term risks associated with atezolizumab in combination with platinum-based chemotherapy is limited. Overlapping toxicities may include neuropathy and gastrointestinal disorders such as anorexia, diarrhea, nausea, and vomiting. Because these risks may represent symptoms of adverse events of special interest, which are reported to the Sponsor within 24 hours, the Sponsor will monitor these events closely. In addition, these risks will be monitored through more frequent evaluation of safety by the independent Data Monitoring Committee (iDMC) during the first year and standard pharmacovigilance activities, including routine signal detection.In summary, treatment with atezolizumab, both as a single-agent and in combination with platinum-based chemotherapy offers the

potential for clinical benefit in previously untreated patients with metastatic urothelial carcinoma.

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

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

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

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4.1)

2. OBJECTIVES AND ENDPOINTS

This is a Phase III, multicenter, randomized, placebo-controlled, partially blind study designed to evaluate the efficacy of atezolizumab given as monotherapy or in combination with platinum-based chemotherapy versus placebo in combination with platinum-based chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who have not received prior systemic therapy.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus platinum-based chemotherapy compared with placebo plus platinum-based chemotherapy on the basis of the following endpoints:

- Co-primary endpoints of progression-free survival (PFS) and OS

  PFS is defined as the time from randomization to the first documented disease progression as determined by the investigator with use of RECIST v1.1, or death due to any cause, whichever occurs first.

  The OS is defined as the time from randomization to death due to any cause.

In addition, a primary efficacy objective is to evaluate the efficacy of atezolizumab monotherapy compared with placebo plus platinum-based chemotherapy on the basis of OS, as defined above.

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives for this study are to evaluate the efficacy of atezolizumab given as either monotherapy or in combination with platinum-based chemotherapy compared with placebo in combination with platinum-based chemotherapy on the basis of the following endpoints:

- ORR, defined as the proportion of patients with a confirmed objective response, either CR or partial response (PR), observed on two assessments ≥28 days apart per RECIST v1.1, based on investigator assessment
- Duration of response (DOR), defined for patients with an objective response as the time from the first documented objective response to documented disease progression per RECIST v1.1, based on investigator assessment, or death due to any cause, whichever occurs first
- Independent review facility progression free survival (IRF-PFS), defined as the time from randomization to the first documented disease progression as determined by blinded independent central review with use of RECIST v1.1, or death due to any cause, whichever occurs first
- Investigator-assessed progression free survival (INV-PFS) in patients treated with atezolizumab monotherapy compared with patients treated with placebo plus platinum-based chemotherapy
- OS rate at 1 year
- PFS rate at 1 year
- Time to deterioration in global health status as measured by the QLQ-C30
- Time to deterioration in physical function as measured by the QLQ-C30

2.1.3 Exploratory Efficacy Objectives

The exploratory efficacy objectives for this study are to evaluate the efficacy of atezolizumab given as either monotherapy or in combination with platinum-based chemotherapy compared with placebo in combination with platinum-based chemotherapy on the basis of the following endpoints:

- Disease control rate (DCR), defined as the proportion of patients with confirmed CR or PR as best response, or stable disease maintained for ≥ 6 months, per RECIST v1.1
- Relationship between tumor tissue PD-L1 expression and measures of efficacy
- Predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status and/or response to study treatment
- Disease and treatment burden as measured by the symptom (e.g., pain, fatigue) and function scores from the QLQ-C30

2.2 HEALTH ECONOMICS OBJECTIVE

Health status will be measured using the EuroQol EQ-5D-5L questionnaire to be included in health economic modeling (EuroQol Group 1990). As such, data from the EQ-5D-5L will not be reported in the Clinical Study Report (CSR).

2.3 SAFETY OBJECTIVES

The safety objectives for this study are to evaluate the safety and tolerability of atezolizumab given as either monotherapy or in combination with platinum-based chemotherapy compared with placebo plus platinum-based chemotherapy on the basis of the following:

- Incidence, nature, and severity of adverse events graded according to National Cancer Institute (NCI CTCAE) Common Terminology Criteria for Adverse Events v4.0
- Changes in vital signs, and clinical laboratory results

2.4 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the pharmacokinetics of atezolizumab when administered as monotherapy or in combination with platinum-based chemotherapy in patients who are treatment-naive:

- PK parameters for atezolizumab include maximum serum concentration (C_{max}) and minimum serum concentration (C_{min}) when appropriate, as data allow.

2.5 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab as monotherapy and in combination with platinum-based chemotherapy on the basis of the following endpoint:

- Incidence of anti-therapeutic antibodies (ATAs) during the study relative to the prevalence of ATAs at baseline

The exploratory immunogenicity objective for this study is to evaluate potential effects of detectable ATAs on the basis of the following endpoint:

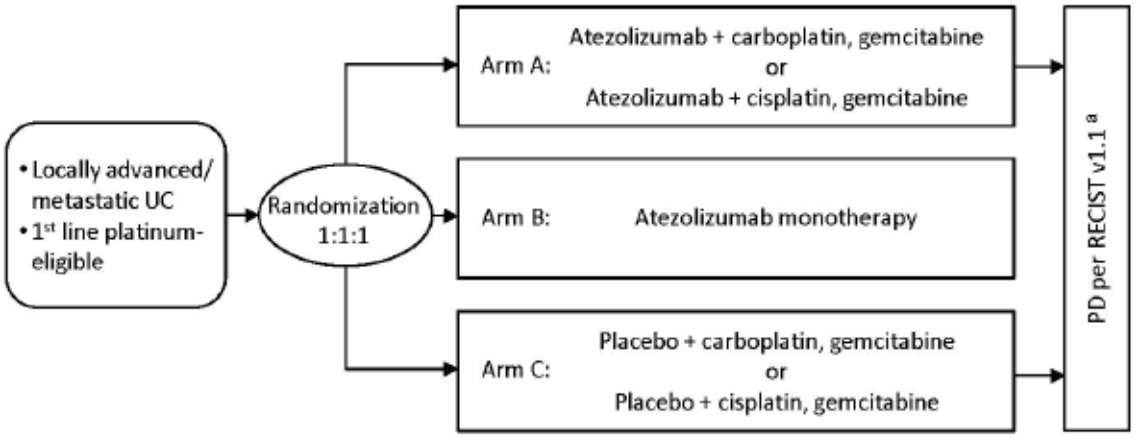
- Correlation between ATA status and efficacy, safety, and PK endpoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, multicenter, randomized, placebo-controlled, partially blind study (IMvigor130) designed to evaluate the safety and efficacy of atezolizumab given as monotherapy or in combination with platinum-based chemotherapy versus placebo in combination with platinum-based chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who have not received prior systemic therapy (see Figure 1).

Figure 1 Study Schema



PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors; UC = urothelial carcinoma.

Notes: A total of 1200 patients will be enrolled at approximately 229 sites globally.

Treatment with platinum-based chemotherapy can continue until progressive disease (PD) per RECIST v1.1 or unacceptable toxicity per investigator discretion. In the case of CR, only two more cycles of platinum-based chemotherapy will be administered after the response confirmation. In specific circumstances, treatment may continue beyond disease progression (see below and Section 4.6.2).

No crossover will be allowed from the control arm to either experimental arm (Arms A and B).

Patients should be considered eligible to receive treatment with platinum-based chemotherapy (either gemcitabine with cisplatin or gemcitabine with carboplatin) and have measurable disease, defined by RECIST v1.1.

Note, the study was initially implemented with randomization to two treatment arms (carboplatin plus gemcitabine with or without atezolizumab) in patients who were ineligible for cisplatin-based chemotherapy (see Section 3.1.1). In Protocol WO30070, Version 3, a third treatment arm was added (open-label atezolizumab monotherapy). In addition, the eligibility criteria were expanded to also allow patients who are eligible for cisplatin-based chemotherapy to enter the study. Protocol WO30070, Version 3 was implemented while recruitment was ongoing. Patients recruited into the study prior to Version 3 will be included in the final analysis.

Tumor specimens from eligible patients will be prospectively tested for PD-L1 IHC expression by a central laboratory prior to randomization. The IHC scores will have three categories (IC0, IC1, IC2/3). Sponsor, patients, and investigators will be blinded to the PD-L1 expression status, but the Sponsor will be able to view aggregate PD-L1 expression data. An exception is the case for any new patients enrolled in Arm B, in which PD-L1 status will be unblinded to the patient and investigator at the time of randomization. However, the Sponsor will not be able to review these scores (see below for further information regarding Protocol Version 6 update based on iDMC recommendation). The study will enroll all eligible patients whose tissue is evaluable for expression testing, regardless of PD-L1 expression status.

This study will enroll approximately 1200 patients at approximately 229 sites globally.

Following implementation of Protocol WO30070, Version 3, patients will be randomized in a 1:1:1 ratio to receive one of the following:

- Arm A (experimental arm): blinded atezolizumab in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin)
- Arm B (experimental arm): open-label atezolizumab monotherapy
- Arm C (control arm): blinded placebo in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin)

Based on an ad-hoc review of survival data of all patients randomized in the study up to 12 March 2018, the study iDMC recommended closure of Arm B (atezolizumab monotherapy) to further accrual of all patients with a PD-L1 expression status of IC0 or IC1. The iDMC did not recommend a change in therapy for patients already randomized to monotherapy on study.

The iDMC recommendation also stated that patients with a PD-L1 expression status of IC2/3 can continue to be randomized to Arm A, B, or C and that Arms A and C should remain unchanged (open to all patients regardless of PD-L1 status).

Based on this recommendation, the study design following implementation of Protocol WO30070, Version 6 is presented below (see Figure 2).

Randomization to the three arms in a 1:1:1 ratio will continue regardless of PD-L1 status.

Prior to randomization, all patients will be informed per the consent form that if randomized to Arm B (atezolizumab monotherapy) and are determined to have a tumor PD-L1 expression status of IC0 or IC1, they will receive chemotherapy combined with atezolizumab instead of atezolizumab monotherapy. The consent will also inform patients who are randomized to Arm B, are found to have with a tumor PD-L1 expression status of IC0 or IC1, and who are not willing to undergo treatment with atezolizumab with chemotherapy should consider treatment outside of the trial rather than proceeding with trial enrollment.

For all new patients randomized to Arm B (open-label atezolizumab monotherapy) after approval of Protocol WO30070, Version 6:

- The PD-L1 status will be unblinded to the investigator and patient at the time of randomization.
- Patients whose PD-L1 expression status of IC2/3 will receive atezolizumab monotherapy.
- Patients with a PD-L1 expression status of IC0 or IC1 will receive open-label atezolizumab plus platinum (carboplatin or cisplatin) and gemcitabine chemotherapy instead of atezolizumab monotherapy.

  If a patient with a PD-L1 expression status of IC0 or IC1 subsequently wished to receive standard-of-care chemotherapy, instead of atezolizumab plus platinum and gemcitabine chemotherapy, will be able to receive standard-of-care chemotherapy of their choice (to be provided outside of the protocol) and continue on survival follow up.

For all patients in Arm B who are currently being treated with open-label atezolizumab monotherapy at the time of approval of Protocol WO30070, Version 6:

- Patients will be informed that the iDMC has not recommended any changes to therapy for those already randomized to atezolizumab monotherapy.
- PD-L1 status may be unblinded to the patient and the investigator upon request.
- Patients with PD-L1 expression status of IC2/3 will continue receiving atezolizumab monotherapy.

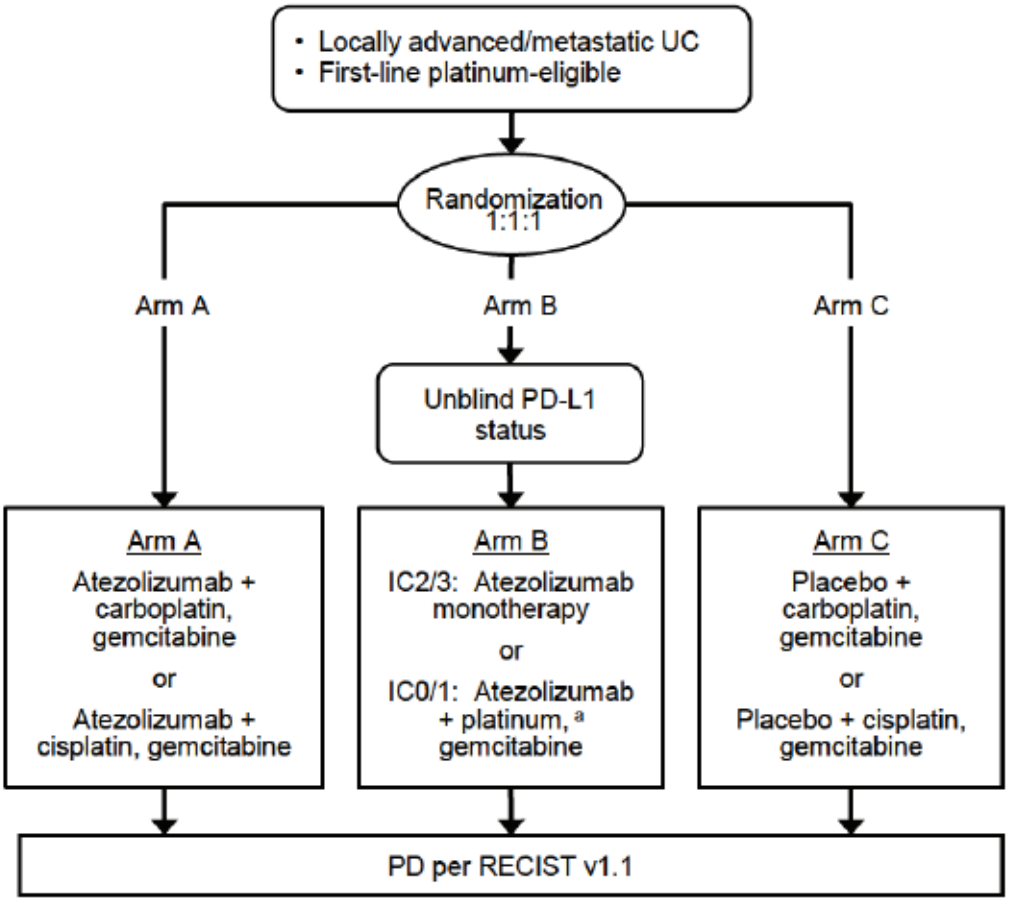
- Patients with PD-L1 expression status of IC0 or IC1 are recommended to continue with atezolizumab monotherapy, as the iDMC did not recommend a change in therapy for patients already randomized to monotherapy on study.

  However, if the patient after discussion of benefit-risk with the treating physician determines that continuation of atezolizumab monotherapy is not considered beneficial, a treatment alternative of atezolizumab plus platinum (cisplatin or carboplatin) and gemcitabine chemotherapy will be provided. These patients should then be treated the same as patients in Arms A and C (see Section 4.3.2.2, Duration of Chemotherapy Treatment).

  If the decision is made to unblind the patient and add platinum (cisplatin or carboplatin) and gemcitabine chemotherapy to the regimen, it must be added before the patient has known progressive disease. Chemotherapy cannot be added to patients in Arm B with documented progressive disease within the study.

- Patients will also have the option to stop study therapy and receive standard-of-care treatment outside of the study by their physician.
- All patients (including those who choose to stop atezolizumab monotherapy) are requested to continue in the study for survival follow up.

Figure 2 Study Schema after Protocol WO30070, Version 6



PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors; UC = urothelial carcinoma

[a] Platinum (cisplatin or carboplatin).

Prior to randomization, the investigator will select which chemotherapy the patient should receive (gemcitabine and carboplatin vs. gemcitabine and cisplatin) if the patient is randomized to Arm A or Arm C. The Galsky criteria (see Section 4.2; Galsky et al. 2011) should be used to guide determination of cisplatin ineligibility. The criteria to determine ineligibility for cisplatin should be the same as the criteria used in the initial implementation of the study.

Randomization will be stratified by the following factors:

- PD-L1 status (IC0 vs. IC1 vs. IC2/3)
- Bajorin model risk factor score/liver metastasis (0 vs. 1 vs. 2 or patients with liver metastasis)
- Investigator-determined chemotherapy (gemcitabine and carboplatin vs. gemcitabine and cisplatin)

Gemcitabine will be administered at a dose of 1000 mg/m^2 by IV infusion on Day 1 and Day 8 of each 21-day cycle.

Carboplatin will be administered at area under the concentration–time curve (AUC) 4.5 by IV infusion on Day 1 of each 21-day cycle.

Cisplatin will be administered at a dose of 70 mg/m^2 by IV infusion on Day 1 of each 21-day cycle. Split dosing of cisplatin is not permitted.

All visits and infusions may be administered with a window of ±3 days, except for the Day 8 visit. The Day 8 dose of gemcitabine may be given no earlier than Day 7 but may be given up to Day 11 (–1 to + 3) of a cycle (see Sections 4.3 and 4.3.2.2).

Gemcitabine and platinum chemotherapy (carboplatin or cisplatin) will be administered until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity.

For patients who receive chemotherapy and who have a CR, only two more cycles of chemotherapy will be administered after the response confirmation.

For patients who receive chemotherapy and who have a PR or stable disease, chemotherapy administration may be discontinued after completion of six cycles, if necessary, to comply with institutional guidelines.

If the initial protocol doses of chemotherapy agents differ from institutional guidelines or local label, the initial doses may be modified to achieve compliance.

Atezolizumab will be administered at a fixed dose of 1200 mg by IV infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1. Placebo for atezolizumab (Arm C) will be administered by IV infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1. In specific circumstances, treatment may continue beyond disease progression (see below and Section 4.6.2). No crossover will be allowed from the control arm to either experimental arm (Arms A and B).

Patients will undergo scheduled tumor assessment at baseline and every 9 weeks (from initiation of the first dose) thereafter for 54 weeks after randomization. After 54 weeks, patients will undergo tumor assessment every 12 weeks until disease progression per RECIST v1.1, death, study termination by the Sponsor, or withdrawal of consent, whichever occurs first. Patients must discontinue treatment at the first occurrence of radiographic progression, per RECIST v1.1, with the following exception: Patients who have achieved a PR or CR of target lesions and who develop new lesions (≤3) that are amenable to surgery or ablative techniques (e.g., radiotherapy, radiofrequency ablation) may continue to receive study treatment if they demonstrate no further progression of disease at the next imaging assessment and continue to demonstrate clinical benefit per

investigator; for these patients, tumor assessments should continue until loss of clinical benefit as determined by the Investigator (see Section 4.6.2). Because gemcitabine is not indicated for use in combination with radiation therapy and has been shown to cause excess toxicity (mucositis, pneumonitis) as well as radiation recall when administered in close proximity to radiation therapy, patients who continue treatment with gemcitabine should not receive radiation to ports that include a significant proportion of lung or mucosal surface (esophagus, intestine). In the absence of disease progression, tumor assessments should continue, regardless of whether patients start new anti-cancer therapy, until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. Follow-up data capture, including subsequent anti-cancer therapies (including targeted therapies and immunotherapies), will continue for each patient until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Patients are required to undergo tumor biopsy sample collection, if clinically feasible as assessed by investigators, at the first evidence of radiographic disease progression. These data will be used to confirm that radiographic findings are consistent with the presence of tumor. In addition, these data will be analyzed for the association between changes in tumor tissue and clinical outcome and to understand further the potential mechanisms of resistance to treatment.

All primary imaging data used for tumor assessment will be collected by the Sponsor to enable a centralized independent review. All primary imaging data used for tumor assessment will be collected by the Sponsor to enable a centralized independent review until the analysis of the co-primary endpoint of progression free survival (PFS) is completed.
Safety assessments will include the incidence, nature, and severity of adverse events, vital signs and laboratory abnormalities graded per the NCI CTCAE v4.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of antibodies to atezolizumab. Patient samples, including archival tumor tissues, as well as serum, plasma, and blood, will be collected for future exploratory biomarker assessments.

An external iDMC will evaluate safety data according to policies and procedures detailed in an iDMC Charter (see Section 3.1.2).

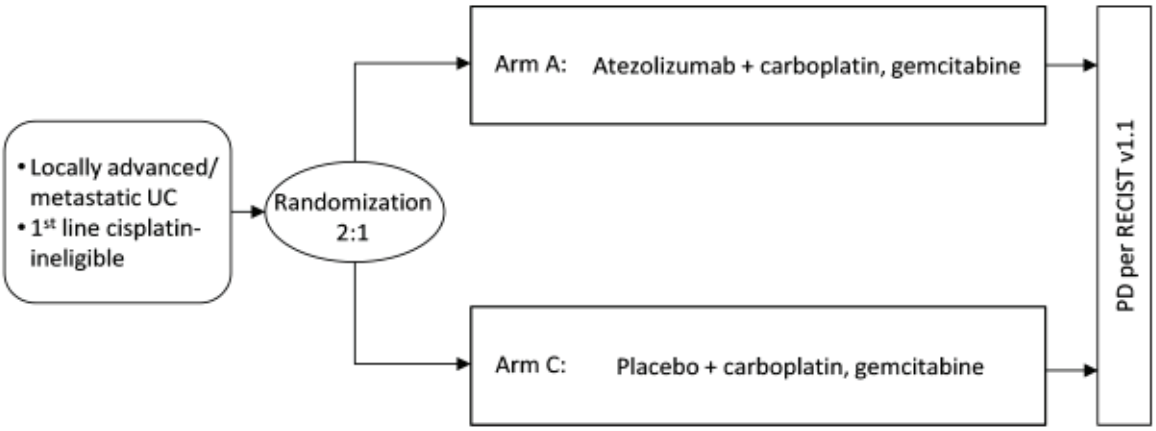
A schedule of assessments is provided in Appendix 1 and Appendix 2.

After approximately 1200 patients have been randomized, enrollment in sites will be closed.

3.1.1 Study Design Prior to Protocol WO30070, Version 3

Study WO30070 was initially implemented with randomization into two treatment arms (carboplatin plus gemcitabine with or without atezolizumab) (see Figure 3).

Figure 3 Study Schema Prior to Protocol Version 3



PD=progressive disease; RECIST=Response Evaluation Criteria in Solid Tumors; UC=urothelial carcinoma.

Patients enrolled prior to Protocol WO30070, Version 3, were randomized in a 2:1 ratio (experimental to control arm) to receive one of the following:

- Arm A (experimental arm): atezolizumab in combination with gemcitabine/carboplatin
- Arm B (control arm): placebo in combination with gemcitabine/carboplatin

Randomization was stratified by the following factors:

- PD-L1 status (IC0 vs. IC1 vs. IC2/3)
- Bajorin model risk factor score/liver metastasis (0 vs. 1 vs. 2 or patients with liver metastasis)
- Prior perioperative chemotherapy (neoadjuvant or adjuvant) (yes vs. no)

  Prior perioperative chemotherapy is defined as at least two cycles of combination chemotherapy, such as cisplatin/gemcitabine or MVAC administered in the neoadjuvant/adjuvant setting or standard radiosensitizing chemotherapy (cisplatin or 5FU/mitomycin) if administered concurrently with radiotherapy.

3.1.2 Independent Data Monitoring Committee

An iDMC will be convened to evaluate safety data during the study. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. The iDMC will conduct its first review of safety data when 20 patients have completed at least one cycle of study treatment. The iDMC will then continue to evaluate study safety data on a periodic basis, approximately every 3 months until 1 year after the enrollment of the first patient in Protocol WO30070, Version 3. After that period, reviews will be conducted approximately every 6 months until the time of the analysis of the co-primary efficacy endpoint of PFS. The Sponsor will remain blinded to the results until the analysis of the co-primary endpoint of PFS occurs.

All summaries and analyses for the iDMC review will be prepared by treatment arm by an external independent Data Coordinating Center. 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 to the Sponsor according to the iDMC Charter. The final decision on any changes to the protocol will rest with the Sponsor.

Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the Institutional Review Boards/Ethics Committees (IRBs/ECs).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date *of the last visit of the last patient in the study/last scheduled procedure shown in the schedule of activities for the last patient in the study globally or the date at which* the required number of deaths has been observed for the final analysis of OS in the global (main) study's intent-to-treat (ITT) population (see Section 6.1.3), *whichever occurs later*. Additionally, the Sponsor may decide to terminate the study at any time (see Section 4.6.3).

The total length of the global (main) study from randomization of the first patient to the end of the study, is expected to be approximately 44 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Atezolizumab Dose and Schedule

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

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

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

Detectable ATAs were observed in patients at all dose levels but were associated with changes in pharmacokinetics for some patients in only the lower dose cohorts (0.3, 1, and 3 mg/kg). It is unclear from currently available data in these lower-dose cohorts if 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 the pharmacokinetics for doses ranging 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 safeguard against both interpatient variability and the potential effect of ATAs that could lead to subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent). From inspection of available observed C_{trough} data, moving further to the 20-mg/kg atezolizumab q3w regimen does not appear to be warranted to maintain targeted C_{trough} levels relative to the proposed 15-mg/kg atezolizumab q3w level.

Simulations do not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight (Bai et al. 2012). On the basis of this analysis, a fixed dose of 1200 mg has been selected (equivalent to an average body weight–based dose of 15 mg/kg).

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

3.3.2 Rationale for Patient Population

Inoperable locally-advanced/metastatic urothelial carcinoma is a uniformly lethal disease with high unmet medical need. With little to no advancement in therapeutic landscape for patients over the last 30 years, the survival for these patients regardless of time of diagnosis or treatment received remains stagnant with no improvement over the last 20 years.

Platinum-based chemotherapy is the current standard of care for patients with previously untreated metastatic urothelial carcinoma. For patients with metastatic urothelial carcinoma who are deemed medically fit, cisplatin-based combination chemotherapy is the preferred initial therapy. Systemic chemotherapy in metastatic urothelial carcinoma is, however, characterized by significant toxicity with poor OS and low response rates and limited durability in a frail population of advancing age and multiple co-morbidities.

Many first-line patients are medically unfit or ineligible to receive treatment with cisplatin-based chemotherapy (cis-ineligible) and need more effective therapeutic options. For patients who are deemed ineligible to receive cisplatin, treatment options include carboplatin-based or non–platinum-based combinations, single-agent regimens, and BSC. For patients who do not receive chemotherapy, the outcomes remain extremely poor.

Immunotherapy in urothelial carcinoma has shown significant promise. Treatment with atezolizumab in treatment-resistant urothelial carcinoma has shown responses in patients with platinum-refractory cancer as well as in patients with 1L disease who are ineligible to receive cisplatin. Responses achieved with atezolizumab in these patient populations appear to be durable (Balar et al. 2016; Rosenberg et al. 2016). Results from the pivotal multicenter Phase II study, IMvigor210, showed that durable responses were achieved in 1L cisplatin-ineligible patients with metastatic urothelial carcinoma who received atezolizumab monotherapy. The ORR in all patients was 24%, and responses were seen in all PD-L1 IC subgroups. The median survival in all patients was 14.8 months and the 1-year OS rate was 57%, which compare favorably with survival data reported with either cisplatin- or carboplatin-based chemotherapy (von der Maase et al. 2005; De Santis et al. 2012). Importantly, atezolizumab was well tolerated, with a low rate of treatment-related Grade 3–4 adverse events and discontinuations due to adverse events (Balar et al. 2016). This raises the potential of chemotherapy-free treatment regimens for 1L patients with metastatic urothelial carcinoma.

Tumor-cell killing by cytotoxic chemotherapy alone can be expected to expose the immune system to high levels of tumor antigens; invigorating tumor-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling and by using the combination of atezolizumab and chemotherapy may result in deeper and more durable responses compared with standard chemotherapy alone.

Safety data from Study GP28328 indicate that atezolizumab can be safely combined with chemotherapy; several combinations have been evaluated and determined to be well tolerated (see Section 1.2.2.1 and the Atezolizumab Investigator's Brochure). No exacerbation of chemotherapy-associated adverse events was reported. Combination treatment with atezolizumab and platinum-based chemotherapy may therefore offer the potential for clinical benefit and a manageable tolerability profile in patients with 1L metastatic urothelial carcinoma.

3.3.3 Rationale for Control Group

3.3.3.1 Choice of Chemotherapy

In accordance with global treatment guidelines, patients with previously untreated urothelial carcinoma typically receive cisplatin-based chemotherapy: MVAC or gemcitabine and cisplatin (see Section 1.1.2). The use of carboplatin- or taxane-based regimens or single-agent therapy is recommended for the significant proportion of patients who are ineligible to receive such cisplatin-based chemotherapy. Participation in clinical studies of new or more-tolerable therapy is also recommended (NCCN 2015).

The efficacy of gemcitabine and cisplatin in treating urothelial carcinoma may derive, at least in part, from the capacity of these agents to stimulate an immune response (Zitvogel et al. 2008). Gemcitabine chemotherapy has been shown to reduce myeloid-derived suppressor cells (MDSC) in murine mouse models and lead to more effective anti-cancer immunity (Suzuki et al. 2005; Ko et al. 2007; Le et al. 2009; Sawant et al. 2013). MDSC are a heterogeneous population of immature myeloid cells that are found circulating in the blood and have been associated with decreased OS in patients with melanoma (Kitano et al. 2014, Weide et al. 2014). MDSC have also been described in both the blood and tumors of patients with urothelial carcinoma, although the role they play is unclear (Eruslanov et al. 2012). Gemcitabine may also have beneficial immune effects mediated through depletion of regulatory T cells in selected animal models (Shevchenko et al. 2013). In a nonclinical study, cisplatin enhanced tumor cell susceptibility to cytotoxic T-cell–mediated killing (Ramakrishnan et al. 2010).

The benefit of carboplatin-based therapy in cisplatin-ineligible patients was demonstrated in the EORTC Trial 30986. In this study, 238 patients with previously untreated advanced urothelial carcinoma and either a poor performance status and/or impaired renal function (GFR <60 but >30 mL/min) were enrolled to receive CarboGem or M-CAVI (De Santis et al. 2012). The confirmed ORR of CarboGem was 36.1% versus 21.0% for the M-CAVI arm. However, there was no evidence of a difference in OS (HR $=0.94$; 95% CI: 0.72, 1.22; $p=0.64$); median OS was 9.3 and 8.1 months, respectively.

Therefore, the combination of platinum-based chemotherapy and immunotherapy is an attractive approach, as both have significant anti-cancer activity in bladder cancer. The safety profile of atezolizumab suggests that it may be safely combined with chemotherapy. Prior testing with other chemotherapy regimens has not shown new safety signals or toxicities (Bendell et al. 2015), and data presented at the American Society of Clinical Oncologists 2015 annual meeting shows that concurrent platinum-based chemotherapy with atezolizumab is associated with high ORRs in non–small cell lung cancer (Liu et al. 2015).

3.3.3.2 Placebo Control

Placebo for atezolizumab will be utilized in this study in combination with platinum-based chemotherapy in order to minimize potential assessment or observer bias in this study.

The use of placebo will allow for a more impartial assessment of overlapping toxicity and the true safety impact of the addition of atezolizumab to platinum-based chemotherapy. In addition, placebo control can aid in the interpretation of the treatment comparison of PFS, which is a co-primary endpoint in this study.

Use of a placebo control can also help minimize up-front patient dropout that can occur in an open-label study following randomization to the control arm. In addition, use of a placebo control may minimize the premature initiation of subsequent therapies or crossover which may otherwise occur when study treatment is not blinded, which makes interpretation of the OS endpoint challenging.

Patients who are randomized to atezolizumab placebo will not be deprived of active therapy because they will receive an active, standard-of-care chemotherapy regimen (i.e., gemcitabine and cisplatin or gemcitabine and carboplatin). Because all study drugs are administered intravenously, the frequency and number of needle-sticks or procedures will be identical for patients in the placebo plus chemotherapy arm and the atezolizumab plus chemotherapy arm.

3.3.4 Rationale for Atezolizumab Monotherapy

Published safety and efficacy data from the IMvigor210 study showed a median OS of 14.8 months (95% CI: 10.1, not evaluable) and a 1-year OS rate of 57%, (95% CI: 48, 66) in patients receiving 1L treatment who have metastatic urothelial carcinoma, are cisplatin-ineligible, and received single-agent atezolizumab (Balar et al. 2016). These data for atezolizumab as a single-agent compare favorably to the OS benefit observed with platinum-based chemotherapy in the 1L metastatic urothelial carcinoma disease setting. A Phase III study of 405 patients showed similar OS for patients who were randomized to gemcitabine and cisplatin or to MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) (14.0 months for gemcitabine and cisplatin vs. 15.2 months for MVAC; hazard ratio [HR] = 1.09; 95% CI: 0.88, 1.34, p = 0.66) with less Grade 3 or 4 toxicity, and as a result, gemcitabine and cisplatin has largely displaced MVAC as the standard of care (von der Maase et al. 2005). The 1-year landmark OS rate for gemcitabine and cisplatin was 58.4% (95% CI: 51.6, 65.2) and for MVAC was 62.6% (95% CI: 55.9, 69.3) (von der Maase et al. 2005). In the European Organisation for Research and Treatment of Cancer (EORTC) Trial 30986, 238 patients who had previously untreated advanced urothelial carcinoma but were ineligible to receive cisplatin-based chemotherapy (poor performance status and/or impaired renal function) were enrolled to receive CarboGem or methotrexate, carboplatin, and vincristine (M-CAVI) (De Santis et al. 2012). The confirmed ORR of CarboGem was 36% versus 20.7% for the M-CAVI arm. The median duration of response (DOR) was 5.3 months in the CarboGem arm (M. De Santis, personal communication). There was no difference in the median OS (9.3 vs. 8.1 months) for CarboGem and M-CAVI, respectively. In the CarboGem arm, 37.0% (44 of 119) and

13.4% (16 of 119) of patients were alive 1 year and 2 years after randomization, respectively (M. De Santis, personal communication).

3.3.5 Rationale for Stratification Factors

In the three-arm portion of the study (Stage 2), patients will be stratified on the basis of PD-L1 expression, Bajorin risk model/liver metastasis, and investigator choice of chemotherapy (gemcitabine and carboplatin or gemcitabine and cisplatin).

PD-L1 Expression (IC0 vs. IC1 vs. IC2/3)

PD-L1 expression is prevalent in many human tumors (e.g., lung, bladder, renal, ovarian, melanoma, malignant lymphoma, multiple myeloma, and colon carcinoma), and elevated PD-L1 expression was reported to be associated with a worse prognosis in patients with several cancers, including lung cancer, renal cell carcinoma, melanoma, colorectal cancer, ovarian cancer, and others (Mu et al. 2011; Herbst et al. 2014; Powles et al. 2014).

Responses to atezolizumab have been observed in patients with metastatic urothelial carcinoma whose tumors demonstrate a PD-L1 IHC score of IC2/3 as well as in patients with an IHC score of IC0 or IC1. In Phase I and II studies of atezolizumab, higher levels of PD-L1 expression have been associated with higher response rates in patients with urothelial carcinoma. Because PD-L1 expression may impact efficacy outcomes, the randomization will be stratified by PD-L1 expression by IHC in order to minimize imbalances between treatment arms within levels of PD-L1 expression.

Bajorin Risk Factor Score/Liver Metastasis (0 vs. 1 vs. 2 or Patients with Liver Metastasis)

The Bajorin risk model is a prognostic model that was developed to predict OS for patients with metastatic urothelial carcinoma who were treated with cisplatin-based chemotherapy (Bajorin et al. 1999). The model includes two pretreatment variables: Karnofsky performance status (less than 80% vs. at least 80%) and presence/absence of visceral (lung, liver, or bone) metastases. A post hoc analysis of the EORTC Trial 30986 in cisplatin-ineligible patients, based on Bajorin risk groups (0, 1, or 2 risk factors), demonstrated that as the number of risk factors increased, OS decreased significantly (De Santis et al. 2012). Because OS is a co-primary efficacy endpoint and the Bajorin risk model identifies risk factors for OS, the randomization will be stratified by Bajorin risk score to minimize imbalances between treatment arms within levels of the Bajorin risk score.

Although the presence of liver metastasis is included as a component of the Bajorin risk model, in the only randomized Phase III study in second-line urothelial carcinoma, comparing vinflunine with BSC and which examined sixteen potential prognostic factors for their association with survival, patients with liver metastasis had the worst OS outcome (Bellmunt et al. 2009). In order to incorporate the importance of the presence of liver metastasis, patients with liver metastasis will be considered to be in the highest

Bajorin risk factor category for the purpose of stratification at randomization. Therefore, the three categories for this modification of the Bajorin risk score will be 0 factors versus 1 factor versus 2 factors or patients with liver metastasis.

Chemotherapy Regimen (Gemcitabine/Carboplatin vs. Gemcitabine/Cisplatin)

Platinum-based chemotherapy is the current standard of care for patients with previously untreated metastatic urothelial carcinoma. For medically fit patients with metastatic urothelial carcinoma, cisplatin-based combination chemotherapy is the preferred initial therapy and is recommended in treatment guidelines (e.g., NCCN, EAU, European Society for Medical Oncology). The prognosis for patients who are eligible to receive cisplatin-based chemotherapy is better compared with patients who are not eligible to receive cisplatin (von der Maase et al. 2005; Sternberg et al. 2007; De Santis et al. 2012) (see also Section 3.3.3.1). Therefore, the randomization will be stratified by choice of chemotherapy, determined by the investigator.

Prior Perioperative Chemotherapy

The rationale for stratifying on the basis of prior perioperative chemotherapy was based on a recent retrospective analysis of patients with advanced urothelial carcinoma and treated with first-line cisplatin-based therapy after previous perioperative cisplatin-based chemotherapy. Longer time from perioperative chemotherapy was shown to be independently prognostic for survival (Necchi et al. 2015). Patients in whom the time from previous perioperative chemotherapy was <52 weeks, 52–104 weeks, and ≥ 104 weeks had median survival of 42, 70, and 162 weeks, respectively.

3.3.6 Rationale for Collection of Tumor Specimens (Fresh and/or Archival)

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 therapy (Topalian et al. 2012). This correlation is also observed with atezolizumab in preliminary data from Study PCD4989g (see Section 1.2.2.1). In this study, tumor specimens from patients will be prospectively tested for PD-L1 expression by a central laboratory during the screening period, and patients who are enrolled will be stratified according to tumor tissue PD-L1 expression. 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. An archival specimen, if available, should also be submitted in patients who choose to undergo a fresh biopsy.

Patients who have 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 urothelial carcinoma may consent (but are not required) to also submit these samples for central testing. Tissue samples that are obtained at multiple times from individual patients may contribute to an improved understanding of the dynamics of PD-L1 expression and relationship with intervening anti-cancer therapy.

DNA and/or RNA extraction may be performed to enable identification of somatic mutations by use of next-generation sequencing (NGS) to increase understanding of disease pathobiology.

3.3.7 Rationale for the Collection of Tumor Specimens at Progression

Collection of a tumor biopsy, if clinically feasible, is required at the time of radiographic progression, to evaluate the utility of the biopsy in distinguishing pseudoprogression and/or tumor-immune infiltration from true progression. Additionally, mechanisms relating to progression, resistance, predictive, prognostic, and pharmacodynamic relationships in tumor biomarkers (including but not limited to PD-L1, CD8, mutation status, and others) as well as efficacy will be evaluated. DNA and/or RNA extraction may be performed to enable identification of somatic mutations, by use of NGS, that are associated with disease progression or acquired resistance to atezolizumab and to increase understanding of disease pathobiology.

3.3.8 Rationale for Blood Sampling for Biomarkers

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.

3.3.9 Rationale for Patient-Reported Outcome Assessments

Currently, there is a paucity of information regarding the disease burden and the impact of treatments on symptom severity/frequency or functioning impact, or more generally, health-related quality of life. No questionnaire that is specific to advanced or metastatic urothelial carcinoma is available. The QLQ-C30 is a validated instrument that is commonly used to document disease burden and the impact of treatment on commonly reported symptoms such as pain, fatigue, and patients' ability to function in their daily activities. A generic questionnaire in this setting will provide a much-needed insight on disease burden and also document whether the increase in quantity of life is not associated with any further clinical deterioration.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 1200 patients with locally advanced or metastatic urothelial carcinoma who have not received prior systemic therapy for urothelial carcinoma will be enrolled.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Considered to be eligible to receive platinum-based chemotherapy, in the investigator's judgment
- ECOG performance status of ≤ 2
- Able to comply with the study protocol, in the investigator's judgment
- Histologically documented, locally advanced (T4b, any N; or any T, N 2–3) or metastatic urothelial carcinoma (M1, Stage IV) (also termed TCC or UCC of the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra)

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

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

- Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens 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.

  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.

  Transurethral resection of bladder tumor (TURBT) specimens must contain a muscle-invasive component (i.e., T2 or greater) of the bladder tumor as verified by local pathology review. If the TURBT specimens do not contain a muscle-invasive component, then specimens obtained at the time of cystectomy/nephroureterectomy (i.e., pT2 or greater) or metastatic spread (i.e., a sample from a metastatic lesion) will be required prior to randomization. An archival specimen, if available, should also be submitted.

  Patients who do not have tissue specimens that meet eligibility requirements may undergo a biopsy during the screening period. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

  Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

  Patients who have additional tissue samples from procedures performed at different times during the course of their urothelial carcinoma may also submit these samples for central testing. Tissue samples that are obtained at multiple

times for individual patients may 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 highest score will be used for stratification and for subsequent analyses.

- No prior chemotherapy for inoperable, locally advanced, or metastatic urothelial carcinoma

  For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for urothelial carcinoma, a treatment-free interval > 12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment naive in the metastatic setting.

  Prior local intravesical chemotherapy or immunotherapy is allowed if completed at least 4 weeks prior to the initiation of study treatment.

- Measurable disease, as defined by RECIST v1.1

  Previously irradiated lesions should not be counted as target lesions unless there has been demonstrated progression in the lesion since radiotherapy and no other lesions are available for selection as target lesions.

- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 28 days prior to the first study treatment:

  ANC ≥ 1500 cells/μL (without granulocyte colony-stimulating factor support within 2 weeks prior to Cycle 1, Day 1)

  WBC counts > 2500 cells/μL

  Lymphocyte count ≥ 300 cells/μL

  Platelet count ≥ 100,000 cells/μL (without transfusion within 2 weeks prior to Cycle 1, Day 1)

  Hemoglobin ≥ 9.0 g/dL

    Patients may be transfused to meet this criterion.

    Patients with a solitary kidney or chronic kidney disease with low erythropoietin production may use erythropoietin-stimulating agents.

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

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

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

  Serum bilirubin ≤ 1.5 × ULN

    Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.

  PTT/aPTT ≤ 1.5 × ULN

  PT ≤ 1.5 × ULN or INR < 1.7

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

Calculated creatinine clearance ≥30 mL/min (Cockcroft-Gault formula)

Serum calcium ≤3 mmol/L

For patients with serum albumin <40 g/L, corrected serum calcium must be ≤ULN

- 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 6 months after the last dose of carboplatin, cisplatin, or gemcitabine or for 5 months after the last dose of atezolizumab

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

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

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

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

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 6 months after the last dose of gemcitabine and/or carboplatin, and/or cisplatin. Men must refrain from donating sperm during this same period.

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

4.1.2 Exclusion Criteria

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

4.1.2.1 Cancer-Specific Exclusions

- Any approved anti-cancer therapy, including chemotherapy or hormonal therapy, within 3 weeks prior to initiation of study treatment; the following exceptions are allowed:

  Palliative radiotherapy for bone metastases or soft tissue lesions should be completed >7 days prior to baseline imaging.

  Hormone-replacement therapy or oral contraceptives

- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to enrollment
- Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging evaluation during screening and prior radiographic assessments

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

  Evaluable or measurable disease outside the CNS

  No metastases to midbrain, pons, medulla, or within 10 mm of the optic apparatus (optic nerves and chiasm)

  No history of intracranial or spinal cord hemorrhage

  No ongoing requirement for corticosteroid as therapy for CNS disease

  If the patient is receiving anti-convulsant therapy, the dose is considered stable.

  No evidence of significant vasogenic edema

  No stereotactic radiation, whole-brain radiation or neurosurgical resection within 4 weeks prior to Cycle 1, Day 1

  Radiographic demonstration of interim stability (i.e., no progression) between the completion of CNS-directed therapy and the screening radiographic study

  Screening CNS radiographic study ≥4 weeks since completion of radiotherapy or surgical resection and ≥2 weeks since discontinuation of corticosteroids

- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.

- Uncontrolled tumor-related pain

  Patients who require pain medication must be on a stable regimen at study entry.

Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment.

Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for locoregional therapy if appropriate prior to enrollment.

- Uncontrolled hypercalcemia defined as any one or more of the following criteria:

  >1.5 mmol/L ionized calcium

  Serum calcium >3 mmol/L

  Corrected serum calcium >ULN (if serum albumin <40 g/L)

  Symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab

    Patients who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.

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

  Patients with localized prostate cancer (defined as Stage ≤pT2c, Gleason score ≤7, and prostate-specific antigen (PSA) at prostate cancer diagnosis ≤20 ng/mL) treated with curative intent and without PSA recurrence are eligible.

  Patients with pre-existing low-risk prostate cancer (defined as Stage cT1/T2a, Gleason score ≤6 and PSA ≤10 ng/mL) who are treatment-naive and undergoing active surveillance are eligible.

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

    Malignancy treated with expected curative intent (e.g., 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

4.1.2.2 General Medical Exclusions

- Life expectancy of <12 weeks
- Pregnant or lactating, or intending to become pregnant during the study

    Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

- Serum albumin <25 g/L

4.1.2.3 Exclusion Criteria Related to Atezolizumab

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy 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, *granulomatosis with polyangiitis*, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 8 for a more comprehensive list of preexisting 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 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis) are permitted provided that they meet the following conditions:

  Rash must cover less than 10% of body surface area (BSA)

  Disease is well controlled at baseline and only requiring low potency topical steroids

  No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
- Patients with prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class III or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina
- Known left ventricular ejection fraction (LVEF) <40%

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF 40%–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. Patients with a history of clinically significant cardiac disease (including anatomic abnormality, coronary disease, congestive

heart failure, abnormal LVEF, arrhythmia, or abnormal ECG) will be required to undergo a screening echocardiogram.

- Positive test for HIV
- Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. A negative HBV DNA test must be obtained in these patients prior to Cycle 1, Day 1.

  Patients who test 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 randomization, including but not limited to hospitalization for complications of infection, bacteremia, severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety
- Therapeutic oral or IV antibiotics within 2 weeks prior to randomization

  Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease (COPD) or for dental extraction) are eligible.
- Major surgical procedure within 4 weeks prior to randomization or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1

  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 within 28 days prior to initiation of study treatment, during treatment, or within 5 months after the last dose of atezolizumab.
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- Prior treatment with CD137 agonists, anti–CTLA-4, anti–PD-1, or anti–PD-L1 therapeutic antibody or pathway-targeting agents
- Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2 [IL-2]) within 4 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 [TNF] agents) within 2 weeks prior to Cycle 1, Day 1 or anticipated requirement for systemic immunosuppressive medications during the study

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

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

4.1.2.4 Exclusion Criteria Related to Gemcitabine

- Known hypersensitivity to gemcitabine

4.1.2.5 Exclusion Criteria Related to Carboplatin

- History of severe allergic reactions to cisplatin or other platinum-containing compounds
- Severe bone marrow depression or significant bleeding

4.1.2.6 Exclusion Criteria Related to Cisplatin

- Cisplatin is contraindicated in patients with preexisting renal impairment. Cisplatin should not be employed in patients with myelosuppression or in patients with hearing impairment.
- Cisplatin is contraindicated in patients with a history of allergic reactions to cisplatin or other platinum-containing compounds.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This study implements a placebo for atezolizumab when given in combination with chemotherapy, including Stage 1 of the study when the chemotherapy regimen was carboplatin and gemcitabine (Arms A and C). For patients who are randomized to Arm A or Arm C, the investigator, patient, and Sponsor will be blinded to atezolizumab/placebo treatment assignment. All other study treatments (atezolizumab monotherapy and chemotherapy) are provided in an open-label fashion.

After written informed consent has been obtained and eligibility has been established (including determination of tumor PD-L1 expression status by central testing), the study site will enter demographic and baseline characteristics in the Interactive Voice/Web Response System (IxRS). For those patients who are eligible for enrollment, the study site will obtain the patient's identification number and treatment assignment from the IxRS.

In Stage 2 (i.e., following implementation of Protocol WO30070, Version 3), patients will be randomized to one of the following treatment arms in a 1:1:1 ratio:

- Arm A (experimental arm): blinded atezolizumab in combination with gemcitabine and carboplatin or gemcitabine and cisplatin
- Arm B (experimental arm): open-label atezolizumab monotherapy
- Arm C (control arm): blinded placebo for atezolizumab in combination with gemcitabine and carboplatin or gemcitabine and cisplatin

Following implementation of Protocol WO30070, Version 6, randomization to the three arms in a 1:1:1 ratio will continue regardless of PD-1 status (see Section 3.1).

For all new patients randomized to Arm B:

- The PD-L1 status will be unblinded to the investigator and patient at the time of randomization.
- Patients whose tumor PD-L1 expression status is IC2/3 will receive atezolizumab monotherapy.
- Patients with a PD-L1 expression status of IC0 or IC1 will receive open-label atezolizumab plus platinum (carboplatin or cisplatin) and gemcitabine chemotherapy instead of atezolizumab monotherapy.

Prior to randomization, the investigator will determine which chemotherapy would be appropriate for the patient (gemcitabine and carboplatin or gemcitabine and cisplatin).

Ineligibility to receive cisplatin-based chemotherapy should be based upon the criteria published by Galsky et al. (2011) and will be documented in the eCRF. Patients who meet at least one of the following criteria should be considered for treatment with carboplatin plus gemcitabine if randomized to Arm A or Arm C; however, the final decision will be made by the investigator:

- Impaired renal function (GFR >30 but <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)
- NCI CTCAE v4.0 Grade ≥ 2 audiometric hearing loss of 25 decibels at two contiguous frequencies
- NCI CTCAE v4.0 Grade ≥ 2 peripheral neuropathy (i.e., sensory alteration or paresthesia, including tingling)
- ECOG performance status of 2

Randomization in Stage 2 will be stratified by the following factors:

- PD-L1 expression status (IC0 vs. IC1 vs. IC2/3)
- Investigator's choice of chemotherapy (gemcitabine and carboplatin or gemcitabine and cisplatin)

- Bajorin model risk factor score/liver metastasis (0 vs. 1 vs. 2 or patients with liver metastasis)

In Stage 1, prior to Protocol WO30070, Version 3 implementation, cisplatin-ineligible patients were randomized 2:1 to Arm A or Arm C using the following stratification factors:

- PD-L1 expression status (IC0 vs. IC1 vs. IC2/3)
- Bajorin model risk factor score/liver metastasis (0 vs. 1 vs. 2 or patients with liver metastasis)
- Prior perioperative chemotherapy (adjuvant or neoadjuvant) (yes vs. no)

For both stages, stratified, permuted-block randomization is used to balance assignment to each treatment within levels of the stratification factors.

Whereas PK samples must be collected from patients who are assigned to the control arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this study. PK samples will also be collected from the atezolizumab monotherapy arm. Personnel who are responsible for performing PK assays and sample data reconciliation will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed and cleaned. Samples from patients assigned to the control arm will not be analyzed except by request (i.e., to evaluate a possible error in dosing).

4.2.1 Emergency Unblinding

Emergency unblinding by the investigator should only be performed in cases where knowledge of the treatment assignment will affect the management of a patient who experiences a treatment-emergent adverse event. However, the Sponsor recognizes that unblinding for non-emergency situations will be of increasing concern to many sites as additional treatment options become available for patients in second-line metastatic urothelial carcinoma.

Single-patient unblinding in non-emergency situations will be allowed at the time of unequivocal disease progression by RECIST v1.1 and study treatment discontinuation to help guide decisions on subsequent treatment. The following conditions must be met prior to unblinding:

- There is a plan to treat the patient with next line of treatment which includes a checkpoint inhibitor, or
- There is a plan to enroll the patient in a subsequent clinical trial that requires knowledge of current study treatment assignment (atezolizumab/placebo) to confirm eligibility

Unblinding should not result in withdrawal of the patient from study. Patients unblinded for subsequent treatment decision-making will continue to be followed for survival per protocol.

Unblinding for reasons other than RECIST v1.1 progression or adverse event management will require Medical Monitor approval.

To protect the integrity of the OS primary endpoint, the Sponsor requests that unblinding only be performed to guide immediate treatment decision-making.

The Principal Investigator can break the treatment code via the IxRS with use of a PIN code issued to him or her at study start. The investigator should document all occurrences of unblinding in the study file and provide an explanation for any premature unblinding (e.g., accidental unblinding). Unblinding should not result in the withdrawal of patients from study treatment (if appropriate) or the study.

For regulatory reporting purposes and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator to be related to study drug.

If the investigator would like to discuss the patient's treatment arm (once known) with the Sponsor, the site may liaise with the unblinded Global Study Manager (GSM). The investigator is to communicate via email with the unblinded GSM directly at: GLOFCT_WO30070-unblindedGSM@msxdl.roche.com. The unblinded GSM will then convey any discussions to the Medical Monitor in a "blinded" fashion, if a case needs medical input. If there is an urgent question pertaining to patient management, the site should call the Medical Monitor but not disclose treatment assignment or unblinding status unless specifically requested.

4.2.2 Unblinding of PD-L1 Status in Arm B

Prior to the iDMC recommendation to stop further recruitment of patients whose tumors have PD-L1 expression status of IC0 or IC1 to receive atezolizumab monotherapy (Section 3.1), results of the PD-L1 expression were blinded to the patient, investigator, and Sponsor. In order to implement the iDMC recommendation, all new patients randomized to Arm B (open-label atezolizumab monotherapy) will have their PD-L1 expression status unblinded to the patient and investigator. The investigator will be informed of the PD-L1 status by an IxRS notification that is triggered by the randomization transaction. The notification will inform the site user if the patient has a PD-L1 expression status of IC0 or IC1 or not.

The iDMC has not recommended any change in therapy for patients previously randomized to Arm B who are currently being treated with open-label atezolizumab monotherapy. However, the investigator may request the PD-L1 status for such patients (see Section 3.1).

If the decision is made to unblind the patient and add platinum (cisplatin or carboplatin) and gemcitabine chemotherapy to the regimen, it must be added before the patient has

known progressive disease. Chemotherapy cannot be added to patients in Arm B with documented progressive disease within the study.

4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are atezolizumab, placebo, gemcitabine, carboplatin, and cisplatin. Patients should receive their first dose of study treatment no later than 5 calendar days after randomization. All visits and infusions may be administered with a window of ± 3 days, except for the Day 8 visit. The Day 8 dose of gemcitabine may be given no earlier than Day 7 but may be given up to Day 11 (−1 to + 3) of a cycle (see Section 4.3.2.2). After the first five cycles, one of three cycles may be delayed by 1 week (28 days instead of 21 days for one cycle) to allow for vacations.

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

4.3.1.2 Placebo for Atezolizumab

The placebo will be identical in appearance to atezolizumab and comprise the same excipients but without atezolizumab drug product. It should be handled, stored, and used in the same manner as atezolizumab.

Placebo will be supplied by the Sponsor.

4.3.1.3 Gemcitabine

For information on the formulation, packaging, and handling of gemcitabine, see the local prescribing information for gemcitabine.

Gemcitabine will be provided by the Sponsor where required by local health authority regulations. Gemcitabine, regardless of how it is sourced to investigational sites, will be considered an IMP.

Following Sponsor notification, gemcitabine may be sourced locally in emergency situations (e.g., site is out of stock of IMP and patient is ready to receive dose) and where sourcing by the Sponsor would result in significant recruitment delays at sites in countries where gemcitabine is commercially available. In these cases, local affiliates/sites will be responsible for sourcing and using the material according to local regulations.

4.3.1.4 Carboplatin

For information on the formulation, packaging, and handling of carboplatin, see the local prescribing information for carboplatin.

Carboplatin will be provided by the Sponsor where required by local health authority regulations. The Sponsor will provide carboplatin to investigational sites as an IMP.

Following Sponsor notification, carboplatin may be sourced locally in emergency situations (e.g., site is out of stock of IMP and patient is ready to receive dose) and where sourcing by the Sponsor would result in significant recruitment delays at sites in countries where carboplatin is commercially available. In these cases, local affiliates/sites will be responsible for sourcing and using the material according to local regulations.

4.3.1.5 Cisplatin

For information on the formulation, packaging, and handling of cisplatin, see the local prescribing information for cisplatin.

Cisplatin will be provided by the Sponsor where required by local health authority regulations. The Sponsor will provide cisplatin to investigational sites as an IMP.

Following Sponsor notification, cisplatin may be sourced locally in emergency situations (e.g., the site is out of stock of IMP and patient is ready to receive dose) and where sourcing by the Sponsor would result in significant recruitment delays at sites in countries where cisplatin is commercially available. In these cases, local affiliates/sites will be responsible for sourcing and using the material according to local regulations.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Atezolizumab and Placebo

The dose level of atezolizumab in this study is 1200 mg administered by IV infusion q3w. Administration of atezolizumab and placebo will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

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

Atezolizumab and placebo infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Infusions of Atezolizumab/Placebo

First Infusion	Subsequent Infusions
• No premedication is administered • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion.	• If patient experienced infusion-related reaction during any previous infusion, premedication with antihistamines may be administered for Cycles ≥2 at the discretion of the treating physician.

Table 1 Administration of First and Subsequent Infusions of Atezolizumab/Placebo (cont.)

First Infusion	Subsequent Infusions
• Infuse atezolizumab (one vial in 250 mL NaCl) over 60 (±15) minutes. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during the infusion at 15, 30, 45, and 60 minutes (±5-minute windows are allowed for all timepoints). • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) at 30 (±10) minutes and 2 hours (±15 minutes) after the infusion. • Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • If the patient tolerated the first infusion well without infusion-associated adverse events, the second infusion may be delivered over 30 (±10) minutes. • If the patient had an infusion-related reaction during the previous infusion, the subsequent infusion must be delivered over 60 (±15) minutes. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during the infusion if clinically indicated or patient experienced symptoms during the previous infusion. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) 30 (±10) minutes after the infusion if clinically indicated or if patient experienced symptoms during the previous infusion. • If no reaction occurs, continue subsequent infusions over 30 (±10) minutes with same schedule for recording vital signs. Record the patient's vital signs during or after the infusion as clinically indicated.

For additional details regarding management of infusion-related reactions, please refer to the Atezolizumab Investigator's Brochure.

For anaphylaxis precautions, refer to Appendix 7.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

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

4.3.2.2 Gemcitabine, Carboplatin, and Cisplatin

Gemcitabine

Gemcitabine will be administered according to the local prescribing information. The starting dose of gemcitabine will be 1000 mg/m^2, administered by IV infusion on Day 1 and Day 8 of each 21-day cycle. Day 8 gemcitabine administration should not occur earlier than Day 7, but can occur up to Day 11. A change of body weight ± 5%

compared to previous measured weight requires that the dose be re-calculated. Dose modifications should be performed according to Section 5.1.6.

Anti-emetic prophylaxis may be administered at the treating physician's discretion according to local practice.

Any dose modification of gemcitabine should be noted on the relevant Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.4.

Carboplatin

Carboplatin will be administered according to the local prescribing information. The starting dose of carboplatin will be calculated to achieve an AUC of 4.5, administered by IV infusion on Day 1 of each 21-day cycle. If institutional guidelines conflict with protocol carboplatin dosing, carboplatin may be administered at a maximum starting AUC of 5.0. A change of body weight ± 5% compared to previous measured weight requires that the dose be re-calculated.

Dose modifications should be performed according to Section 5.1.6. Carboplatin-based chemotherapy is considered to be moderately emetogenic, and the appropriate anti-emetic prophylaxis should be considered. The use of a nonsteroidal anti-emetic regimen consisting of 5-HT3 receptor and NK1R antagonists is encouraged if feasible (NCCN 2013).

Patients will be allowed to switch from carboplatin to cisplatin chemotherapy in the event the patient becomes eligible to receive cisplatin-based therapy, i.e., do not meet any of the cisplatin-ineligibility criteria in Section 4.2. Change in protocol chemotherapy is not allowed at the time of disease progression by RECIST v1.1.

Any dose modification of carboplatin should be noted on the relevant Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.4.

Cisplatin

Cisplatin will be administered according to the local prescribing information. The starting dose of cisplatin will be 70 mg/m^2, administered by IV infusion on Day 1 of each 21-day cycle. Split dosing of cisplatin is not permitted. A change of body weight ± 5% compared to previous measured weight requires that the dose be re-calculated.

Dose modifications should be performed according to Section 5.1.6. Potential side effects from cisplatin include cumulative nephrotoxicity, myelosuppression, nausea, and vomiting. The use of a nonsteroidal anti-emetic regimen consisting of 5-HT3 receptor and NK1R antagonists is encouraged if feasible (NCCN 2013).

Any dose modification of cisplatin should be noted on the relevant Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.4.

Patients will be allowed to switch from cisplatin to carboplatin chemotherapy if they become ineligible for cisplatin due to toxicity, or from carboplatin to cisplatin chemotherapy in the event that patient becomes eligible to receive cisplatin. Changes in protocol chemotherapy will not be allowed for the reason of suspected or confirmed disease progression by RECIST v1.1.

Note: If the initial protocol doses of gemcitabine, carboplatin, and cisplatin differ from institutional guidelines or local label, the initial doses may be modified to achieve compliance.

Duration of Chemotherapy Treatment

Gemcitabine and platinum chemotherapy (carboplatin or cisplatin) will be administered until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity.

For patients in the combination arms who receive chemotherapy (Arms A and C) and who have a CR, only two more cycles of chemotherapy will be administered after the response confirmation.

For patients in the combination arms who receive chemotherapy and who have a PR or stable disease, chemotherapy administration may be discontinued after completion of six cycles, if necessary, to comply with institutional guidelines.

Patients in Arm B who are unblinded with a PD-L1 score of 0/1 and who subsequently have chemotherapy added to their regimen should follow the same rules as patients in Arms A and C regarding duration of chemotherapy, as described above (see Section 3.1).

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (atezolizumab/placebo, gemcitabine, carboplatin, and cisplatin) 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 with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.3.4 Post-Study Access to Atezolizumab

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

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

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

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

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

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

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

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study drug to the 90-day follow-up visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

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

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician for management of adverse events. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. The Medical Monitor is available to advise as needed. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as an appetite stimulant is acceptable while the patient is enrolled in the study.

Corticosteroid use for nausea prophylaxis with cisplatin is permitted. Non-steroidal antiemetic prophylaxis is recommended with Cycle 1 of carboplatin; however, corticosteroids may be used with subsequent cycles in patients experiencing significant nausea/vomiting. Investigators may follow institutional guidelines if they conflict with these recommendations. As corticosteroids may mitigate the effect of atezolizumab, investigators are encouraged to use the lowest doses that will achieve the desired effect.

After the completion of Cycle 1, certain forms of radiotherapy may be considered for palliation if patients are deriving benefit (e.g., treatment of known bony metastases, symptomatic hematuria). Study drug administration may be continued during radiotherapy for patients being treated with atezolizumab/placebo monotherapy; however, cisplatin/carboplatin and gemcitabine dosing must be held during administration of radiotherapy, and the guidance for gemcitabine administration should be followed (see Section 4.4.2.2).

The use of granulocyte colony-stimulating factors is allowed to support patients per local guidelines/practice.

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

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

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

4.4.2 Prohibited Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority–approved or experimental, is prohibited unless otherwise specified in the protocol. This includes but is not limited to the following:

- Chemotherapy (other than gemcitabine, carboplatin, and cisplatin), hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy (except for maintenance therapies outlined in Section 4.4.1)

  Patients who have achieved a PR or CR of target lesions and who develop new lesions (≤3) that are amenable to surgery or ablative techniques (e.g., radiotherapy, radiofrequency ablation) may continue to receive study treatment if they demonstrate no further progression of disease at the next imaging assessment and continue to demonstrate clinical benefit per the investigator.

- Patients must not receive live, attenuated vaccines (e.g., FluMist®) within 28 days prior to initiation of study treatment, at any time during the study treatment, or within 5 months after the last dose of atezolizumab.

4.4.2.1 Prohibited and Cautionary Therapy for Patients Treated with Atezolizumab

The concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, their use for patients in the study is allowed at the discretion of the investigator, provided that there are no known interactions with any study treatment. As noted in Section 4.4.2, herbal therapies that are intended for the treatment of cancer are prohibited.

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

Patients should not receive immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of atezolizumab. Systemic corticosteroids and anti–TNF-α agents may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating The Medical Monitor is available to advise as needed. If feasible, alternatives to these agents should be considered.

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

The above lists of medications are not necessarily comprehensive. The Medical Monitor is available to advise if questions arise regarding medications not listed above.

4.4.2.2 Prohibited and Cautionary Therapy for Gemcitabine-Treated Patients

Gemcitabine is not indicated for use in combination with radiation therapy. Patients should not receive gemcitabine within 7 days before or after radiation therapy. Concurrent therapy (given together or ≤7 days apart) with gemcitabine and thoracic radiation has led to life-threatening mucositis, especially esophagitis and pneumonitis. Excessive toxicity has not been observed when gemcitabine is administered more than 7 days before or after radiation. Radiation recall has been reported in patients who receive gemcitabine after prior radiation.

4.4.2.3 Prohibited and Cautionary Therapy for Carboplatin-Treated Patients

The renal effects of nephrotoxic compounds may be potentiated by carboplatin.

Aluminum reacts with carboplatin, causing precipitate formation and loss of potency; therefore, needles or IV sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

4.4.2.4 Prohibited and Cautionary Therapy for Cisplatin-Treated Patients

Simultaneous use of myelosuppressive agents or radiation will boost the effects of cisplatin's myelosuppressive activity. The occurrence of nephrotoxicity caused by cisplatin may be intensified by concomitant treatment with antihypertensive agents containing furosemide, hydralazine, diazoxide, and propranolol.

Concomitant administration of ototoxic (e.g., aminoglycosides, loop diuretics) medicinal products will potentiate the toxic effect of cisplatin on auditory function.

Simultaneous use of antihistamines, buclizine, cyclizine, loxapine, meclozine, phenothiazines, thioxanthenes, or trimethobenzamides may mask ototoxic symptoms (such as dizziness and tinnitus).

In the event of the simultaneous use of oral anticoagulants, it is advisable to more frequently check the INR.

4.5 STUDY ASSESSMENTS

Please see Appendix 1 and Appendix 2 for the schedule of assessments performed during the study. If the timing of a protocol-mandated study visit coincides with a holiday or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly.

4.5.1 Informed Consent Forms and Screening Log

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

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before 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.

Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry (except where otherwise specified) may be used for screening assessments and do not need to be repeated. If re-screening is required, then HBV, HCV, HIV, CRP, and autoantibody testing from the initial screening may be acceptable for screening assessment if performed <60 days prior to Cycle 1 Day 1.

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, vaccines, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the initiation of study drug. A history of pleural or pericardial effusion or of ascites requiring intervention should be entered in the medical history.

Demographic data will include age, ECOG performance status, sex, and self-reported race/ethnicity. The age-adjusted Charlson comorbidity index will be completed for each patient (Appendix 9).

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, and neurological systems. Any abnormality that is identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Height and weight should be measured and recorded on the eCRF.

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

4.5.4 Vital Signs

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

For all patients at the first infusion and thereafter if clinically indicated or if patient experienced symptoms during the previous infusion, vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before and 30 (±10) minutes after the infusion (see Table 1). Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

4.5.5 Tumor and Response Evaluations

Measurable and non-measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor assessments are to be performed at the timepoints specified in Appendix 1, every 9 weeks (± 3 business days) for 54 weeks and every 12 weeks (± 6 business days) regardless of drug delays or interruptions until disease progression per RECIST 1.1 or loss of clinical benefit (for patients who continue study treatment beyond initial radiographic disease progression; see Section 4.6.2 for details), death, or loss to follow-up, whichever occurs first.

After the first five cycles, one of three cycles may be delayed by 1 week (28 days instead of 21 days for one cycle) to allow for vacations.

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

Screening assessments must include CT scans (with oral or IV contrast unless contraindicated) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. In patients for whom CT scans with contrast are contraindicated (e.g., patients with contrast allergy or impaired renal clearance), MRIs of the chest, abdomen, and pelvis with a non-contrast spiral CT scan of the chest may be used.

A CT (with contrast if not contraindicated) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. Patients with treated asymptomatic CNS metastases may be eligible, provided they meet all of the criteria detailed in Section 4.1.2.1.

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

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

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

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

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

For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should be based on the tumor type, the anatomic location of the disease, and should be optimized to allow for comparison with the prior timepoints if possible. Each case should be discussed with the local radiologist to determine if substitution of these other approaches is possible and, if not, if the patient should be considered not evaluable per RECIST v1.1, until that point when the patient has progression by RECIST criteria, at which point they would be evaluable for PD. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

4.5.6 Patient-Reported Outcomes

The QLQ-C30 is a self-report questionnaire that assesses multiple dimensions of health-related–quality of life among cancer patients (Aaronson et al. 1993, Hjermstad et al. 1995, Osoba et al. 1997). Responses to this 30-item questionnaire are categorized into five functional domains (i.e., physical, role, emotional, cognitive, and social) (scored on a 4-point Likert scale), one global health status domain (scored on a 7-point Likert scale), three symptom domains (i.e., fatigue, nausea/vomiting, pain), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties; (scored on a 4-point Likert scale) (see Appendix 4). Each score is transformed into a 0–100-point scale. In the five functional scales and the global health status scale, a high score means a "high level of functioning or global health status." In the case of symptom scales and single items, a higher score implies a "high level of symptoms or problems."

The EQ-5D-5L is generic preference-based health utility questionnaire that provides a single index value for health status (see Appendix 5). The EQ-5D-5L comprises questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are used to build a composite of the patient's health status. In addition, the EQ-5D-5L includes a visual analog scale for the patient to rate his or her current health status. The EQ-5D-5L will be utilized in this study for the purpose of deriving utilities for economic modeling.

The patient-reported outcome (PRO) questionnaires will be translated as required into the local language. PROs will be collected via an electronic device ePRO (electronic questionnaires). In circumstances when the electronic device is not available (e.g., device failure or due to supply issues), the PROs will be collected via the validated paper questionnaire. The data from the validated questionnaire will be subsequently entered into the PRO database following instruction from the Sponsor.

The PRO questionnaires should be completed prior to the administration of study treatment and/or prior to any other study assessments that could bias patient response.

The PRO questionnaires (QLQ-C30 and EQ-5D-5L) will be completed on Cycle 1, Day 1 (first healthcare interaction); on Day 1 of each subsequent cycle; at the treatment discontinuation visit, which is within 30 days after the last treatment dose; and at any visits after disease progression and/or when OS is evaluated *up until the fourth survival follow-up visit. Completion of the PRO questionnaires will be discontinued after the final OS analysis*.
If survival follow-up visits are conducted by telephone, the PRO questionnaires (QLQ-C30 and EQ-5D-5L) should be conducted over the phone using the proxy module on the PRO device and following the instructions in the PRO manual.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for hematology, serum chemistries, coagulation, urinalysis, and 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 biomarkers, ATA assays, C-reactive protein (CRP) testing, 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 (PTT/aPTT and either PT or INR)
- Serum pregnancy test during screening and serum or urine pregnancy tests (a positive urine test result will be confirmed with a serum pregnancy test) 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)
- Serum ferritin
- All patients will be tested for HIV within 3 months prior to inclusion into the study, and patients with a positive HIV test result will be excluded from the clinical study.
- All patients will have a tuberculin (PPD) skin test or interferon gamma release assay performed locally within 3 months prior to inclusion into the study, and patients with active TB will be excluded from the clinical study.
- HBV serology (HBsAg, antibody to HBsAg [anti-HBs], anti-HBc)

  A negative HBV DNA test is required on or before Cycle 1, Day 1 if a patient has negative serology for HBsAg and positive serology for anti-HBc.
- HCV serology (anti-HCV): HCV antibody for all patients; HCV RNA for patients with a positive HCV antibody test

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:

- C-reactive protein (CRP)
- ATA assays

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

- PK assays

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

- Auto-antibody testing

  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 EDTA-plasma and serum for the determination of changes in blood-based biomarkers. Blood samples may be processed to obtain peripheral blood mononuclear cells (PBMCs) and their derivatives (e.g., RNA).

- Archival or Freshly Collected Tumor Tissue Samples for Eligibility

  Representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, must be submitted 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 on the basis of 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, 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 urothelial carcinoma may consent (but are not required) to also submit these samples for central testing. Tissue samples obtained at multiple times for individual patients may 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 or non-inherited biomarkers identified through NGS [next generation

sequencing] on extracted DNA and/or RNA) in archival and freshly collected 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.

For fresh biopsy specimens (i.e., after the initiation of the screening period), acceptable samples include core-needle biopsies for deep tumor tissue 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.

- Tumor Samples at the Time of Radiographic Progression

  Patients in all treatment arms will undergo a tumor biopsy to obtain a tumor sample, unless not clinically feasible, at the time of radiographic disease progression.

  Acceptable samples include:

  Core needle biopsies for deep tumor tissue; at least three cores, embedded into a single paraffin block, should be submitted for evaluation

  Excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous or mucosal lesions

  Tumor tissue resection

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

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

- For patients who consent to the optional collection of tumor samples for the Research Biosample Repository (RBR):

  Patients may agree to provide optional tumor biopsies by providing consent on the Optional RBR Informed Consent Form, which is separate from the main study Informed Consent Form. For patients who agree to optional biopsies, tissue samples for biopsy may be collected per investigator discretion, preferably of growing lesions pre-treatment (unless a sample collection was performed during screening to meet tissue eligibility requirements).

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

Use and storage of remaining samples from study-related procedures

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (RBR; see Section 4.5.10), biological samples will be destroyed when the final CSR has been completed, with the following exceptions:

Serum samples collected for PK and immunogenicity analysis that may be used for additional method development, assay validation and characterization will be destroyed no later than 5 years after the final Clinical Study Report has been completed. When a patient withdraws from the study, samples that are collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.3.

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

4.5.8 Anti-Therapeutic Antibody Testing

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 and Worobec 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 Cardiac Testing

4.5.9.1 Electrocardiograms and Evaluations of Left Ventricular Ejection Fraction

A twelve-lead electrocardiogram (ECG) is required at screening, at the end-of-treatment visit, and at any point in the study when clinically indicated. 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.

Patients with a history of clinically significant cardiac disease (including anatomic abnormality, coronary disease, congestive heart failure, abnormal LVEF, arrhythmia, or abnormal ECG) will be required to undergo a screening echocardiogram. However, a baseline evaluation of LVEF should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

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

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

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

4.5.10.3 Optional Samples for Roche Biosample Repository

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

- Remaining blood derivatives (serum, plasma, PBMCs and their derivatives) after study-related tests have been performed
- Remaining FFPE tissue freshly collected (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 before treatment)

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

- Blood sample for DNA isolation

  Blood sample for genetic biomarker analysis: a blood sample for DNA isolation will be collected from patients who have consented to optional RBR sampling at baseline as shown in the schedule of assessments in Appendix 1. If, however, the RBR 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 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.

The above sample may be sent to one or more laboratories for analysis of germline mutations, somatic mutations via whole genome sequencing (WGS), NGS, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. A WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

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

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.

4.5.10.4 Confidentiality

Confidentiality for All RBR Specimens

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

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

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

Given the complexity and exploratory nature of the analyses of the RBR samples, data derived from RBR specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any research conducted using RBR 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 RBR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.5.10.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. 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 appropriate RBR Subject Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the Sample Withdrawal of Informed Consent/Withdrawal eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from Study WO30070 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study WO30070.

4.5.10.7 Monitoring and Oversight

The RBR 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. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

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

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

However, patients will not be followed for any reason after consent has been withdrawn for the study. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient has not withdrawn consent from the study, starting from the treatment discontinuation visit, survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (±7 days) until death, loss to follow-up, or study termination by the Sponsor. All patients will be followed for survival and new anti-cancer therapy (including targeted therapy and immunotherapy) 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.

Before considering a patient lost to follow-up, at least 3 different documented attempts to contact them should be made. 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)

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

4.6.2 Study Treatment Discontinuation

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

- Intolerable toxicity related to study treatment

  Blinded atezolizumab can continue to be administered following discontinuation from chemotherapy.

- Any medical condition that may jeopardize the patient's safety if he or she continues to receive study treatment

  Unblinding of study treatment should not result in the discontinuation of patients from study treatment, if appropriate.

- Use of another systemic anti-cancer therapy (see Section 4.4.2)
- Pregnancy
- Radiographic disease progression per RECIST v1.1

Exception: On the basis of atezolizumab treatment experience, new lesions in the setting of shrinking target lesions can frequently be transient in their appearance and/or growth and may be due to an active immune response at the lesion site. Patients will be

permitted to continue study therapy after RECIST v1.1 criteria for progressive disease are met if they meet ALL of the following criteria:

- Patients must have achieved a PR or CR of target lesions.
- Patients must have ≤3 new lesions that are amenable to surgical resection or local ablative therapy (e.g., radiation therapy or radiofrequency ablation).
- Patients must have no further progression of disease at the next imaging assessment and continue to demonstrate clinical benefit per the investigator.
- Evidence of clinical benefit (defined as the stabilization or improvement of disease-related symptoms) as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- Patients must have no decline in ECOG performance status that can be attributed to disease progression.
- Patients must have an absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing.
- Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of progression.

Patients who meet ALL of these criteria may continue study therapy.

The primary reason for study drug discontinuation should be documented on the appropriate eCRF.

4.6.3 Study and Site Discontinuation

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

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

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

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

- Excessively slow recruitment or no recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Atezolizumab is approved for the treatment of urothelial carcinoma and for the treatment of non–small cell lung cancer. Atezolizumab is approved for one or more of these indications in multiple countries globally. The safety plan for patients in this study is based on clinical experience with atezolizumab in completed and ongoing studies. The anticipated important safety risks for atezolizumab are outlined below. Refer to the Atezolizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients who are at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below. Anaphylaxis precautions are provided in Appendix 7.

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

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

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: *infusion related reactions* (IRRs)*, including cytokine release syndrome,* and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, *facial paresis, myelitis,* meningoencephalitis, myocarditis, *pericardial disorders,* nephritis, myositis, and severe cutaneous adverse reactions. *In addition,*

immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis . Refer to the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with Gemcitabine, Carboplatin, or Cisplatin

For adverse reactions, warnings, and precautions for gemcitabine and carboplatin, see local prescribing information. Other specific instructions can be found in Section 4.3.2.2, Section 5.1.6, and Section 5.1.7.

5.1.3 General Plan to Manage Safety Concerns

5.1.3.1 Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies with atezolizumab, the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, and clinical data from gemcitabine, carboplatin, and cisplatin 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 (e.g., FluMist®) within 4 weeks before the initiation of study treatment are excluded from the study (see Section 4.1.2 for additional details).

5.1.3.2 Monitoring

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 signs or symptoms of autoimmune conditions and infection.

All serious adverse events and protocol-defined events of special interest (see Sections 5.2.2 and 5.2.3) will be reported in an expedited fashion. In addition, the Medical Monitor and investigators will review and evaluate observed adverse events on a regular basis. Administration of atezolizumab/placebo will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Guidelines for managing anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below (see Section 5.1.4). Refer to Sections 5.2–5.6 for details on safety reporting during the study.

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

5.1.4 Atezolizumab/Placebo Dose Modification

There will be no dose reduction for atezolizumab/placebo in this study. Patients may temporarily suspend study treatment *with atezolizumab/placebo* for up to 12 weeks beyond the last dose if they experience adverse events that require a dose to be withheld. If atezolizumab/*placebo* is withheld because of related adverse events for > 12 weeks beyond the last dose given, then the patient will be discontinued from atezolizumab/*placebo* and will be followed for safety and efficacy as specified in Section 5.4.4.

If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming atezolizumab/*placebo* after a hold of > 12 weeks, the study drug may be restarted. The Medical Monitor is available to advise as needed.

If patients must be tapered off steroids used to treat adverse events, atezolizumab/*placebo* may be withheld for additional time beyond > 12 weeks from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤ 10 mg/day. The acceptable length of interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Management of atezolizumab-specific adverse events is presented in Section 5.1.5.

5.1.5 Management of Atezolizumab/Placebo-Specific Adverse Events

Toxicities associated or possibly associated with atezolizumab/placebo 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 following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections.

- *Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.*
- *In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.*
- *Consider holding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5□1 mg/kg/day of prednisone or equivalent) may be administered.*
- *For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.*
- *Hold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1□2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.*
- *In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.*
- The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event.* The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.

5.1.5.1 Pulmonary Events

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. 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, COPD, or pulmonary hypertension. *COVID-19 evaluation should be performed per institutional guidelines where relevant.* Management guidelines for pulmonary events are provided in Table 2.

Table 2 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c,d] • For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

Table 2 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

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

5.1.5.2 Hepatic Events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. *Patients e*ligible *for study treatment* must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases; liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 3.

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 3 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

5.1.5.3 Gastrointestinal Events

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 4.

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

Table 4 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • *If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.* • Patient referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

Table 4 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

5.1.5.4 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 5.

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

Table 5 Management Guidelines for Endocrine Events

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

TSH=thyroid-stimulating hormone.

Table 5 Management Guidelines for Endocrine Events (cont.)

Event	Management
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

Table 5 Management Guidelines for Endocrine Events (cont.)

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

MRI = magnetic resonance imaging.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

5.1.5.5 Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 6.

Table 6 Management Guidelines for Ocular Events

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

5.1.5.6 *Immune-Mediated Cardiac events*

Management guidelines for cardiac events are provided in Table 7.

5.1.5.7 Immune-Mediated Myocarditis

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

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

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 7.

5.1.5.8 *Immune-Mediated Pericardial Disorders*

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

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

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

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

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated

according to the guidelines in Table 7. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 7 Management Guidelines for Immune-Mediated Cardiac Events

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

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

5.1.5.9 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 CRS with atezolizumab may receive premedication with antihistamines or antipyretics and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

Infusion related reactions 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.

The 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 8.

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

Table 8 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in Table 16. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor. [e] • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.

Table 8 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

Event	Management
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in Table 16. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in Table 16. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

Table 8 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

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

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

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

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

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

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

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

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

5.1.5.10 Pancreatic Events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 9.

Table 9 Management Guidelines for Pancreatic Events, Including Pancreatitis

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

Table 9 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

5.1.5.11 Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 10.

Table 10 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation, and if indicated, biopsy. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

5.1.5.12 Neurologic Disorders

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 11, *with specific guidelines for myelitis provided in Table 12.*

Table 11 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • *Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.*
Immune-mediated neuropathy, ~~including~~ *facial paresis,* Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • *For general immune-mediated neuropathy:* – If event resolves to Grade 1 or better, resume atezolizumab. [b] – If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • *For facial paresis:* – *If event resolves fully, resume atezolizumab.* [b] – *If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated neuropathy, *including facial paresis*, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

Table 11 Management Guidelines for Neurologic Disorders (cont.)

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

Table 12 Management Guidelines for Immune-Mediated Myelitis

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

5.1.5.13 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 13.

Table 13 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

5.1.5.14 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 14.

Table 14 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

Table 14 Management Guidelines for Renal Events (cont.)

Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

5.1.5.15 Immune-Mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 15.

Table 15 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.

Table 15 Management Guidelines for Immune-Mediated Myositis (cont.)

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

Table 15 Management Guidelines for Immune-Mediated Myositis (cont.)

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

5.1.5.16 Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Immune-mediated reactions may involve any organ system and may lead to HLH and macrophage activation syndrome (MAS).

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

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

- Fever ≥38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin <90 g/L (9 g/dL) (<100 g/L [10 g/dL] for infants <4 weeks old)
  - Platelet count $<100 \times 10^9$/L (100,000/μL)
  - ANC $<1.0 \times 10^9$/L (1000/μL)

- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

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

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

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 16.

Table 16 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

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

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

5.1.6 Gemcitabine, Carboplatin, and Cisplatin Dose Modifications

The NCI CTCAE, v4.0 must be used to grade the severity of adverse events.

The investigator may attribute toxicity to gemcitabine, carboplatin, cisplatin, or placebo/atezolizumab and use stepwise dose modifications according to Table 18. Placebo/atezolizumab dose reductions are not permitted. Placebo/atezolizumab treatment may be interrupted or discontinued because of toxicity. Dose modifications of chemotherapy are based on the previous cycle. Dose re-escalations are only permitted for the Day 8 gemcitabine dose adjustment for hematologic parameters (see Table 17). If a patient's cisplatin-gemcitabine chemotherapy is discontinued for reasons of toxicity, he or she is permitted to commence treatment with carboplatin-gemcitabine chemotherapy.

All of the following are appropriate based upon the attribution of toxicity by the investigator and recommended toxicity management as outlined in Table 17 and Table 19:

- Withholding both chemotherapy agents
- Withholding placebo/atezolizumab or both of the chemotherapy agents

If the criteria for Day 1 chemotherapy are not met for Cycle 2 or greater, both the chemotherapy and atezolizumab should be delayed for 1 week and should continue on a q3w schedule once dosing restarts. Atezolizumab can be administered concurrently with Day 1 chemotherapy if there are no indications for withholding atezolizumab and it is felt to be clinically appropriate by the investigator.

If the criteria for treatment on Day 1 are not met, treatment will be withheld for 1 week, and the CBC will be rechecked weekly until the criteria for chemotherapy treatment are met before proceeding with further treatment. Dose modifications of gemcitabine for hematologic toxicity are allowed and will be based on blood counts obtained within 1 day prior to Day 1 and Day 8 of each cycle of therapy. Treatment with filgrastim or pegfilgrastim may be used if needed. Treatment with sargramostim is not allowed.

If dose delay for hematologic toxicity is required for more than one cycle, the patient should have a dose reduction to the next dose-level for both gemcitabine and cisplatin/carboplatin.

Guidelines for gemcitabine, carboplatin, and cisplatin dose modifications are shown in Table 17 and Table 19.

Table 17 Gemcitabine, Carboplatin, and Cisplatin Dose Modification for Myelosuppression on the Day of Treatment [b]

Neutrophils ($\times 10^9$ cells/L)		Platelets ($\times 10^9$ cells/L)	Gemcitabine Dose	Carboplatin Dose	Cisplatin Dose
Day 1					
≥1.5	AND	≥100	No dose reduction	No dose reduction	No dose reduction
<1.5	OR	<100	DELAY [a]	DELAY [a]	DELAY
Day 8 [b]					
≥1.5	AND	≥100	No dose reduction	—	—
1.0–1.49	OR	75–99.9	No dose reduction	—	—
0.5–0.99	OR	50–74.9	500mg/m^2	—	—
<0.5	OR	<50	Withhold	—	—

[a] Delay dose until neutrophils ≥1.5 or platelets ≥100.

[b] Dose modifications for neutrophil or platelet values on the day of treatment should be applied only for the treatment day or cycle in which the myelosuppression occurs. Overall dose modifications for subsequent cycles should follow the dose levels in Table 18 below.

Table 18 Dose-Modification Levels

	Starting Dose	Dose Level –1	Dose Level –2	Dose Level –3	Dose Level –4
Atezolizumab or Placebo	1200 mg fixed dose	Dose reductions not permitted	Dose reductions not permitted	Dose reductions not permitted	Dose reductions not permitted
Cisplatin [a]	70 mg/m^2	60 mg/m^2	50 mg/m^2	Discontinue	Discontinue
Gemcitabine [b]	1,000 mg/m^2	900 mg/m^2	800 mg/m^2	700 mg/m^2	Discontinue
Carboplatin [a,c] (AUC)	4.5	4.0	3.5	Discontinue	Discontinue

AUC = area under the concentration–time curve.

[a] No dose re-escalation is allowed after a dose reduction to a lower dose level.

[b] Dose re-escalations of gemcitabine are only permitted after an adjustment of the Day 8 gemcitabine dose. The maximum re-escalation permitted is to the previous Day 1 dose administered. The Day 8 dose reduction only applies to Day 8 and does not count towards the allowed number of dose reductions per patient.

[c] Patients will be allowed to receive a starting dose of AUC of 5.0 of carboplatin if this is institutional practice. In such cases, patients will be allowed to have 3 dose reductions to reach dose level –2.

Table 19 Gemcitabine, Carboplatin, and Cisplatin General Dose Modifications

Toxicity	Definition	Gemcitabine Dose	Carboplatin Dose	Cisplatin Dose
Febrile Neutropenia	ANC $<0.5\times10^9$/L plus fever that requires IV antibiotics with or without hospitalization	Dose reduction to next dose level with no dose re-escalation for all future doses [a]	Dose reduction to next dose level with no dose re-escalation for all future doses	Dose reduction to next dose level with no dose re-escalation for all future doses
Other Toxicities	NCI CTCAE v4 Grade 3/4 toxicity (except alopecia)	Delay treatment until toxicity has returned to ≤Grade 1. At Grade ≤1 toxicity level, treatment may be resumed with dose reduction to the next dose-level and no dose re-escalation for all future doses. If further toxicity occurs, an additional dose reduction to the next dose-level with no dose re-escalation for all future doses may be allowed after discussion with the Medical Monitor.		

IV=intravenous; NCI CTCAE v4=National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.

[a] Dose re-escalations of gemcitabine are only permitted after an adjustment of the Day 8 gemcitabine dose.

If a delay of more than 42 days from last dose is required for recovery for any hematologic or non-hematologic toxicity and/or more than two dose reductions are necessary, gemcitabine and carboplatin or gemcitabine and cisplatin should be permanently discontinued. However, if toxicity can be clearly attributable to a single chemotherapy agent, then the investigator can determine whether to stop both agents or continue with a single chemotherapy agent alone (i.e., gemcitabine or carboplatin or cisplatin alone).

Patients who discontinue both gemcitabine and carboplatin or gemcitabine and cisplatin or only carboplatin/cisplatin permanently for adverse events should continue treatment with gemcitabine with atezolizumab or placebo or single-agent atezolizumab or placebo until disease progression, as long as patients are experiencing clinical benefit in the opinion of the investigator.

Patients who discontinue single-agent atezolizumab or placebo due to an adverse event may continue chemotherapy per protocol until unacceptable toxicity or disease progression.

5.1.7 Management of Gemcitabine-Specific Adverse Events

Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome, has been reported. In some cases, these pulmonary events can lead to fatal respiratory failure despite discontinuation of therapy. The onset of pulmonary symptoms may occur up to 2 weeks after the last dose of gemcitabine. Discontinue gemcitabine in patients who develop unexplained dyspnea, with or without bronchospasm, or have any evidence of pulmonary toxicity.

Hemolytic uremic syndrome can occur in patients treated with gemcitabine. Gemcitabine should be permanently discontinued in patients who develop hemolytic uremic syndrome or microangiopathic hemolysis.

See the local prescribing information/institution guidelines for gemcitabine for further guidance on gemcitabine-specific toxicities and adverse event management.

Patients who discontinue gemcitabine permanently (e.g., for adverse events) may continue treatment with carboplatin/cisplatin. Treatment with atezolizumab/placebo can continue until disease progression as long as patients are experiencing clinical benefit in the opinion of the investigator.

5.1.8 Management of Carboplatin-Specific Adverse Events

Anaphylactic-like reactions to carboplatin have been reported and may occur within minutes of carboplatin administration. There is increased risk of allergic reactions including anaphylaxis in patients who were previously exposed to platinum therapy. Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

See the local prescribing information/institution guidelines for carboplatin for further guidance on carboplatin-specific toxicities and adverse event management.

Patients who discontinue carboplatin permanently (e.g., for adverse events) may continue treatment with gemcitabine. Treatment with atezolizumab/placebo can continue until disease progression as long as patients are experiencing clinical benefit in the opinion of the investigator.

5.1.9 Management of Cisplatin-Specific Adverse Events

Cumulative nephrotoxicity, myelosuppression, nausea, and vomiting have been reported. Ototoxicity, manifested by tinnitus and/or high-frequency hearing loss, can be significant. Anaphylactic-like reactions to cisplatin have been reported. Facial swelling, bronchospasm, tachycardia, and hypotension may occur within minutes of cisplatin administration. Other side effects include fatigue; anorexia; weight loss; diarrhea; serum electrolyte disturbances including hyponatremia, hypomagnesemia, and hypocalcemia; edema of the lungs or extremities; vascular toxicities; neurotoxicity including cerebral

infarction, seizures and dizziness; ocular toxicity with visual disturbances; peripheral neuropathy; autonomic neuropathy; infertility; muscle cramps; and hepatic toxicity. Other rare side effects include cardiac abnormalities, hiccoughs, elevated serum amylase, rash, and alopecia. Local soft-tissue injury has been reported following extravasation of cisplatin.

Renal Insufficiency and Nephrotoxicity

If on Day 1 of any cycle, the creatinine > 1.5 mg/dL and calculated estimated GFR < 60 mL/min, treatment will be withheld for 1 week and creatinine and estimated GFR will be rechecked. If recovery to creatinine ≤ 1.5 mg/dL or estimated GFR ≥ 60 mL/min occurs, the patient will be re-treated with a cisplatin dose that is one level lower than the prior cycle. A patient can be discontinued cisplatin-gemcitabine chemotherapy for reasons of toxicity and is permitted to commence treatment with carboplatin-gemcitabine chemotherapy. Additional hydration should be considered on the day of treatment or on the day following treatment. Any patient who requires dose reduction after a reduction to dose level −2 will be discontinued from chemotherapy.

Neurologic Toxicity

If neurologic toxicity ≥ Grade 2 occurs at any point in the cycle, then gemcitabine and cisplatin should be withheld for 1 week. If resolution to Grade 1 occurs, the patient will be re-treated with a cisplatin dose that is one level lower than the prior cycle. If the toxicity does not resolve to Grade 1, then cisplatin will be discontinued but the patient can commence treatment with carboplatin if it is felt by the investigator to be clinically appropriate.

Ototoxicity

If ototoxicity is suspected, audiometry will be performed to assess hearing. For loss of greater than 25 decibels in two consecutive hearing frequencies, therapy will be withheld for 1 week, and audiometry assessment will be repeated. If hearing loss is resolved, then the patient will be re-treated with a cisplatin dose that is one level lower than the prior cycle. Patients will not undergo routine audiology monitoring for this study.

Cardiovascular Toxicity

If a patient develops ≥ Grade 3 cardiovascular toxicity during any cycle of therapy, then treatment should be permanently discontinued.

Gastrointestinal Toxicity

Patients who develop nausea or vomiting that persists at Grade 3 or 4 should be treated with maximal medical therapy, and treatment should be withheld until the patient's recovery. After the patient has fully recovered, therapy at the same dose and schedule can resume with appropriate prophylactic medications.

Other Non-Hematological Toxicities

For any Grade 3 or 4 chemotherapy-related toxicity that is not mentioned above, the treatment should be withheld until the patient recovers, and the possibility of resumption of therapy should be discussed with the Medical Monitor.

Patients who develop a symptomatic Grade 4 venous thromboembolic event will not be eligible for re-treatment.

See the local prescribing information/institution guidelines for cisplatin for further guidance on cisplatin-specific toxicities and adverse event management.

Patients who discontinue cisplatin permanently (e.g., for adverse events) may continue treatment with gemcitabine. A patient can discontinue cisplatin-gemcitabine chemotherapy for reasons of toxicity, and is permitted to commence treatment with carboplatin-gemcitabine chemotherapy. Dosing with atezolizumab/placebo should continue until disease progression as long as patients are experiencing clinical benefit in the opinion of the investigator.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

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

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

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

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see

Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- 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, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10\times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release *syndrome*, influenza-like illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, *optic neuritis*)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders
- *Myelitis*
- *Facial paresis*
- *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**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported during the study until the end of the special reporting period (defined as 90 days after the last dose of study drug or initiation of another anti-cancer therapy, whichever occurs first). All other adverse events 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. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

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

Table 20 Adverse Event Severity Grading Scale for Events Not Specifically Listed in National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

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

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, 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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

For adverse events, a diagnosis (if known) rather than individual signs and symptoms should be recorded on the Adverse Event eCRF (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 drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "injection-site reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF.

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 studies, certain abnormal values may not qualify as adverse events.

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

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

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

clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$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 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of urothelial carcinoma should be recorded on the Death Attributed to Progressive Disease eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent monitoring committee 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").

After the adverse event reporting period, deaths attributed to progression of urothelial carcinoma should be recorded on the Death Attributed to Progressive Disease eCRF, and deaths not attributed to progression of urothelial carcinoma should be recorded on the Study Discontinuation eCRF.

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 Worsening of Urothelial Carcinoma

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or to perform an efficacy 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 suffered an adverse event.

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

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

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

- Accidental overdoses or medication errors (see Section 5.4.4 for details on reporting requirements)

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

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], M.D.
Email:
Mobile Telephone No.:

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

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Clinical Trial Adverse Event/Special Situations 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 initiation of another anti-cancer therapy, whichever occurs first. All other adverse events will be reported until 30 days after the last dose of study drug or initiation of another anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Clinical Trial Adverse Event/Special Situations 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 through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab or placebo or 6 months after last dose of gemcitabine, carboplatin, or cisplatin, whichever is longer. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after last dose of gemcitabine, carboplatin, or cisplatin. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and

submit to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

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

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

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.4.4 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose

- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For atezolizumab, placebo, gemcitabine, carboplatin, and cisplatin, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with atezolizumab, placebo, gemcitabine, carboplatin, and cisplatin, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

During the adverse event reporting period (defined in Section 5.4.2), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

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

5.5.2 Sponsor Follow-Up

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

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the serious adverse event reporting period (defined as 90 days [Section 5.3.1] after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

During survival follow-up, deaths attributed to progression of urothelial carcinoma should be recorded on the Death Attributed to Progressive Disease eCRF, and deaths not attributed to progression of urothelial carcinoma should be recorded on the Study Discontinuation eCRF.

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

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

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

- Atezolizumab Investigator's Brochure
- The E.U. Summary of Product Characteristics for carboplatin
- The E.U. Summary of Product Characteristics for gemcitabine
- The E.U. Summary of Product Characteristics for cisplatin

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This study consists of two stages:

- Stage 1: This study was initially implemented with two treatment arms (carboplatin plus gemcitabine with or without atezolizumab, Arms A and C) in patients who are ineligible for cisplatin-based therapy.
- Stage 2: In Protocol WO30070, Version 3, a third treatment arm was added (atezolizumab monotherapy, Arm B). In addition, the eligibility criteria were expanded to also allow patients who are eligible for cisplatin-based chemotherapy to enter the study. Protocol WO30070, Version 3 will be implemented while recruitment is ongoing.

Analysis populations are defined as follows:

- For the comparison of efficacy in Arm A versus Arm C, the ITT population is defined as all patients randomized to Arm A or Arm C in Stages 1 and 2, whether or not the assigned study treatment was received.
- For the comparison of efficacy in Arm B versus Arm C, the ITT population includes only patients concurrently enrolled in Stage 2 and only those who had been randomized at the time of approval of Protocol WO30070, Version 6 (see Section 3.1).
- The PD-L1 IC2/3 population for the comparison of Arm B versus Arm C is defined as all patients randomized in Stage 2 with a PD-L1 status of IC2/3. This includes patients who were randomized to Arm B or Arm C after implementing the iDMC recommendation in Protocol WO30070, Version 6.
- The measurable disease population is defined as patients in the ITT population with measurable disease at baseline.
- The DOR-evaluable population is defined as patients with an objective response.

- The PRO-evaluable population is defined as patients with a non-missing baseline PRO assessment.
- The safety-evaluable population is defined as patients who received any amount of any component of the study treatments. Patients will be analyzed according to the treatment received. In particular, patients randomized to the monotherapy arm after approval of Protocol WO30070, Version 6 who received combination open-label atezolizumab and chemotherapy will be pooled with patients in Arm A for safety analyses.

6.1 DETERMINATION OF SAMPLE SIZE

A total of approximately 1200 patients will be randomized to the study (Stage 1 and Stage 2 combined).

Enrollment of approximately 1200 patients is based on the following assumptions: approximately 258 patients are projected to be enrolled in Stage 1 and allocated 2:1 to Arm A (atezolizumab in combination with platinum therapy) or Arm C (placebo in combination with platinum therapy). Approximately 942 patients are projected to be enrolled in Stage 2 and allocated 1:1:1 to Arm A, Arm B (atezolizumab monotherapy), or Arm C.

Simulations were performed to check the expected power of the analyses of co-primary endpoints PFS and OS for this sample size as described in the following sections.

6.1.1 Type I Error Control

The type I error (α) for this study is 0.025 (one-sided). There are two co-primary efficacy endpoints for this study: PFS by investigator assessment per RECIST v1.1 and OS. To control the overall type I error rate (Bretz et al. 2009) while accounting for two co-primary endpoints, α will be split between PFS ($\alpha = 0.01$) and OS ($\alpha = 0.015$) (Figure 4). Because type I error will be controlled accounting for two co-primary endpoints, the study will be considered a positive study if statistical significance is achieved for either of the co-primary endpoints.

Formal treatment comparisons of PFS and OS in Arm A versus Arm C will be performed in a hierarchical fashion in which α may be recycled (Burman et al. 2009) as follows:

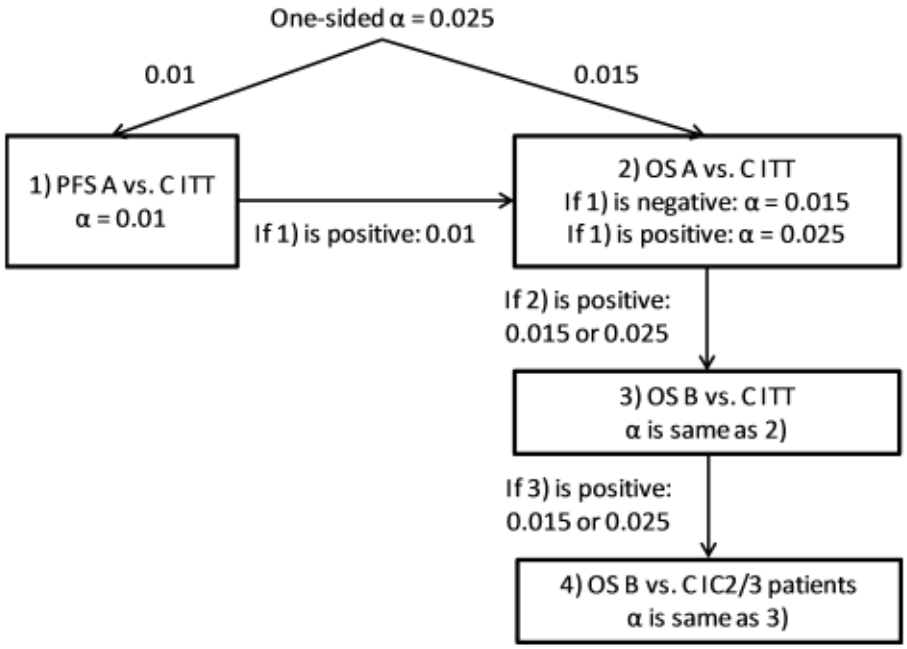
1. The PFS in Arm A versus Arm C of the ITT population will be evaluated at $\alpha = 0.01$ (one-sided).
2. If PFS results in Arm A versus Arm C of the ITT population are statistically significant at $\alpha = 0.01$, then $\alpha = 0.01$ will be recycled to OS in Arm A versus Arm C of the ITT population, and OS in Arm A versus Arm C of the ITT population will be evaluated at $\alpha = 0.025$ (one-sided). If PFS results in Arm A versus Arm C of the ITT population are not statistically significant at $\alpha = 0.01$, then no recycling of α will occur, and OS in Arm A versus Arm C of the ITT population will be evaluated at $\alpha = 0.015$ (one-sided).

3. OS will also be compared between the ITT population of Arm B and Arm C using a hierarchical approach as follows: If the duration of OS is shown to be statistically significantly different between Arm A and Arm C at the appropriate α level (see Step 2 above), then the duration of OS in the ITT population of Arm B and Arm C will be compared at the same α level. If the OS results for Arm A versus Arm C of the ITT population are not statistically significant, formal treatment comparison of OS in the ITT population of Arm B versus Arm C will not be performed.
4. If the comparison in Step 3 above is statistically significant at the appropriate α level, then OS will be compared between the PD-L1 IC2/3 population of Arm B and Arm C at the same α level.

Interim analyses of OS and the final analysis of OS will be based on the α allocated to the comparison of OS, as described above. Statistical significance at the interim analysis of OS will be evaluated as described in Section 6.8.1.

The PFS and OS analysis hierarchy and α allocation including possible α recycling are shown in Figure 4.

Figure 4 Progression-Free Survival and Overall Survival Analysis Hierarchy, Alpha Allocation and Alpha Recycling



ITT = intent-to-treat; PFS = progression-free survival; OS = overall survival.

It is important to note that the decision to change from a two-arm to a three-arm design was informed by external information only. At the time of the decision, there were less than 5 patients enrolled in Stage 1 of the study, and there was no interim look at study data prior to the protocol amendment. Additionally, the two-arm study was

placebo-controlled, and the Sponsor had no access to treatment codes assigned at randomization. Therefore, the change does not result in inflation of the type I error.

Comparisons for PFS and OS will be based on a stratified log-rank test. All comparisons between Arm A and Arm C will include patients enrolled in Stage 1 and Stage 2 of the study. A possible effect of study stage (due to different randomization ratio) on the treatment effect of Arm A versus Arm C will be taken into account as follows: for Arm A versus Arm C comparisons (of PFS or OS), data from Stage 1 and Stage 2 will be analyzed separately; the final p-value will be a combination of the p-values from the log-rank test from the two stages. The method for p-value combination will be the inverse normal approximation (Wassmer 2006). The weights will be based on the expected number of events in the two stages and will be pre-specified in the Statistical Analysis Plan (SAP). A one-sided test will be performed in each stage, because it is possible to observe treatment effects in opposite directions in the two stages.

This approach will ensure that each comparison is performed between concurrently enrolled groups with the same patient characteristics. However, if the number of patients enrolled in Stage 1 is deemed too small to introduce bias, data from Stage 1 and Stage 2 will be pooled for all analyses.

6.1.2 Co-Primary Endpoint: Progression-Free Survival

The duration of PFS will be compared between Arm A and Arm C. It is projected that the ITT population for the comparison of Arm A versus Arm C will include approximately 886 patients.

The analysis of the co-primary endpoint of PFS will take place when approximately 667 PFS events in the ITT population for the comparison of Arm A versus Arm C have occurred (75% of 886 randomized patients) on the basis of the following assumptions:

- Stratified log-rank test combining data from Stage 1 and Stage 2
- $\alpha = 0.01$ (significance level for combined p-value, one-sided)
- Approximately 91% power
- Median PFS in the control arm of 6.8 months and estimated median PFS in the atezolizumab arm of 9.1 months (an increase of 2.3 months, corresponding to a HR of 0.75)
- Dropout rate of 5% annually
- No interim analysis of PFS

Accrual of the planned number of patients is projected to occur over 21 months.

On the basis of these assumptions, the required number of PFS events in the ITT population is projected to occur at Month 30 from the time the first patient is randomized.

6.1.3 Co-Primary Endpoint: Overall Survival

The co-primary endpoint of OS will be compared between Arms A and C, and between Arms B and C in a hierarchical fashion as described in Section 6.1.1.

Arm A versus Arm C

It is projected that the ITT population for the comparison of Arm A versus Arm C will include approximately 886 patients.

The final analysis will take place when approximately 667 OS events in the ITT population for the comparison of Arm A versus Arm C have occurred (75% of 886 randomized patients) on the basis of the following assumptions:

- Stratified log-rank test combining data from Stage 1 and Stage 2
- $\alpha = 0.015$ (one-sided)
- Approximately 99% power
- Median OS in the control arm of 12 months and estimated median OS in the atezolizumab arm of 17.1 months (an increase of 5.1 months, corresponding to a HR of 0.70)
- Dropout rate of 5% annually
- One interim analysis to be performed at the time of the PFS analysis. Note that the addition of a second interim analysis does not result in a noticeable reduction of statistical power(see Section 6.8.1).

Based on observed survival up to the final PFS/first interim OS analysis, the required number of events is projected to occur at Month 55 from the time the first patient was randomized.

Arm B versus Arm C

The final analysis of OS in Arm B versus Arm C will be performed when 75% of the patients have died, or at the time of the final analysis in Arm A versus Arm C, whichever is later.

Prior to the iDMC recommendation to stop further recruitment of patients with PD-L1 status of IC0 or IC1 to atezolizumab monotherapy (see Section 3.1), the statistical power was determined as follows. The expected number of patients for the comparison of Arm B versus Arm C, defined as all patients concurrently randomized during Stage 2 of the study, was approximately 628 patients. The final analysis was planned when approximately 471 OS events in the ITT population for Arm B and Arm C have occurred (75% of 628 patients) on the basis of the following assumptions:

- Stratified log-rank test using data from Stage 2 patients only
- $\alpha = 0.015$ (one-sided)
- Approximately 88% power

- Median OS in the control arm of 12 months and estimated median OS in the atezolizumab arm of 16.4 months (an increase of 4.4 months, corresponding to a HR of 0.73)
- Dropout rate of 5% annually
- One interim analysis to be performed at the time of the PFS analysis (see Section 6.8.1)

Due to the modification to Arm B following the iDMC recommendation (Protocol WO30070, Version 6), the actual number of patients included in the analysis is expected to be approximately 600. The ratio of deaths observed at the time of the final OS analysis to the total number of patients to be included in the analysis will be kept at 75%. If the analysis is performed after 450 deaths have been observed (75% of 600), the statistical power would be approximately 86%.

An additional statistical comparison of OS in patients in Arm B versus Arm C with a PD-L1 status of IC2/3 will be performed as described in Section 6.1.1.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment and reasons for discontinuation from the study will be summarized by treatment arm for the ITT population. Major protocol deviations, including major deviations of inclusion and/or exclusion criteria, will be summarized by treatment arm for the ITT population. Study treatment administration and reasons for discontinuation from study treatment will be summarized for treated patients.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic characteristics (such as age, sex, race/ethnicity), baseline disease characteristics (e.g., ECOG performance status), and stratification factors will be summarized by treatment arm for the ITT population. Continuous variables will be summarized using means, standard deviations, medians, and ranges. Categorical variables will be summarized by frequencies and percentages.

Baseline measurements are the last available data obtained prior to the patient receiving the first dose of study treatment.

6.4 EFFICACY ANALYSES

The efficacy analyses for PFS and OS will be performed on all randomized patients (ITT population) for the respective treatment arm comparison according to the analysis hierarchy described in Section 6.1. Patients will be grouped according to the treatment assigned at randomization. Analysis of secondary and exploratory efficacy endpoints will be performed for randomized patients in the ITT population or as specified in Section 6.4.2.1 and Section 6.4.2.2.

6.4.1 Co-Primary Efficacy Endpoints

The co-primary efficacy endpoints are PFS as assessed by the investigator using RECIST v1.1 and OS. Because type I error will be controlled accounting for two co-primary endpoints, the study will be considered a positive study if statistical significance is achieved for either of the co-primary endpoints.

The PFS is defined as the time from randomization to the first documented disease progression as assessed by the investigator using RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment. Data for patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

For U.S. registration purposes, the co-primary efficacy endpoint of PFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits.

The OS is defined as the time from randomization to death due to any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.

The following analyses will be performed for both PFS and for OS. PFS and OS will be compared between treatment arms with the use of the stratified log-rank test. For the comparisons of Arm A versus Arm C, a possible effect of study stage will be taken into account as described in Section 6.1.1.

The HR for PFS and OS will be estimated using a stratified Cox regression model. The 95% CI for the HR will be provided. The stratification factors will be the same as the randomization stratification factors, with values as recorded in the IxRS. Results from an unstratified analysis will also be presented. Kaplan-Meier methodology will be used to estimate median PFS and OS for each treatment arm, and Kaplan-Meier plots will be constructed to provide a visual description of the difference between the treatment and control arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS and OS for each treatment arm (Brookmeyer and Crowley 1982).

For the primary analysis of OS in the ITT population for Arm B versus Arm C, all available data for these patients (before and after implementation of the iDMC recommendation in Protocol WO30070, Version 6) will be included.

However, if a substantial number of patients with a PD-L1 expression status of IC0 or IC1 randomized to Arm B prior to implementation of Protocol WO30070, Version 6 choose to switch to the combination of atezolizumab and chemotherapy, additional

sensitivity analyses may be performed to account for treatment switching. A sensitivity analysis will also be performed on patients randomized to Arm B or Arm C prior to implementation of Protocol WO30070, Version 6 that will include their data only up to the time of implementation of the iDMC recommendation.

The analysis of OS in the PD-L1 IC2/3 population for Arm B versus Arm C will use the same methods as that for the ITT population for Arm B versus Arm C, except that PD-L1 status will not be one of the stratification factors. The analysis will include all available data for these patients (before and after implementation of the iDMC recommendation of Protocol WO30070, Version 6).

The exploratory efficacy analyses for PFS and OS are described in Section 6.7.2 and Section 6.7.3.

6.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints will be analyzed for the ITT population unless specified otherwise in Section 6.4.2.1 and Section 6.4.2.2.

6.4.2.1 Objective Response Rate

The analysis population for ORR will be all patients in the ITT population with measurable disease at baseline.

An objective response is defined as either a confirmed CR or a PR, observed on two consecutive assessments ≥28 days apart, as determined by the investigator by use of RECIST v1.1. Patients who do not meet these criteria, including patients without any post-baseline tumor assessment, will be considered non-responders.

The ORR is defined as the proportion of patients who had an objective response. The ORR will be compared between treatment arms with use of the stratified Cochran-Mantel-Haenszel test. The stratification factors will be the same as those described in the analysis of the primary endpoint of PFS. An estimate of ORR and its 95% CI will be calculated using the Clopper Pearson method for each treatment arm. The CIs for the difference in ORRs between the experimental arms and the control arm will be determined using the normal approximation to the binomial distribution.

Time to response (TTR) will be summarized for descriptive purposes by treatment arm for patients who achieved a confirmed response. The TTR is defined as the time between the date of randomization and the date of first occurrence of a CR or PR (whichever status is recorded first).

6.4.2.2 Duration of Response

The DOR will be assessed in patients who had an objective response as determined by the investigator by use of RECIST v1.1. The DOR is defined as the time from the first occurrence of a CR or PR (whichever status is recorded first) until the first date

progressive disease or death is documented, whichever occurs first. Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR plus 1 day. The DOR is based on a non-randomized subset of patients (specifically, patients who achieved an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes. The methodologies detailed for the PFS analysis will be used for the DOR analysis.

6.4.2.3 Progression-Free Survival by an Independent Review Facility

The IRF-PFS is defined as the time from randomization to the first documented disease progression as assessed by an independent review facility (IRF) using RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment. Data for patients with no postbaseline tumor assessment will be censored at the date of randomization plus 1 day.

As for INV-PFS, an analysis of IRF-PFS will also be performed with the additional censoring rule for missed visits (see Section 6.4.1). Data for patients with an IRF-PFS event who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.

The HR will be estimated using a stratified Cox-regression model with the same stratification factors as for INV-PFS. The 95% CI for the HR will be provided. Kaplan-Meier methodology will be used to estimate median IRF-PFS for each treatment arm, and Kaplan-Meier plots will be constructed. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS and OS for each treatment arm (Brookmeyer and Crowley 1982).

Exploratory efficacy analyses for IRF-PFS are described in Section 6.7.2.

6.4.2.4 Timepoint Analysis of Overall Survival

The OS rates at 1, 2, and 3 years will be estimated by use of Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated by use of the standard error derived from Greenwood's formula. The 95% CI for the difference in OS rates between the two treatment arms will be estimated by use of the normal approximation method.

6.4.2.5 Timepoint Analysis of Progression Free Survival

The INV-PFS and IRF-PFS rates at 6 month intervals (e.g., 6 months, 1 year, etc.) will be estimated by use of Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated by use of the standard error derived from Greenwood's formula. The 95% CI for the difference in PFS rates between the two treatment arms will be estimated by use of the normal approximation method.

6.4.2.6 Patient-Reported Outcomes

The QLQ-C30 data will be scored according to the EORTC scoring manual (Fayers 2001). For all questionnaire subscales, if more than 50% of the constituent items are completed, a prorated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing.

The primary PRO endpoint is time to deterioration in global health status in the PRO-evaluable population, which will be compared between treatment groups as a secondary efficacy endpoint with use of the log rank test (two-sided). Deterioration in global health status is defined as a change from baseline of at least 10 points. Data for patients without a post-baseline assessment will be censored at the date of randomization plus 1 day. The HR will be estimated using a stratified Cox proportional hazards model and its 95% CI will be provided. Kaplan-Meier methodology will be used to estimate the median time to deterioration in health status, and Kaplan-Meier curves will be produced.

Time to deterioration of the physical function score on the QLQ-C30 will be analyzed using the same methodology as for time to deterioration in global health status. Deterioration in physical function score is defined as a change from baseline of at least 10 points.

The two scales aforementioned (i.e., global health status and physical function) and all other QLQ-C30 scales will be summarized descriptively as absolute mean scores and for single scores as percent of patients per category. Change from baseline for each post-baseline assessment for each treatment arm will also be documented for the PRO-evaluable population among patients with a post-baseline assessment.

Analyses of PRO data will be performed in patients who have a valid baseline assessment.

6.4.3 Handling of Missing Data

For PFS, patients who are alive without a date of disease progression will be analyzed as censored observations on the date of the last tumor assessment. If no post-baseline tumor assessment is available, PFS will be censored at the date of randomization plus 1 day. In the analysis of PFS for U.S. registration purposes, data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits (see Section 6.4.1).

For OS, patients who are not reported as having died will be analyzed as censored observations on the date they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization plus 1 day.

For objective response, patients without any post-baseline assessment will be considered non-responders.

For DOR, data for patients who have not progressed and who have not died at the time of analysis will be censored at the time of the last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR plus 1 day.

For TTD with use of the EORTC, patients who have not deteriorated at the time of analysis will be censored at the last time they completed an assessment. If no post-baseline assessment is performed, patients will be censored at the randomization date plus 1 day.

6.5 SAFETY ANALYSES

Safety analyses will be performed on the safety-evaluable population, which is defined as all randomized patients who receive any amount of any component of study treatments. Patients will be summarized according to the treatment actually received. Patients will be allocated according to whether any full or partial dose of atezolizumab was received. Specifically, for patients randomized to the placebo arm, if atezolizumab was received by mistake, patients will be grouped under the atezolizumab plus chemotherapy arm in the safety analyses.

For the analyses of safety, data from patients enrolled before and after Protocol WO30070, Version 3 will be pooled by treatment arm. In addition, safety data will be analyzed in subgroups by investigator choice of chemotherapy.

Exposure to study treatment will be summarized to include treatment duration, number of doses, and dose intensity.

Verbatim description of adverse events will be summarized by mapped term, appropriate thesaurus level, and graded according to NCI CTCAE v4.0. All adverse events occurring during or after the first study-drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, Grade ≥ 3 adverse events, adverse events of special interest, adverse events leading to treatment discontinuation, and adverse events leading to treatment interruption will be summarized. Multiple occurrences of the same event will be counted once at the maximum severity.

Selected laboratory data will be summarized by treatment arm and grade.

Changes in selected vital signs will be summarized by treatment arm.

Deaths and causes of death reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation will be summarized by treatment arm.

6.6 PHARMACOKINETIC ANALYSES

PK samples will be collected in this study as outlined in Appendix 2. Atezolizumab serum concentration data ([C_{min}] and [C_{max}]) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, and SDs, as appropriate.

Additional PK analyses will be conducted as appropriate.

6.7 EXPLORATORY ANALYSES

6.7.1 Disease Control Rate by Investigator Assessment per RECIST v1.1

The DCR is defined as the rate of patients with confirmed CR or PR as best response or stable disease maintained for ≥ 6 months per RECIST v1.1.

The methodologies outlined for the ORR analysis will be used for the DCR analysis based on investigator assessment.

6.7.2 Exploratory Analyses of Progression-Free Survival

6.7.2.1 Non-Protocol Therapy

The impact of non-protocol therapy on INV-PFS and IRF-PFS will be assessed depending on the number of patients who receive non-protocol therapy before a PFS event. If > 5% of patients received non-protocol therapy before a PFS event in any treatment arm, a sensitivity analysis will be performed for the comparisons between treatment arms in which patients who receive non-protocol therapy before a PFS event will be censored at the last tumor assessment date before receipt of non-protocol therapy.

6.7.2.2 Subgroup Analysis

To assess the consistency of the study results in subgroups defined by demographics (e.g., age, sex, and race/ethnicity), baseline characteristics (e.g., ECOG performance status, hemoglobin, time from prior chemotherapy) and stratification factors (Bajorin model risk factor score/liver metastasis; investigator choice of chemotherapy, and PD-L1 IHC IC status), the duration of PFS in these subgroups will be examined. Summaries of PFS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median PFS, will be produced separately for each level of the categorical variables.

6.7.3 Exploratory Analyses of Overall Survival

6.7.3.1 Subsequent Anti-Cancer Therapy

A sensitivity analysis may be performed to examine the impact of subsequent anti-cancer therapy on the comparison of OS between treatment arms. The methodology for this sensitivity analysis will be specified in the SAP.

6.7.3.2 Loss to Follow-Up

The impact of loss to follow-up on OS will be assessed depending on the number of patients who are lost to follow-up. If >5% of patients are lost to follow-up for OS in any treatment arm, a sensitivity analysis will be performed for the comparisons between treatment arms in which patients who are lost to follow-up will be considered as having died at the last date they were known to be alive.

6.7.3.3 Subgroup Analysis

To assess the consistency of the study results in subgroups defined by demographics (e.g., age, sex, and race/ethnicity), baseline characteristics (e.g., ECOG performance status, hemoglobin, time from prior chemotherapy) and stratification factors (Bajorin model risk factor score/liver metastasis; investigator choice of chemotherapy and PD-L1 IHC status), OS in these subgroups will be examined. Summaries of OS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median survival time, will be produced separately for each level of the categorical variables.

6.7.4 Exploratory Subgroup Analysis in Patients with a PD-L1 status of IC0 or IC1 Randomized to Arm B after Protocol WO30070, Version 6

Efficacy data for patients with a PD-L1 status of IC0 or IC1 randomized to Arm B after implementation of the iDMC recommendation of Protocol WO30070, Version 6 will not be included in any formal efficacy analyses; instead, descriptive summaries of efficacy results will be provided for this group of patients.

6.7.5 Exploratory Biomarker Analysis

Exploratory biomarker analyses will be performed in an effort to better understand the association of these markers with study-drug response, including efficacy and/or adverse events. The tumor biomarkers include but are not limited to PD-L1 and CD8, as defined by IHC, qRT-PCR, or other methods. Additional pharmacodynamic analyses will be conducted as appropriate.

6.7.6 Exploratory Analyses using the EQ-5D-5L

Health states will be defined for each patient at each timepoint according to Euro QoL instructions. A total of 3125 possible health states could be defined. The health states, defined by the EQ-5D-5L descriptive system, will then be converted into a single index value. The index values, presented in country specific value sets, are a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years that are used to inform economic evaluations of healthcare interventions.

Note that these exploratory analyses will not be included in the CSR.

6.8 INTERIM ANALYSES

6.8.1 Planned Interim Analyses

There are no interim analyses planned for PFS in this study.

A total of three efficacy analyses of OS are planned (two interim analyses and the final analysis). The final analysis of OS in Arm A versus Arm C will be performed when approximately 667 OS events in Arm A and Arm C of the ITT population have occurred. Based on observed survival up to the final PFS/interim OS analysis, the required number of events is projected to occur at Month 55 from the time the first patient was randomized.

The interim and final analyses of OS in Arms A versus C and Arms B versus C will be performed according to the analysis hierarchy described in Section 6.1.1.

The first interim OS analysis will be conducted by the Sponsor at the time of the final PFS analysis.

The second interim OS analysis will take place after approximately 12 months of additional follow-up compared with the clinical cut-off date for the primary analysis, or when at least 579 patients (68%) have died in Arm A and C, whichever is later.

Because the patient populations enrolled during Stage 1 and Stage 2 are considered independent, standard methods of group sequential designs apply.

If the required number of OS events in Arm B versus Arm C has not been reached at the time of the second interim or final OS analysis in Arm A versus Arm C, then two further interim analyses for the comparison of Arm B versus Arm C may be performed at the time of these analyses.

To control type I error for OS, the stopping boundaries for the OS interim and final analyses are to be computed for the appropriate alpha level (see Section 6.1.1) with use of the Lan-DeMets implementation of the O'Brien-Fleming use function.

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, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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

PRO data will be collected through the use of an electronic device provided by a vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records (21 CFR Part 11). Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

The 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. The 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. The 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 PATIENT-REPORTED OUTCOME DATA

Patients will use an electronic device to capture PRO data. The data will be transmitted to a centralized database maintained by the electronic device vendor.

Once the study is complete, the data, audit trail, and study and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

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

7.5 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.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data, 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.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

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 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 the last patient has completed 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 and IRB/EC. 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 229 sites globally will participate in the study, and approximately 1200 patients will be randomized.

Randomization will occur through an IxRS. Central facilities will be used for study assessments throughout the study (e.g., specified laboratory tests, and PK analyses). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be convened to evaluate safety data during the study according to policies and procedures detailed in an iDMC Charter.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a

journal manuscript reporting primary clinical study results within 6 months after the availability of the respective CSR. In addition, for all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

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

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

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

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

9.6 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).

10. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

Adashek ML, Feldman M. Cytokine release syndrome resulting from anti–programmed death-1 antibody: raising awareness among community oncologist. J Oncol Practice 2019;15:502–4.

American Cancer Society. Cancer Facts & Figures 2015. Accessed 20 January 2016. Available at http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf.

Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 2012;51:119–35.

Bajorin DF, Dodd PM, Mazumdar M, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 1999;17:3173–81.

Balar AV, Galsky MD, Loriot Y, et al. Atezolizumab (atezo) as first-line (1L) therapy in cisplatin-ineligible locally advanced/metastatic urothelial carcinoma (mUC): Primary analysis of IMvigor210 cohort 1 [abstract]. J Clin Oncol 2016;34:LBA4500a.

Bellmunt J, Mullane SA, Werner L, et al. Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma. Ann Oncol 2015;26:812.

Bellmunt J, Orsola A, Leow JJ, et al. ESMO Guidelines Working Group. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii40–8.

Bellmunt J, Theodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009;27:4454–61.

Bendell JC, Powderly JD, Lieu CH, et al. Safety and efficacy of MPDL3280A (anti-PDL1) in combination with bevacizumab (bev) and/or FOLFOX in patients (pts) with metastatic colorectal cancer (mCRC). J Clin Oncol 2015;33(Suppl 3):704a

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54:307–14.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739–45.

Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010;28:3167–75.

Bretz F, Maurer W, Brannath W, et al. A graphical approach to sequentially rejective multiple test procedures. Stat Med 2009;28:586–604.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29–41.

Burman CF, Sonesson C, Guilbaud O, et al. A recycling framework for the construction of bonferroni-based multiple tests. Stat Med 2009;28:739–61.

Butte MJ, Keir ME, Phamduy TB. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Chalasani V, Chin JL, Izawa JI. Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. Can Urol Assoc 2009;3:S193–8.

De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC Study 30986. J Clin Oncol 2012;30:191–9.

Dong H, Zhu G, Tamada K, et al. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. Nat Med 1999;5:1365–9.

Dreicer R, Hoffman-Censits JH, Flaig TW, et al. Updated efficacy and > 1-y follow up from IMvigor210: Atezolizumab (atezo) in platinum (plat) treated locally advanced/metastatic urothelial carcinoma (mUC) [abstract]. 2016 American Society of Clinical Oncology: abstract 4515.

European Association of Urology [EAU]. European Association of Urology guidelines (2014). Accessed on 25 Nov 2014 from http://www.uroweb.org/guidelines/online-guidelines/.

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

Eruslanov E, Neuberger M, Daurkin I, et al. Circulating and tumor-infiltrating myeloid cell subsets in patients with bladder cancer. Int J Cancer 2012;130(5):1109–19.

Fayers PM. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. Eur J Cancer 2001;37:1331–4.

Faraj SF, Munari E, Guner G, et al. Assessment of tumoral PD-L1 expression and intratumoral CD8+ T cells in urothelial carcinoma. Urology 2015;85:703.

Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Can 2015;136:E359–86.

Frebel H, Nindl V, Schuepbach RA, et al. Programmed death 1 protects from fatal circulatory failure during systemic virus infection of mice. J Exp Med 2012;209:2485–99.

Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. Lancet Oncol 2011;12:211–4.

Galsky MD, Sonpavde G. The effectiveness of chemotherapy in "real world" patients with metastatic bladder cancer. Presented at: 2015 European Cancer Congress; September 25-29, 2015; Vienna, Austria. Poster 2624.

Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti–PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014;515:563–7.

Hjermstad MJ, Fossa SD, Bjordal K, et al. Test/retest study of the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire. J Clin Oncol 1995;13:1249–54.

Hoffman-Censits JF, Grivas P, Van Der Heijden MS, et al. IMvigor210, a phase II trial of atezolizumab (MPDL3280A) in platinum-treated locally advanced or metastatic urothelial carcinoma (mUC). J Clin Oncol 2016;34 (suppl 2S; abstr 355).

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annual Rev Immunol 2008;26:677–704.

Kitano S, Postow MA, Ziegler CG, et al. Computational algorithm-driven evaluation of monocytic myeloid-derived suppressor cell frequency for prediction of clinical outcomes. Cancer Immuno Res 2014;2:812–21.

Ko HJ, Kim YJ, Kim YS, et al. A combination of chemoimmunotherapies can efficiently break self-tolerance and induce antitumore immunity in a tolerogenic murine tumor model. Cancer Res 2007;67;7477–86.

Koren E, Smith HW, Shores E, et al. Recommendations on risk-based strategies for detection and characterization of antibodies against biotechnology products. J Immunol Methods 2008;333:1–9.

Le HK, Graham L, Cha E, et al. Gemcitabine directly inhibits myeloid derived suppressor cells in BALB/c mice bearing 4T1 mammary carcinoma and augments expansion of T cells from tumor-bearing mice. Int Immunopharmacol 2009;9:900–9.

La Rosée P. Treatment of hemophagocytic lymphohistiocytosis in adults. Hematology Am Soc Hematol Educ Protram 2015;1:190–6.

La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465–77.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625–38.

Liu SV, Powderly JD, Camidge DR, et al. Safety and efficacy of MPDL3280A (anti-PDL1) in combination with platinum-based doublet chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). J Clin Oncol 2015;33:8030a.

Loehrer PJ Sr, Einhorn LH, Elson PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol 1992;10:1066–73.

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355–62.

Mu CY, Huang JA, Chen Y, et al. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. Med Oncol. 2011;28:682–8

Nakanishi J, Wada Y, Matsumoto K, et al. Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. Cancer Immunol Immunother 2007;56:1173–82.

National Comprehensive Cancer Network (NCCN). Bladder Cancer, Version 2(2015). http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed 30 March 2015.

[NCCN] National Comprehensive Cancer Network. Recommendations of the NCCN COVID-19 Vaccination Advisory Committee [resource on the Internet]. 2021 [cited: 28 May 2021]. Available from: https://www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v2-0.pdf?sfvrsn=b483da2b_2.

NCCN. Clinical Practice Guidelines in Oncology, Antiemesis, Version 1. 2013. Available at http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf.

Necchi A, Pond GR, Giannatempo P, et al. Cisplatin-based first-line therapy for advanced urothelial carcinoma after previous perioperative cisplatin-based chemotherapy. Clin Genitourinary Cancer 2015;13:178–84.

Osoba D, Aaronson N, Zee B, et al. Modification of the EORTC QLQ-C30 (Version 2.0) based on content validity and reliability testing in large samples of patients with cancer. The Study Group on Quality of Life of the EORTC and the Symptom Control and Quality of Life Committees of the NCI of Canada Clinical Trials Group. Qual Lif Res 1997;6:103–8.

Pal SK, Lin YI, Yuh B, et al. Conditional Survival in de novo metastatic urothelial carcinoma. PLoS ONE 2015;10: e0136622.

Powles T, Eder JP, Fine GD, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014;515:558–62.

Ramakrishnan R, Assudani D, Nagaraj S, et al. Chemotherapy enhances tumor cell susceptibility to CTL-mediated killing during cancer immunotherapy in mice. J Clin Invest 2010;120:1111–24.

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481–9.

Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323–35.

Rosenberg AS, Worobec AS. A risk-based approach to immunogenicity concerns of therapeutic protein products. BioPharm Intl 2004;17:34–42.

Rosenberg JE, Hoffmann-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platium-based chemotherapy: a single arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Rotz SJ, Leino D, Szabo S, et al. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. Pediatr Blood Cancer 2017;64:e26642.

Sawant A, Schafer CC, Jin TH, et al. Enhancement of antitumor immunity in lung cancer by targeting myeloid-derived suppressor cell pathways. Caner Res 2013;73:6609–20.

Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908–14.

Shevchenko I, Karakhanova S, Soltek S, et al. Low-dose gemcitabine depletes regulatory T cells and improves survival in the orthotopic Panc02 model of pancreatic cancer. Int J Cancer 2013;133:98–107.

[SITC] Society for Immunotherapy of Cancer. Society for Immunotherapy of Cancer statement on SARS-CoV-2 vaccination and cancer immunotherapy [resource on the Internet]. Press release: 23 December 2020 [cited: 28 May 2021]. Available from: https://www.sitcancer.org/aboutsitc/press-releases/2020/sitc-statement-sars-cov-2-vaccination-cancer-immunotherapy.

Sonpavde G, Galsky MD, Latini D, et al. Cisplatin-ineligible and chemotherapy-ineligible patients should be the focus of new drug development in patients with advanced bladder cancer. Clin Genitourin Cancer 2014;12:71–3.

Sternberg CN, Yagoda A, Scher HI, et al. Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. Cancer 1989;64:2448–58.

Sternberg CN, Yagoda A, Scher HI, et al. Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. J Urol 1985;133:403–7.

Sternberg CN, Donat SM, Bellmunt J, et al. Chemotherapy for bladder cancer: treatment guidelines for neoadjuvant chemotherapy, bladder preservation, adjuvant chemotherapy, and metastatic cancer. Urology 2007;69(1 Suppl):62–79.

Surveillance, Epidemiology, and End Results Program (SEER), 2015 http://seer.cancer.gov/statfacts/html/urinb.html: Accessed 13 September 2015.

Suzuki E, Kapoor V, Jassar AS, et al. Gemcitabine selectively eliminates splenic Gr-1+/CD11b+ myeloid suppressor cells in tumor-bearing animals and enhances antitumor immune acitivy. Clin Cancer Res 2005;11(18):6713–21.

Thompson RH, Boorjian SA, Kim SP, et al. Eligibility for neoadjuvant/adjuvant cisplatin-based chemotherapy among radical cystectomy patients. BJU Int 2014;113:E17–21.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012;366:2443–54.

von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23:4602–8.

Wassmer G. Planning and analyzing adaptive group sequential survival trials. Biom J 2006;48:714–29.

Weide B, Martens A, Zelba H, et al. Myeloid-derived suppressor cells predict survival of patients with advanced melanoma: comparison with regulatory T cells and NY-ESO-1 or melan-A-specific T cells. Clin Cancer Res 2014;20(6):1601–9.

Witjes JA, Comperat E, Cowan NC, et al. European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines.Eur Urol 2014;65:778–92.

Yang J, Riella LV, Chock S. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol 2011;187:1113–9.

Zhang J, Dickinson SI, Clark ND, et al. Expression of PD-L1 in primary urothelial carcinoma. J Clin Oncol 2013;31:4541.

Zitvogel L, Apetoh L, Ghiringhelli F, et al. Immunological aspects of cancer chemotherapy. Nat Rev Immunol 2008;8(1)59–73.

Appendix 1
Schedule of Assessments

Assessment Window (Days) [b]	Screening [a]		Treatment Cycles (Each cycle = 21 days)				Treat. Discon. (≤30 Days) [d]	90–Day Follow-Up [e]	Survival Follow-Up (~ 3 Months [±7] days) [f]
			Platinum/Gem + Atezolizumab or Platinum/Gem + Placebo			Atezolizumab/ Placebo Monotherapy			
	–28 to –1	–7 to –1	Day 1	Day 8 [c]	Day 15	Day 1			
Informed consent [a]	x								
Medical, surgical, and cancer histories, including demographic information [g]	x								x Cancer treatment
Age-adjusted Charlson comorbidity index	x								
HIV, HBV, HCV serology [h]	x								
TB test [i]	x								
Concomitant medications [j]	x		x			x	x	x	
Screening CT/MRI (chest/abdomen/pelvis/head) [k]	x								
Tumor assessment [l]	x		Every 9 weeks (±3 business days) for 54 weeks and every 12 weeks (±6 business days) thereafter until disease progression or loss of clinical benefit (see Section 4.6.2), death, or loss of follow-up						
Complete physical examination [m]	x						x		
Limited physical examination [n]			x [o]			x [o]		x	
ECOG performance status	x		x [o]			x [o]	x		
Vital signs [p]	x		x			x	x		
12-lead ECG [q]	x						x		
Echocardiogram [q]	x								

Appendix 1
Schedule of Assessments (cont.)

Assessment Window (Days) [b]	Screening [a]		Treatment Cycles (Each cycle = 21 days)				Treat. Discon. (≤ 30 Days) [d]	90 Day Follow-Up [e]	Survival Follow-Up (~ 3 Months [±7] days) [f]
			Platinum/Gem + Atezolizumab or Platinum/Gem + Placebo			Atezolizumab/ Placebo Monotherapy			
	–28 to –1	–7 to –1	Day 1	Day 8[c]	Day 15	Day 1			
Weight [r,s]	x		x				x		
Height	x								
Hematology [t]	x		x	x	x [t]	x	x	x	
Serum chemistry [u]	x		x			x	x	x	
Serum pregnancy test [v]		x	x [v]			x [v]	x [v]		
Coagulation panel (PTT/aPTT, INR)	x						x		
Urinalysis [w]	x		x			x	x	x	
TSH, free T3, free T4 [x]	x		x [x]			x [x]	x	x	
Serum ferritin	x		x [x]			x [x]	x	x	
Optional blood sample for RBR DNA [y]		x							
Blood samples for pharmacodynamics biomarkers [z]			x			x			
CRP		x [aa]	x [aa]			x [aa]	x		
Autoantibody testing	x		x [aa]			x [aa]	x		
Serum sample for PK sampling [bb]			x			x	x		x [z]
Serum sample for ATA [cc]			x [cc]			x [cc]	x		x [cc]
Assessment Window (Days) [b]	Screening [a]		Treatment Cycles (Each cycle = 21 days)						

Appendix 1
Schedule of Assessments (cont.)

	–28 to –1	–7 to –1	Platinum/Gem + Atezolizumab or Platinum/Gem + Placebo			Atezolizumab/ Placebo Monotherapy	Treat. Discon. (≤30 Days) [d]	90 Day Follow-Up [e]	Survival Follow-Up (~ 3 Months [±7] days) [f]
			Day 1	Day 8 [c]	Day 15	Day 1			
Archival and/or fresh FFPE tumor tissue specimen or 15 unstained slides for eligibility [dd]	x								
PROs (QLQ-C30 and EQ-5D-5L) [ee]			x			x	x		x
Fresh biopsy at the time of radiographic progression [ff]			x						
Optional RBR tumor biopsy samples [gg]			x						
Atezolizumab/placebo infusion [hh]			x			x			
Gemcitabine infusion [r]			x	x					
Carboplatin or cisplatin infusion [s]			x						
Adverse events [c]	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Assessments (cont.)

anti-HBc = antibody against hepatitis B core antigen; ATA = anti-therapeutic antibody; AUC = area under the concentration–time curve; CRP = C-reactive protein; discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC = European Organisation for Research and Treatment of Cancer; ePRO = electronic patient-reported outcome; EQ-5D-5L = Euro QoL 5-Dimensions 5-Level; FFPE = formalin fixed paraffin embedded; Gem = gemcitabine; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IGRA = interferon-gamma release assay; IV = intravenous; LVEF = left ventricular ejection fraction; PD = progressive disease; PD-L1 = programmed death-ligand 1; PK = pharmacokinetic; Platinum = cisplatin or carboplatin; PRO = patient-reported outcome; QLQ-C30 = Quality-of-life Questionnaire Core 30; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; TB = tuberculosis; TBNK = T, B, and natural killer; TSH = thyroid-stimulating hormone.

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

[a] Written informed consent is required for performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry (except where otherwise specified) may be used for screening assessments rather than repeating such tests. If re-screening is required, then HBV, HCV, HIV, CRP, and autoantibody testing from the initial screening may be acceptable for screening assessment if performed< 60 days from Cycle 1 Day 1.

[b] The first dosing day (Cycle 1, Day 1) should occur within 5 days from date of randomization. All visits and infusions may be administered with a window of ± 3 days, except for the Day 8 visit. Day 8 dose of gemcitabine may be given no earlier than Day 7 but may be given up to Day 11 (–1 to + 3) of a cycle. Blood counts for gemcitabine dosing should be obtained within 1 day prior to Day 1 and Day 8 of each cycle of therapy.

[c] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug or initiation of another anti-cancer therapy, whichever occurs first. All other adverse events 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. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-related procedures until a final outcome can be reported. During the chemotherapy plus atezolizumab/placebo period, adverse events are to be collected at Day 15 if a clinic visit is made.

[d] Patients will be asked to return to the clinic not more than 30 days after the last treatment for a treatment discontinuation visit.

[e] Window of ± 2 weeks is allowed for 90 Day Follow-Up visit. The 90-day follow-up visit should occur 90 days after the final dose of study drug or until the initiation of another anti-cancer therapy, whichever occurs first.

[f] Starting from the treatment discontinuation visit, survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 7 days) until death, loss to follow-up, or study termination by the Sponsor. All patients will be followed for survival and new anti-cancer therapy (including targeted therapy and immunotherapy) 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 the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

[g] Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Demographic information includes age, sex, and self-reported race/ethnicity. Reproductive status and smoking history should also be captured.

[h] All patients will be tested for HIV locally prior to the inclusion into the study, and HIV-positive patients will be excluded from the clinical study. HBsAg, anti-HBc antibody and anti-HBs antibody should be collected during screening and tested locally. In patients who have positive serology for the anti-HBc antibody, HBV DNA should be collected and tested prior to Cycle 1, Day 1.

[i] All patients will have tuberculin (PPD) skin test or IGRA performed locally prior to inclusion into the study, and patients with active TB will be excluded from the clinical study.

[j] 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 initiation of study drug should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

[k] All patients will have imaging during screening to establish measurable lesions per RECIST v1.1 Screening assessments must include CT scans (with oral or IV contrast unless contraindicated) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis and brain. In patients for whom CT scans with contrast are contraindicated (e.g., patients with contrast allergy or impaired renal clearance), MRIs of the chest, abdomen, and pelvis with a non-contrast spiral CT scan of the chest may be used. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. For further information see section 4.5.5.

Appendix 1
Schedule of Assessments (cont.)

[l] Tumor assessments performed as standard-of-care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. The same radiographic procedure must be used throughout the study for each patient. Results must be reviewed by the investigator before dosing at the next cycle. Tumor assessments will be performed at baseline, every 9 weeks (approximately every three cycles) following randomization for 54 weeks, and every 12 weeks thereafter, with additional scans as clinically indicated. Assessments will continue until disease progression per RECIST 1.1. or loss of clinical benefit (for patients who continue study treatment beyond initial radiographic disease progression; see Section 4.6.2 for details). Tumor assessments should continue regardless of whether patients start new anti-cancer therapy in the absence of disease progression unless they withdraw consent. Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity), should continue to undergo scheduled tumor assessments as if they were on the protocol schedule until the patient dies, experiences disease progression per RECIST v1.1, withdraws consent, or until the study closes, whichever occurs first. If an optional biopsy is to be performed at approximately the same timepoint of a tumor assessment or as a result of the radiographic determination (e.g., response or progression), samples should be acquired after all imaging scans have been performed, if at all possible. Investigators may perform additional scans or more-frequent assessments if clinically indicated. After the first five cycles, one of three cycles may be delayed by 1 week (28 days instead of 21 days for one cycle) to allow for vacations.

[m] Complete physical exam includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

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

[o] ECOG performance status, limited physical examination, local laboratory assessments, and CRP assessment may be obtained ≤ 96 hours before Day 1 of each cycle (note: CRP at Cycle 3 and every other cycle thereafter; see footnote x).

[p] Vital signs include heart rate, respiratory rate, blood pressures, and temperature. For the first atezolizumab infusion, the patient's vital signs should be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes and 2 hours (± 15 minutes) after the infusion. For subsequent atezolizumab infusions, vital signs will be collected within 60 minutes before the infusion. Vital signs need to be collected during the infusion and 30 (± 10) minutes after the infusion only if clinically

[q] Twelve-lead ECGs are required as part of the screening assessment, at the end of treatment visit, and when clinically indicated. ECGs will be reviewed by the investigator to determine patient eligibility at screening. Patients with a history of clinically significant cardiac disease (including anatomic abnormality, coronary disease, congestive heart failure, abnormal LVEF, arrhythmia, or abnormal ECG) will be required to undergo a screening echocardiogram. However, a baseline evaluation of LVEF should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease.

Appendix 1
Schedule of Assessments (cont.)

[r] Gemcitabine will be administered at a dose of 1000 mg/m2 by IV infusion on Day 1 and Day 8 of each 21-day cycle, until PD or unacceptable toxicity. Weight will be measured for dose calculations (baseline weight should be used to calculate dose unless there is a greater than 5% weight change). Day 8 gemcitabine should not be administered any earlier than Day 7, but can be administered up to Day 11. Dose modifications of gemcitabine for hematologic toxicity are allowed and will be based on blood counts obtained within 1 day prior to Day 1 and Day 8 of each cycle of therapy.

[s] For patients receiving carboplatin-based chemotherapy: carboplatin will be administered at AUC 4.5 by IV infusion on Day 1 of each 21-day cycle, until PD or unacceptable toxicity. If institutional guidelines conflict with protocol carboplatin dosing, carboplatin may be administered at a maximum starting dose of AUC of 5. Weight will be measured for dose calculations (baseline weight should be used to calculate dose unless there is a greater than 5% weight change). For patients receiving cisplatin-based chemotherapy: Cisplatin will be administered at a dose of 70 mg/m2 by IV infusion on Day 1 of each 21-day cycle, until PD or unacceptable toxicity. Weight will be measured for dose calculations (baseline weight should be used to calculate dose unless there is a greater than 5% weight change).

[t] 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. During chemotherapy plus atezolizumab/placebo the assessment at Day 15 is required at C1 and C2, thereafter at investigator discretion.

[u] Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, total protein, and albumin. In countries where serum bicarbonate is not considered a standard chemistry measurement (e.g., Japan), serum bicarbonate is not required as a laboratory study in the screening or on-study serum measurements.

[v] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to Cycle 1, Day 1, every two cycles during the study treatment, and as clinically indicated thereafter. In countries where urine pregnancy testing is considered a standard, urine pregnancy testing may substitute for serum pregnancy testing.

[w] Urine dipstick includes specific gravity, pH, glucose, protein, ketones, and blood. Urine dipstick and 24-hr urine collection may be performed up to 7 days before Cycle 1, Day 1. Screening urine tests performed up to 7 days before Cycle 1, Day 1 do not need to be repeated for Cycle 1. Indicated Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

[x] TSH, free T3, free T4, and serum ferritin should be evaluated every two cycles (starting at Cycle 2).

[y] Blood for DNA isolation will be collected from patients who have consented to optional RBR sampling at baseline, after the patient is randomized to the study but before study treatment. If, however, the RBR 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.

[z] See Appendix 2 for details of the pharmacodynamic sampling schedule.

Appendix 1
Schedule of Assessments (cont.)

[aa] Includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody. Baseline auto-antibody testing to be collected at screening or on Cycle 1, Day 1 prior to the first dose of study drug. If re-screening is required, auto-antibody testing may be performed within 60 days prior to Cycle 1, Day 1. Baseline CRP testing can be collected up to 7 days prior to Cycle 1, Day 1. CRP and autoantibody testing to be performed on Day 1 of Cycle 3 and every other cycle thereafter.

[bb] See Appendix 2 for details of the PK sampling schedule.

[cc] See Appendix 2 for details of the ATA sampling schedule.

[dd] 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, bone metastases, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation. After signing the Informed Consent Form, retrieval and submission of archival tumor sample can occur outside the 28-day screening period.

[ee] The PRO questionnaires (QLQ-C30 and EQ-5D-5L) will be completed by patients on Day 1 of each cycle and at the end-of-treatment visit and will also be completed by patients at any visits after disease progression and/or when OS is evaluated *up until the fourth survival follow-up visit. Completion of the PRO questionnaires will be discontinued after the final OS analysis*. All PRO questionnaires are required to be completed prior to the administration of study treatment and/or prior to any other study assessment(s) to ensure that the validity of the instruments is not compromised and to ensure that data quality meets regulatory requirements.

[ff] Tumor specimens are required at the time of disease progression per RECIST v1.1, unless the location of the tumor renders the biopsy medically unsafe or infeasible per investigator decision. *Collection of tumor biopsy samples will be discontinued after the final OS analysis*. Tumor biopsy samples will be collected by core needle or excisional/punch biopsy if deemed feasible per investigator discretion. Preferably, growing lesions should be selected.

[gg] Optional tumor biopsies may be obtained at other timepoints at the investigator's discretion if patient has provided RBR consent. *Collection of tumor biopsy samples will be discontinued after the final OS analysis.* Tumor biopsy samples will be collected by core needle or excisional/punch biopsy if deemed feasible per investigator discretion. Preferably, growing lesions should be selected.

[hh] The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes.

[ii] Day 8 visit not required once gemcitabine dosing has been discontinued or if gemcitabine is not being administered for that particular cycle.

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Visit	Timepoint	Sample Type
Cycle 1, Day 1	Predose	Serum atezolizumab ATA Serum atezolizumab pharmacokinetics Plasma PD biomarker Serum PD biomarker Blood PBMC
	30 (±10) minutes after end of atezolizumab infusion	Serum atezolizumab pharmacokinetics
Cycle 3, Day 1	Predose	Plasma PD biomarker Serum PD biomarker Blood PBMC
Cycles 2, 3, and 4, Day 1	Predose	Serum atezolizumab ATA Serum atezolizumab pharmacokinetics
Cycle 8, and every eighth cycle thereafter, Day 1	Predose	Serum atezolizumab ATA Serum atezolizumab pharmacokinetics
Radiographic Progression	At Visit	Plasma PD biomarker Serum PD biomarker
Treatment discontinuation visit [a]	At visit	Serum atezolizumab ATA Serum atezolizumab pharmacokinetics
120 (±30) days after last dose of atezolizumab/placebo	At visit	Serum atezolizumab ATA Serum atezolizumab pharmacokinetics

ATA = anti-therapeutic antibody; NA = not applicable; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic.

Notes: Except for Day 1 of Cycle 1, all other predose visits and assessments during the treatment period should be performed within –3 days of the scheduled date.

Collection of all Pharmacokinetic, Immunogenicity, and Biomarker Samples will be discontinued after the final OS analysis.

[a] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit 30 days after the last dose of study drug.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication

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

MEASURABILITY OF TUMOR AT BASELINE

Definitions. At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable Tumor Lesions

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

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

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

Non-Measurable Tumor Lesions

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

---

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

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

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

Special Considerations Regarding Lesion Measurability

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

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

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

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of Lesions

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

Method of Assessment

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

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

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

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

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

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

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

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

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

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

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

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

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

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

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

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

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

RESPONSE CRITERIA

Evaluation of Target Lesions

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

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

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

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

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

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

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

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

Special Notes on the Assessment of Target Lesions

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

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

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

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

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

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

Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

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

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

Special Notes on Assessment of Progression of Non-Target Disease

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

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

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

New Lesions

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

Note: On the basis of atezolizumab treatment experience, new lesions in the setting of shrinking target lesions can frequently be transient in their appearance and/or growth and may be due to an active immune response at the lesion site. Investigators are encouraged to further assess whether these lesions truly represent disease progression through biopsy, subsequent radiographic assessment, or other methods.

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

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

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

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

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

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 Timepoint Response: Patients with Target Lesions (With or Without Non-Target Lesions)

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

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

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

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

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

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

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

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen

in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

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

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

Table 3 Best Overall Response When Confirmation Is Required

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

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

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

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

Special Notes on Response Assessment

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

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective

progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables: Table 1, Table 2, and Table 3.

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

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

Appendix 4
European Organisation for Research and Treatment of Cancer QLQ-C30

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

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

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

Please go on to the next page

Appendix 4
European Organisation for Research and Treatment of Cancer QLQ-C30 (cont.)

ENGLISH

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 5
Euro QoL EQ-5D-5L

Health Questionnaire

English version for the USA

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

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 ❑

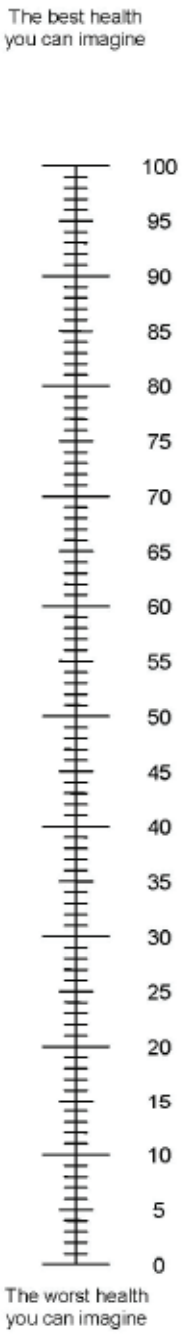
ANXIETY / DEPRESSION

- 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 5
Euro QoL EQ-5D-5L (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 6
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 7
Anaphylaxis Precautions

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

EQUIPMENT NEEDED

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

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

PROCEDURES

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

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

Appendix 8
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 listed in the table below are excluded from participating in the study (see Section 4.1.2.3 for specific exceptions). Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction *or pericardial disorder* while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Appendix 8
Preexisting Autoimmune Diseases (cont.)

Autoimmune Diseases and Immune Deficiencies

Acute disseminated encephalomyelitis	Interstitial cystitis
Addison's disease	Kawasaki's disease
Ankylosing spondylitis	Lambert-Eaton myasthenia syndrome
Antiphospholipid antibody syndrome	Lupus erythematosus
Aplastic anemia	Lyme disease - chronic
Autoimmune hemolytic anemia	Meniere's syndrome
Autoimmune hepatitis	Mooren's ulcer
Autoimmune hypoparathyroidism	Morphea
Autoimmune hypophysitis	Multiple sclerosis
Autoimmune myelitis	Myasthenia gravis Neuromyotonia
Autoimmune myocarditis	Opsoclonus myoclonus syndrome
Autoimmune oophoritis	Optic neuritis
Autoimmune orchitis	Ord's thyroiditis
Autoimmune thrombocytopenic purpura	Pemphigus
Behcet's disease	Pernicious anemia
Bullous pemphigold	Polyarteritis nodusa
Chronic fatigue syndrome	Polyarthritis
Chronic inflammatory demyelinating polyneuropathy	Polyglandular autoimmune syndrome
Chung-Strauss syndrome	Primary biliary cholangitis
Crohn's disease	Psoriasis
Dermatomyositis	Reiter's syndrome
Diabetes mellitus type 1	Rheumatoid arthritis
Dysautonomia	Sarcoidosis
Epidermolysis bullosa acquista	Scleroderma
Gestational pemphigoid	Sjögren's syndrome
Giant cell arteritis	Stiff-Person syndrome
Goodpasture's syndrome	Takayasu's arteritis
Graves' disease	Ulcerative colitis
Guillain-Barré syndrome	Vitiligo
Hashimoto's disease	Vogt-Kovanagi-Harada disease
IgA nephropathy	*Granulomatosis with polyangiitis*
Inflammatory bowel disease	

Appendix 9
Age-Adjusted Charlson Comorbidity Index

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 (zero if 40 or less)

Age-Adjusted Charlson Comorbidity Index scores will be calculated by the method previously reported by Charlson et al. [1] in which comorbid conditions are weighted and scored, with additional points added for age.

REFERENCE

[1] 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):373–83.

Signature Page for Protocol - WO30070 - TECENTRIQ - v11 - Global/Core - Publishe
System identifier: RIM-CLIN-461737

Approval Task	[redacted] Company Signatory 17-Dec-2022 02:07:26 GMT+0000