

Official Title: A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) COMPARED WITH CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC UROTHELIAL BLADDER CANCER AFTER FAILURE WITH PLATINUM CONTAINING CHEMOTHERAPY

NCT Number: NCT02302807

Document Dates: Protocol Amendment/Version 8: 01-Mar-2018

SAP Version 1: 03-Aug-2016

A PROTOCOL

TITLE: A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) COMPARED WITH CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC UROTHELIAL BLADDER CANCER AFTER FAILURE WITH PLATINUM-CONTAINING CHEMOTHERAPY

PROTOCOL NUMBER: GO29294

VERSION NUMBER: 8

EUDRACT NUMBER: 2014-003231-19

IND NUMBER: 120827

TEST PRODUCT: Atezolizumab (RO5541267)

MEDICAL MONITOR: [REDACTED], M.D.

SPONSOR: F. Hoffmann-La Roche Ltd

DATE FINAL: Version 1: 5 September 2014

DATES AMENDED: Version 2: 14 January 2015

Version 3: 26 March 2015

Version 4: 21 September 2015

Version 5: 8 March 2016

Version 6: 21 June 2016

Version 7: 28 October 2016

Version 8: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name

[REDACTED]

Title

[REDACTED]

Date and Time (UTC)

01-Mar-2018 22:03:46

CONFIDENTIAL

This clinical study is being sponsored globally by F. Hoffmann-La Roche Ltd of Basel, Switzerland. However, it may be implemented in individual countries by Roche's local affiliates, including Genentech, Inc. in the United States. The information contained in this document, especially any unpublished data, is the property of F. Hoffmann-La Roche Ltd (or under its control) and therefore is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from Roche except to the extent necessary to obtain informed consent from persons to whom the drug may be administered.

PROTOCOL AMENDMENT, VERSION 8: RATIONALE

Protocol GO29294 has been amended to comply with the [REDACTED] requirement to include guidelines on the management of atezolizumab specific adverse events which are also included in the Atezolizumab Investigator's Brochure. The resulting changes are summarized below:

- Section 5.1.1 has been amended to align with current atezolizumab risk language.
- Information regarding management of atezolizumab-specific adverse events has been added to Appendix 9. Appendix 9 has been added. (Sections 4.3.2.1, 4.4.1, 4.5.7.5, 5.1, 5.1.4, and 5.1.5)

Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

PROTOCOL AMENDMENT ACCEPTANCE FORM	12
PROTOCOL SYNOPSIS	13
1. BACKGROUND	28
1.1 Background on Urothelial Bladder Cancer.....	28
1.1.1 First-Line Treatment for Urothelial Bladder Cancer	28
1.1.2 Second-Line Treatment for Urothelial Bladder Cancer	30
1.1.3 Targeted Therapy for Urothelial Bladder Cancer	32
1.2 Background on Atezolizumab	32
1.2.1 Summary of Nonclinical Studies	32
1.2.2 Clinical Experience with Atezolizumab	33
1.2.2.1 Ongoing Clinical Studies.....	33
1.2.2.2 Clinical Safety	34
1.2.2.3 Clinical Activity.....	35
1.2.2.4 Clinical Pharmacokinetics and Immunogenicity	37
1.3 Study Rationale and Benefit-Risk Assessment.....	38
2. OBJECTIVES.....	40
2.1 Efficacy Objectives	40
2.1.1 Primary Efficacy Objective	40
2.1.2 Secondary Efficacy Objectives	40
2.2 Safety Objectives.....	40
2.3 Pharmacokinetic Objective	40
2.4 Patient-Reported Outcome Objective	41
2.5 Exploratory Objectives.....	41
3. STUDY DESIGN	41
3.1 Description of Study	41
3.1.1 Independent Data Monitoring Committee	45
3.2 End of Study	45
3.3 Rationale for Study Design	45
3.3.1 Rationale for Study Design	45

3.3.2	Rationale for Primary and Secondary Endpoints	45
3.3.3	Rationale for Inclusion of All Patients (All Levels of PD-L1 Expression by Immunohistochemistry) in the Study.....	46
3.3.4	Rationale for Testing Atezolizumab in Patients with UBC Who Have Failed Prior Platinum Therapy	46
3.3.5	Rationale for Control Arm Therapy	47
3.3.5.1	Vinflunine.....	47
3.3.5.2	Paclitaxel or Docetaxel	47
3.3.6	Rationale for Stratification Factors.....	47
3.3.7	Rationale for Atezolizumab Dosage	48
3.3.8	Rationale for Collection of Archival and/or Pre-Treatment Tumor Specimens	49
3.3.9	Rationale for Blood Sampling for Biomarkers and for Collection of Optional Tumor Specimens	50
3.3.10	Rationale for Patient-Reported Outcome Assessments	50
3.3.11	Rationale for Allowing Patients to Continue Atezolizumab Treatment beyond Initial Progression per RECIST v1.1	50
3.4	Outcome Measures	51
3.4.1	Efficacy Outcome Measures.....	51
3.4.1.1	Primary Efficacy Outcome Measure	51
3.4.1.2	Secondary Efficacy Outcome Measures.....	51
3.4.2	Safety Outcome Measures	51
3.4.3	Pharmacokinetic Outcome Measures.....	51
3.4.4	Patient-Reported Outcome Measure	52
3.4.5	Exploratory Outcome Measures	52
4.	MATERIALS AND METHODS	52
4.1	Patients.....	52
4.1.1	Inclusion Criteria.....	52
4.1.2	Exclusion Criteria.....	56
4.1.2.1	Cancer-Specific Exclusions	56
4.1.2.2	General Medical Exclusions	58

4.1.2.3	Exclusion Criteria Related to Paclitaxel	58
4.1.2.4	Exclusion Criteria Related to Docetaxel	58
4.1.2.5	Exclusion Criteria Related to Vinflunine.....	59
4.1.2.6	Exclusion Criteria Related to Atezolizumab	59
4.2	Method of Treatment Assignment and Blinding	61
4.3	Study Treatment.....	61
4.3.1	Formulation, Packaging, and Handling.....	61
4.3.1.1	Atezolizumab	61
4.3.1.2	Vinflunine, Paclitaxel, and Docetaxel.....	62
4.3.2	Dosage, Administration, and Compliance.....	62
4.3.2.1	Atezolizumab	62
4.3.2.2	Paclitaxel	63
4.3.2.3	Docetaxel.....	63
4.3.2.4	Vinflunine.....	63
4.3.3	Investigational Medicinal Product Accountability	64
4.3.4	Post-Trial Access to Atezolizumab	64
4.4	Concomitant Therapy	65
4.4.1	Permitted Therapy	65
4.4.2	Excluded Therapy.....	66
4.4.2.1	Excluded and Cautionary Therapy for Atezolizumab-Treated Patients.....	66
4.4.3	Concomitant Medications with Paclitaxel.....	67
4.4.4	Concomitant Medications with Docetaxel	68
4.4.5	Concomitant Medications with Vinflunine	68
4.5	Study Assessments	68
4.5.1	Informed Consent Forms and Screening Log	69
4.5.2	Description of Study Assessments	69
4.5.2.1	Medical History and Demographic Data	69
4.5.2.2	Physical Examinations.....	69
4.5.2.3	Vital Signs.....	69
4.5.2.4	Tumor and Response Evaluations.....	70
4.5.2.5	Laboratory, Biomarker, and Other Biological Samples.....	71

4.5.3	Anti-Therapeutic Antibody Testing (Atezolizumab-Treated Patients Only)	74
4.5.4	Cardiac and Pulmonary Function Tests	74
4.5.4.1	Electrocardiograms	74
4.5.5	Patient-Reported Outcomes	75
4.5.6	Optional Biopsies and Samples for RCR (Optional Future Research)	76
4.5.6.1	Overview of the Roche Clinical Repository	76
4.5.6.2	Approval by the Institutional Review Board or Ethics Committee	76
4.5.6.3	Optional Samples for Roche Clinical Repository	76
4.5.6.4	Confidentiality	77
4.5.6.5	Consent to Participate in the Roche Clinical Repository	78
4.5.6.6	Withdrawal from the Roche Clinical Repository	78
4.5.6.7	Monitoring and Oversight	79
4.5.7	Timing of Study Assessments	79
4.5.7.1	Screening and Pre-Treatment Assessments	79
4.5.7.2	Assessments during Treatment	79
4.5.7.3	Assessments at Treatment Discontinuation Visit	80
4.5.7.4	Follow-Up Assessments	80
4.5.7.5	Adverse Events	81
4.5.7.6	Anti-Therapeutic Antibody and Pharmacokinetic Assessments	81
4.5.7.7	Survival and Subsequent Anti-Cancer Therapy	81
4.6	Patient, Study, and Site Discontinuation	81
4.6.1	Patient Discontinuation	81
4.6.1.1	Discontinuation from Study Drug	82
4.6.2	Study and Site Discontinuation	83
5.	ASSESSMENT OF SAFETY	84
5.1	Safety Plan	84
5.1.1	Risks Associated with Atezolizumab	84
5.1.2	Risks Associated with Vinflunine, Paclitaxel, and Docetaxel	84

5.1.3	General Plan to Manage Safety Concerns	85
5.1.3.1	Eligibility Criteria	85
5.1.3.2	Monitoring	85
5.1.4	Atezolizumab Dose Modification.....	85
5.1.5	Management of Atezolizumab-Specific Adverse Events.....	86
5.1.5.1	Systemic Immune Activation.....	87
5.1.6	Paclitaxel Dose Modification and Management of Specific Adverse Events	87
5.1.7	Docetaxel Dose Modification and Management of Specific Adverse Events	88
5.1.7.1	Other Specific Toxicities Not Requiring Dose Adjustment.....	89
5.1.8	Vinflunine Dose Modification and Management of Specific Adverse Events	90
5.2	Safety Parameters and Definitions	93
5.2.1	Adverse Events	93
5.2.2	Serious Adverse Events (Immediately Reportable to the Sponsor).....	93
5.2.3	Adverse Events of Special Interest (Immediately Reportable to the Sponsor).....	94
5.3	Methods and Timing for Capturing and Assessing Safety Parameters.....	95
5.3.1	Adverse Event Reporting Period	95
5.3.2	Eliciting Adverse Event Information	96
5.3.3	Assessment of Severity of Adverse Events	96
5.3.4	Assessment of Causality of Adverse Events	96
5.3.5	Procedures for Recording Adverse Events.....	97
5.3.5.1	Diagnosis versus Signs and Symptoms.....	97
5.3.5.2	Adverse Events Occurring Secondary to Other Events.....	97
5.3.5.3	Persistent or Recurrent Adverse Events.....	98
5.3.5.4	Abnormal Laboratory Values	98
5.3.5.5	Abnormal Vital Sign Values	99
5.3.5.6	Deaths	99
5.3.5.7	Preexisting Medical Conditions.....	100

5.3.5.8	Worsening of Urothelial Bladder Cancer.....	100
5.3.5.9	Hospitalization or Prolonged Hospitalization.....	100
5.3.5.10	Adverse Events Associated with an Overdoses or Error in Drug Administration	101
5.3.5.11	Patient-Reported Outcome Data	101
5.4	Immediate Reporting Requirements from Investigator to Sponsor.....	101
5.4.1	Emergency Medical Contacts	102
5.4.2	Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest.....	102
5.4.2.1	Events that Occur prior to Study Drug Initiation.....	102
5.4.2.2	Events that Occur after Study Drug Initiation.....	103
5.4.3	Reporting Requirements for Pregnancies.....	103
5.4.3.1	Pregnancies in Female Patients	103
5.4.3.2	Pregnancies in Female Partners of Male Patients.....	104
5.4.3.3	Abortions	104
5.4.3.4	Congenital Anomalies/Birth Defects	104
5.5	Follow-Up of Patients after Adverse Events	104
5.5.1	Investigator Follow-Up.....	104
5.5.2	Sponsor Follow-Up	105
5.6	Adverse Events that Occur After the Adverse Event Reporting Period.....	105
5.7	Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees.....	105
6.	STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN.....	106
6.1	Determination of Sample Size	106
6.2	Analyses Timing	107
6.3	Summaries of Conduct of Study	107
6.4	Summaries of Treatment Group Comparability	107
6.5	Efficacy Analyses	107
6.5.1	Primary Efficacy Endpoint.....	107
6.5.2	Secondary Efficacy Endpoints.....	108
6.5.2.1	Objective Response Rate.....	109

6.5.2.2	Progression-Free Survival	109
6.5.2.3	Duration of Objective Response	109
6.5.3	Handling of Missing Data.....	110
6.6	Safety Analyses	110
6.7	Pharmacokinetic Analyses.....	111
6.8	Outcome Analyses	111
6.9	Exploratory Analyses	112
6.10	Sensitivity Analyses	112
6.10.1	Loss to Follow-Up	112
6.10.2	Subsequent Anti-Cancer Therapy	113
6.11	Subgroup Analysis.....	113
6.12	Interim Analyses	113
7.	DATA COLLECTION AND MANAGEMENT	113
7.1	Data Quality Assurance	113
7.2	Electronic Case Report Forms.....	114
7.3	Source Data Documentation.....	114
7.4	Use of Computerized Systems	114
7.5	Retention of Records	115
8.	ETHICAL CONSIDERATIONS.....	115
8.1	Compliance with Laws and Regulations	115
8.2	Informed Consent	115
8.3	Institutional Review Board or Ethics Committee	116
8.4	Confidentiality	117
8.5	Financial Disclosure	117
9.	STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION	117
9.1	Study Documentation	117
9.2	Protocol Deviations.....	118
9.3	Site Inspections	118
9.4	Administrative Structure.....	118
9.5	Publication of Data and Protection of Trade Secrets	118
9.6	Protocol Amendment Sections	119

10. REFERENCES	120
----------------------	-----

LIST OF TABLES

Table 1	Randomized Phase III Trials in Previously Untreated Patients.....	30
Table 2	Randomized Phase II Trials of Second-Line Therapy.....	31
Table 3	Efficacy-Evaluable Patients with UBC Dosed by 20 November 2013 in Study PCD4989g: ORR per RECIST v1.1 by PD-L1 Tumor Expression	37
Table 4	Dose Levels for Paclitaxel.....	88
Table 5	Guidelines for Management of Specific Docetaxel-Related Adverse Events.....	88
Table 6	Guidelines for Management of Hepatotoxicity in Docetaxel-Treated Patients.....	89
Table 7	Guidelines for the Management of Edema in Docetaxel-Treated Patients.....	90
Table 8	Dose Delay Guidelines for Vinflunine.....	90
Table 9	Dose Modification Guidelines for Vinflunine.....	91
Table 10	Dose Modification Guidelines for Vinflunine in Patients with Renal Impairment or Elderly Patients.....	92
Table 11	Adverse Event Severity Grading Scale	96

LIST OF FIGURES

Figure 1	Study Schema.....	42
Figure 2	Conditions for Continuing Atezolizumab in the Presence of Increased Radiographic Tumor Size.....	83

LIST OF APPENDICES

Appendix 1	Schedule of Assessments.....	125
Appendix 2	Anti-Therapeutic Antibody, Pharmacodynamic, and Pharmacokinetic Sampling Schedule.....	132
Appendix 3	Modified Response Evaluation Criteria in Solid Tumors	133
Appendix 4	Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication.....	141
Appendix 5	Patient-Reported Outcomes Instruments.....	153
Appendix 6	Preexisting Autoimmune Diseases	157

Appendix 7	Anaphylaxis Precautions.....	158
Appendix 8	Eastern Cooperative Oncology Group Performance Status Scale	159
<i>Appendix 9</i>	<i>Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab</i>	<i>160</i>

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE: A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) COMPARED WITH CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC UROTHELIAL BLADDER CANCER AFTER FAILURE WITH PLATINUM-CONTAINING CHEMOTHERAPY

PROTOCOL NUMBER: GO29294

VERSION NUMBER: 8

EUDRACT NUMBER: 2014-003231-19

IND NUMBER: 120827

TEST PRODUCT: Atezolizumab (RO5541267)

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 of this form to the Sponsors or their designee. Contact details will be provided to the investigator prior to study start.

PROTOCOL SYNOPSIS

TITLE: A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) COMPARED WITH CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC UROTHELIAL BLADDER CANCER AFTER FAILURE WITH PLATINUM-CONTAINING CHEMOTHERAPY

PROTOCOL NUMBER: GO29294

VERSION NUMBER: 8

EUDRACT NUMBER: 2014-003231-19

IND NUMBER: 120827

TEST PRODUCT: Atezolizumab (RO5541267)

PHASE: III

INDICATION: Urothelial bladder cancer

SPONSOR: F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

For the primary and secondary efficacy objectives, a comparison of the treatment arms will be performed in different patient subpopulations according to tumor PD-L1 expression as evaluated by immunohistochemistry (IHC). The IHC scores will have three categories (IC0, IC1, and IC2/3), which will also be used for stratification (IHC score of IC0/1 vs. IHC score of IC2/3).

Primary Efficacy Objective

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of atezolizumab treatment compared with chemotherapy treatment with respect to overall survival (OS) in patients with locally advanced or metastatic urothelial bladder cancer (UBC) who have progressed during or following a platinum-containing regimen

Secondary Efficacy Objectives

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab compared with chemotherapy with respect to anti-tumor effects as measured by objective response rate (ORR) per investigator with use of Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
- To evaluate the efficacy of atezolizumab compared with chemotherapy with respect to anti-tumor effects as measured by progression-free survival (PFS) per investigator with use of RECIST v1.1
- To evaluate the efficacy of atezolizumab compared with chemotherapy with respect to anti-tumor effects as measured by duration of objective response (DOR) per RECIST v1.1

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab compared with chemotherapy

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

Pharmacokinetic Objective

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

- To characterize the pharmacokinetics of atezolizumab in patients with locally advanced or metastatic UBC who have progressed during or following a platinum-containing regimen

Patient-Reported Outcome Objective

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

- To evaluate and compare PROs of patient health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30)

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab with respect to anti-tumor effects as measured by PFS, ORR, and DOR per modified RECIST
- To evaluate and compare disease control rate (DCR) between the two treatment arms
- To evaluate the relationship between tumor tissue programmed death–ligand 1 (PD-L1) expression and measures of efficacy
- To assess 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
- To assess health status as measured using the EuroQol 5-Dimension, 3-level version (EQ-5D [3L]) questionnaire for health economic modeling

Study Design

Description of Study

This is a 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 UBC who have progressed during or following a platinum-containing regimen. Within the chemotherapy control arm, the percentage of patients who are treated with a taxane (paclitaxel or docetaxel) will be capped at 40%. Until that cap is reached, the selection of the specific chemotherapy (vinflunine or taxane) for patients who are randomized to the chemotherapy arm will be per investigator's choice.

Male and female patients aged ≥ 18 years with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 who have histologically or cytologically proven, locally advanced or metastatic UBC and who have experienced disease progression during or following treatment for advanced disease consisting of platinum-based therapy are eligible.

Patients who experience disease progression during or within 12 months following completion of a platinum-based adjuvant or neoadjuvant regimen will also be eligible for enrollment into the study.

Patients must have received at least one platinum containing regimen (e.g., gemcitabine and cisplatin [GC], methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC], carboplatin and gemcitabine [CarboGem], etc.) for locally advanced or metastatic UBC. The maximum number of prior therapies in the locally advanced or metastatic setting is restricted to two.

Tumor specimens from eligible patients will be prospectively tested for PD-L1 expression by a central laboratory. Both patients and investigators will be blind to the PD-L1 expression status. The study will enroll all patients whose tissue is evaluable for expression testing, regardless of PD-L1 expression status.

This study will enroll approximately 931 patients, including a minimum of 230 patients with a PD-L1 IHC score of IC2/3 and a minimum of 537 patients with a PD-L1 IHC score of IC1/2/3 (enrollment of all patients will continue to reach the minimum requirement of patients with a PD-L1 IHC score of IC2/3). Patients will be randomized in a 1:1 ratio to receive either atezolizumab or chemotherapy (vinflunine, paclitaxel, or docetaxel; see protocol for stratification factors):

- Arm A (experimental arm): Atezolizumab 1200 mg every 3 weeks (q3w)
- Arm B (control arm): Vinflunine 320 mg/m² q3w, paclitaxel 175 mg/m² q3w, or docetaxel 75 mg/m² q3w

Atezolizumab will be administered intravenously at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. Patients will receive atezolizumab as long as they continue to experience clinical benefit in the opinion of the investigator until unacceptable toxicity or symptomatic deterioration attributed to disease progression (i.e., pain secondary to disease or unmanageable ascites, etc.) as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status.

During treatment, patients will be permitted to continue atezolizumab treatment after RECIST v1.1 criteria for progressive disease are met if they meet all of the following criteria:

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

Patients treated with atezolizumab in whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the investigator if they continue to meet the criteria above.

Patients randomized to the chemotherapy arm will receive vinflunine, paclitaxel, or docetaxel per the investigator's choice. Vinflunine 320 mg/m², paclitaxel 175 mg/m², or docetaxel 75 mg/m² will be administered intravenously on Day 1 of each 21-day cycle until disease progression per standard RECIST v1.1 or unacceptable toxicity.

Given the unique characteristics associated with the chemotherapy arm, including toxicities (i.e., mucositis, neutropenia, febrile neutropenia, and alopecia) and the premedications required (i.e., steroid, anti-emetics, and potentially growth factor support), this will be an open-label study.

No crossover will be allowed from the control arm to the experimental arm.

Patients will undergo scheduled tumor assessment at baseline and every 9 weeks thereafter for 54 weeks following randomization. After 54 weeks from randomization, patients will undergo tumor assessment every 12 weeks until disease progression per modified RECIST or until treatment discontinuation (for patients who continue to receive atezolizumab following disease progression). For patients randomized to the chemotherapy arm, assessments will continue until disease progression per RECIST v1.1, regardless of whether treatment has been discontinued. 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 Sponsor. 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 Sponsor.

For patients randomized to the atezolizumab arm, response will be assessed by the investigator with use of RECIST v1.1 and modified RECIST. For patients randomized to the chemotherapy arm, response will be assessed by the investigator with use of RECIST v1.1 only.

Primary imaging data used for tumor assessment may be collected by the Sponsor to enable centralized, independent review of response endpoints if needed.

Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (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 and plasma and whole 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.

Number of Patients

This study will enroll approximately 931 patients, including a minimum of 230 patients with a PD-L1 IHC score of IC2/3 and a minimum of 537 patients with a PD-L1 IHC score of IC1/2/3.

Target Population

Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry:

- Signed Informed Consent Form
- Ability to comply with protocol
- Age \geq 18 years
- Histologically or cytologically documented locally advanced (T4b, any N; or any T, N 2–3) or metastatic (M1, Stage IV) UBC (also termed transitional cell carcinoma [TCC] or urothelial cell carcinoma [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).
- Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:
 - Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)
 - No ongoing requirement for corticosteroids as therapy for CNS disease
 - No stereotactic radiation within 7 days
 - No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
 - Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to enrollment [or randomization], if all other criteria are met.
- 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; patients with fewer than 15 unstained slides available at baseline (but no fewer than 10) may be eligible following discussion with Medical Monitor.
 - Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.
 - 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 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 meeting 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 having additional tissue samples from procedures performed at different times during the course of their UBC will be requested (but not required) to also submit these samples for central testing. Tissue samples obtained at multiple times for individual patients will greatly contribute to an improved understanding of the dynamics of PD-L1 expression and relationship with intervening anti-cancer therapy. In situations where multiple specimens were received from different sites or at different times, the highest score will be used for both primary and secondary analyses.

- Disease progression during or following treatment with at least one platinum-containing regimen (e.g., GC, MVAC, CarboGem, etc.) for inoperable, locally advanced or metastatic UBC or disease recurrence

A regimen is defined as patients receiving at least two cycles of a platinum-containing regimen.

Patients who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment with a platinum-containing adjuvant/neoadjuvant regimen will be considered as second-line patients.

Patients may have received no more than two prior regimens of treatment (including the required platinum-based regimen) for their advanced UBC. Patients must have demonstrated disease progression during or following all prior regimen(s).

Patients who have received one cycle of a platinum-containing regimen but discontinued because of a Grade 4 hematologic toxicity or a Grade 3/4 non-hematologic toxicity may also be eligible.

Patients with disease progression following chemoradiotherapy must demonstrate progression outside the prior radiotherapy port.

- ECOG performance status of 0 or 1
- Life expectancy ≥ 12 weeks
- Measurable disease, as defined by RECIST v1.1

Previously irradiated lesions should not be counted as target lesions.

- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 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 $> 2500/\mu\text{L}$

Lymphocyte count $\geq 500/\mu\text{L}$

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

Hemoglobin ≥ 9.0 g/dL

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

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

Patients with documented liver metastases: AST and/or ALT $\leq 5 \times \text{ULN}$

Patients with documented liver or bone metastases: alkaline phosphatase $\leq 5 \times \text{ULN}$

Serum bilirubin $\leq 1.0 \times \text{ULN}$

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

INR and aPTT $\leq 1.5 \times \text{ULN}$

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

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

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 5 months after the last dose of atezolizumab, 3 months after the last dose of vinflunine and 6 months from the last dose of paclitaxel or docetaxel.

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

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

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

- 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 3 months after the last dose of vinflunine and 6 months from the last dose of paclitaxel or docetaxel. Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 28 days after the last dose of vinflunine, paclitaxel, or docetaxel.

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

Exclusion Criteria

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

Cancer-Specific 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 trial with therapeutic intent within 28 days prior to enrollment
- Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) 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, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)

No history of intracranial or spinal cord hemorrhage

No ongoing requirement for dexamethasone 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 with 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 requiring 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 > 12 mg/dL
 - Corrected serum calcium > ULN (if serum albumin < 4.0 g/dL)
 - 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.

Patients who are receiving denosumab prior to enrollment must be willing and eligible to discontinue its use and replace it with a bisphosphonate instead while on study.

- Malignancies other than UBC within 5 years prior to Cycle 1, Day 1
 - Patients with localized low risk prostate cancer (defined as Stage \leq T2b, Gleason score \leq 7, and prostate-specific antigen [PSA] at prostate cancer diagnosis \leq 20 ng/mL) treated with curative intent and without PSA recurrence are eligible.
 - Patients with low risk prostate cancer (defined as Stage T1/T2a, Gleason score \leq 6, and PSA \leq 10 ng/mL) who are treatment-naïve and undergoing active surveillance are eligible.
 - Patients with malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death < 5% at 5 years) are eligible provided they meet all of the following criteria:
 - Malignancy treated with expected curative intent (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent)
 - No evidence of recurrence or metastasis by follow-up imaging and any disease-specific tumor markers

General Medical Exclusions

- Pregnant and lactating
- Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina
- Patients with a known left ventricular ejection fraction (LVEF) <40% will be excluded.
Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF <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.
- Severe infections within 4 weeks prior to randomization including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received therapeutic oral or intravenous (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) 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
- Inability to understand the local language(s) for which the EORTC QLQ-C30 and EQ-5D (3L) questionnaires are available

Exclusion Criteria Related to Paclitaxel

- Prior treatment with paclitaxel for assignment of paclitaxel in the chemotherapy control arm prior to randomization
- History of severe hypersensitivity to paclitaxel or to other drugs formulated with polyoxyethylated castor oil

Exclusion Criteria Related to Docetaxel

- Prior treatment with docetaxel for assignment of docetaxel in the chemotherapy control arm prior to randomization
- History of severe hypersensitivity to docetaxel or to other drugs formulated with polysorbate 80
- Grade ≥ 2 peripheral neuropathy as defined by NCI CTCAE v4.0 criteria
- Inability to discontinue use of strong cytochrome P450 (CYP)3A4 inhibitors including but not limited to ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, or voriconazole

Exclusion Criteria Related to Vinflunine

- Prior treatment with vinflunine for assignment of vinflunine in the chemotherapy control arm prior to randomization
- History of severe hypersensitivity to vinflunine or other vinca alkaloids

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, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis
 - Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study.
 - Patients with controlled Type 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.
- Serum albumin < 2.5 g/dL
- Positive test for HIV
- Patients with active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C
 - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.
 - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Active tuberculosis (TB)
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study
 - Influenza vaccination should be given during influenza season only (approximately October through March in the Northern Hemisphere and approximately April through September in the Southern Hemisphere). Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist®) 28 days prior to randomization, during treatment or within 5 months following the last dose of atezolizumab (for patients randomized to atezolizumab).
- Prior treatment with CD137 agonists, anti-programmed death-1 (PD-1), or anti-PD-L1 therapeutic antibody or pathway-targeting agents
 - Patients who have had prior anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) may be enrolled, provided the following requirements are met:
 - Minimum of 12 weeks from the first dose of anti-CTLA-4 and > 6 weeks from the last dose
 - No history of severe immune-related adverse effects from anti-CTLA-4 (NCI CTCAE Grade 3 and 4)
- Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin [IL]-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to randomization

- 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 randomization or anticipated requirement for systemic immunosuppressive medications during the trial

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

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 the study is defined as the date when all patients have one of the following:

- Experienced an OS event
- Been lost to follow-up
- Withdrawn consent

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

Outcome Measures

Efficacy Outcome Measures

Primary Efficacy Outcome Measure

- OS, defined as the time between the date of randomization and death due to any cause

Secondary Efficacy Outcome Measures

- ORR, defined as the proportion of patients with an objective response (either a complete response [CR] or partial response [PR]) as determined by the investigator with use of RECIST v1.1
- PFS, defined as the time between the date of randomization and the date of first documented disease progression as determined by the investigator with use of RECIST v1.1 or death due to any cause, whichever occurs first
- DOR, defined as the time between the date of first documented response and the date of first documented disease progression as determined by the investigator with use of RECIST v1.1 or death due to any cause, whichever occurs first

Safety Outcome Measures

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

Pharmacokinetic Outcome Measures

- Maximum observed serum atezolizumab concentration (C_{max}) after infusion on Day 1 of Cycle 1
- Minimum observed serum atezolizumab concentration (C_{min}) prior to infusion on Day 1 of Cycles 1, 2, 3, 4, 8, and 16, at treatment discontinuation, and at 120 days (± 30 days) after the last dose of atezolizumab

Patient-Reported Outcome Measure

- UBC cancer symptoms, patient functioning, and HRQoL as measured by the EORTC QLQ-C30

Exploratory Outcome Measures

- PFS, ORR, and DOR with use of modified RECIST for patients randomized to atezolizumab
- DCR, defined as the rate of patients with complete or partial response as best response or stable disease maintained for ≥ 18 weeks per RECIST v1.1
- Status of tumor immune-related or disease type-related exploratory biomarkers in archival and/or freshly obtained tumor tissues and association with disease status and/or response to atezolizumab
- Status of exploratory biomarkers in plasma, whole blood, or serum (including but not limited to cytokines such as interleukin 6 [IL-6]) collected before or during treatment with atezolizumab or at progression and association with disease status and/or response to atezolizumab
- Utility scores of the EQ-5D (3L) for use in economic models
- Items from the EORTC QLQ-C30 that are not included in the main PRO outcome measure

Length of Study

The length of study will be approximately 25 months from first patient in (FPI).

Investigational Medicinal Products

Test Product

Atezolizumab is administered at a dose of 1200 mg by IV infusion on Day 1 of each 21-day cycle.

Comparators

Vinflunine is administered at a dose of 320 mg/m² by IV infusion on Day 1 of each 21-day cycle.

Paclitaxel is administered at a dose of 175 mg/m² over 3 hours by continuous IV infusion on Day 1 of each 21-day cycle.

Docetaxel is administered at a dose of 75 mg/m² on Day 1 of each 21-day cycle.

Statistical Methods

Primary Analysis

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

The primary analysis will occur when approximately 152, 403, and 652 deaths have been observed in the following populations: patients with an IHC score of IC2/3, patients with an IHC score of IC1/2/3, and intent-to-treat (ITT) populations respectively, whichever occurs later.

Comparisons with respect to OS between the treatment and control arms will be tested using a hierarchical fixed-sequence procedure based on a stratified log-rank test at two-sided level of 5% significance within the following populations: patients with an IHC score of IC2/3, patients with an IHC score of IC1/2/3, and in the ITT population.

Determination of Sample Size

This study will enroll approximately 931 patients, including a minimum of 230 patients with a PD-L1 IHC score of IC2/3 and a minimum of 537 patients with a PD-L1 IHC score of IC1/2/3.

The number of events required to demonstrate efficacy of the atezolizumab experimental arm over the chemotherapy arm (i.e., vinflunine, paclitaxel, or docetaxel) with regard to OS are estimated based on the following assumptions:

- Two-sided significance level of 5%
- 94% for the primary analysis of OS in the population of patients with an IHC score of IC2/3 with an HR of 0.57, corresponding to an improvement in median OS from 7.5 months to 13.2 months

- 98% power for the primary analysis of OS in the population of patients with an IHC score of IC1/2/3 with an HR of 0.68, corresponding to an improvement in median OS from 7.5 months to 11 months
- 97% power for the primary analysis of OS in the ITT population with an HR of 0.74, corresponding to an improvement in median OS from 7.5 months to 10.1 months
- 1:1 randomization ratio
- Dropout rate of 5% per year over 24 months

Interim Analyses

No interim efficacy analyses are planned for this study.

An iDMC will be set up to evaluate safety results approximately every 6 months after FPI. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an external independent Data Coordinating Center (iDCC). Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
anti-HBc	antibody to hepatitis B core antigen
anti-HBs	antibody to hepatitis B surface antigen
ASCO	American Society of Clinical Oncology
ATA	anti-therapeutic antibody
BSC	best supportive care
CarboGem	carboplatin and gemcitabine
CL	clearance
C _{max}	maximum observed serum concentration
C _{min}	minimum observed serum concentration
CR	complete response
CRCL	creatinine clearance
CRF	Case Report Form
CRP	C-reactive protein
CT	computed tomography
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
C _{trough}	trough concentration
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of objective response
EBV	Epstein-Barr virus
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	electronic patient-reported outcome
EQ-5D (3L)	EuroQoL 5-Dimension, 3-level version
ESMO	European Society of Medical Oncology
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FOLFOX	leucovorin, 5-fluorouracil, oxaliplatin
FPI	first patient in
GC	gemcitabine and cisplatin
HBsAg	hepatitis B surface antigen

Abbreviation	Definition
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	U.S. Health Insurance Portability and Accountability Act
HR	hazard ratio
HRQoL	health-related quality of life
IC	PD-L1 tumor-infiltrating immune cell
ICH	International Conference on Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
IGRA	interferon-gamma release assay
IMP	investigational medicinal product
IND	U.S. Investigational New Drug application
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
IxRS	interactive Web/voice response system
LFT	liver function test
LVEF	left ventricular ejection fraction
M-CAVI	methotrexate, carboplatin, and vincristine
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
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
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic

Abbreviation	Definition
PPD	purified protein derivative
PRO	patient-reported outcome
PSA	prostate-specific antigen
q3w	every 3 weeks
QLQ-C30	Quality-of-Life Questionnaire Core 30
QTcF	Fridericia-corrected QT
RCC	renal cell carcinoma
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
TB	tuberculosis
TC-99m	Technetium-99m
TCC	transitional cell carcinoma
TFPC	time from prior chemotherapy
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
UBC	urothelial bladder cancer
UICC	Union Internationale Contre le Cancer
UCC	urothelial cell carcinoma
ULN	upper limit of normal
V _{ss}	volume of distribution at steady state

1. **BACKGROUND**

1.1 **BACKGROUND ON UROTHELIAL BLADDER CANCER**

Urothelial bladder cancer (UBC, also termed transitional cell carcinoma [TCC] or urothelial cell carcinoma [UCC] of the urinary tract) is the most common cancer of the urinary system worldwide with UBC of the bladder being the predominant histologic type and location. Although less common, UBC may originate in the renal pelvis, ureter, or urethra. It was estimated that in 2013, there would be 72,570 new cases of bladder cancer and 15,210 deaths in the United States ([American Cancer Society 2013](#)). Similar worldwide data estimate that there were 112,308 deaths in men and 37,974 in females in 2008 ([GLOBOCAN 2008](#)).

The overall 5-year survival rate for metastatic UBC is approximately 5.4% ([National Cancer Institute 2013](#)). Poor prognostic factors for survival in patients with metastatic UBC include advanced stage of disease at the time of initial diagnosis, Karnofsky Performance Status (KPS) <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](#)).

The majority of urothelial tumors arise in the bladder with the remainder originating in the renal pelvis, urethra, or ureter. UBC is the most common histologic subtype associated with bladder cancer and accounts for greater than 90% of all UBC 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 ([Chalasan et al. 2009](#)).

1.1.1 **First-Line Treatment for Urothelial Bladder Cancer**

Patients with previously untreated UBC typically receive platinum-based chemotherapy. The first evidence that chemotherapy produced a significant benefit in patients with advanced UBC came in the mid-1980s; two studies showed that the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) produced overall response rates greater than 70% with approximately 35% of patients achieving a complete response (CR; [Sternberg et al. 1985; 1989](#)). Subsequently, two prospective randomized Phase III trials demonstrated the superiority of MVAC with regard to OS in patients with advanced disease ([Logothetis et al. 1990; Loehrer et al. 1992](#)). In an effort to develop a less toxic regimen, the combination of gemcitabine and cisplatin (GC) was tested against MVAC in the Phase III setting following the demonstration of activity in earlier phase trials. In the Phase III trial, patients allocated to GC had a similar overall survival (OS) to those randomized to MVAC (14.0 months for GC 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 (including neutropenia, neutropenic sepsis, and mucositis) and, as a result, GC has largely displaced MVAC as the standard of care ([von der Maase et al. 2005](#)).

The benefit conferred by cisplatin-based chemotherapy regimens appears to have reached a plateau in median OS (13–15 months) and leaves a significant population in need of salvage therapy options.

Poor performance status, impaired renal function, advanced age, and multiple comorbidities (e.g., neuropathy, congestive heart failure, and hearing loss) are fairly common in patients with advanced UBC and can prohibit the use of cisplatin-based regimens. Carboplatin-based regimens are feasible in these patients, but trials suggest they are less effective than cisplatin-based regimens ([Dogliotti et al. 2007](#)). The benefit of carboplatin-based therapy in medically “unfit” patients was demonstrated in the European Organisation for the Research and Treatment of Cancer (EORTC) Trial 30986. In this trial, 238 patients with previously untreated advanced UBC and either a poor performance status and/or impaired renal function (glomerular filtration rate [GFR] < 60 but > 30 mL/min) were enrolled to gemcitabine and carboplatin (CarboGem) or methotrexate, carboplatin, and vincristine (M-CAVI; [De Santis et al. 2012](#)). The objective response rate (ORR) of CarboGem was 41% versus 30% for the M-CAVI arm and demonstrated no difference in the median OS (9.3 vs. 8.1 months). Notably, those with both impaired renal function and poor performance status had especially poor outcomes and increased acute toxicity with combination chemotherapy in this trial.

Despite the limited survival benefit conferred by cytotoxic chemotherapy, platinum-based regimens remain the standard first-line option for most patients with locally advanced and metastatic UBC. Virtually all patients progress following first-line chemotherapy, with median progression-free survival (PFS) ranging from 7.7 months to 8.3 months. As a result, most patients with UBC will continue to need more effective second-line treatment options.

A summary of randomized Phase III trials in previously untreated patients is provided in [Table 1](#).

Table 1 Randomized Phase III Trials in Previously Untreated Patients

First-Line Therapy Regimen (Reference)	No. of Patients	ORR (%)	Median OS (months)
Cisplatin-based regimens			
MVAC vs. Cis (Loehrer et al. 1992)	246	36 vs. 11	12.5 vs. 8.2
MVAC vs. CISCA (Logothetis et al. 1990)	110	65 vs. 46	12.6 vs. 10
MVAC vs. HD-MVAC (Sternberg et al. 1985)	263	58 vs. 72	14.1 vs. 15.5
MVAC vs. GC (von der Masse et al. 2005)	405	49 vs. 46	15.2 vs. 14
MVAC vs. CaP (Dreicer et al. 2004)	85	36 vs. 28	15.4 vs. 13.8
MVAC/GCSF vs. CD/GCSF (Bamias et al. 2004)	220	54 vs. 37	14.2 vs. 9.3
Cisplatin-based regimen vs. carboplatin-based regimen			
GC vs. CarboGem (Dogliotti et al. 2007)	110	49 vs. 40	12.8 vs. 9.8
Carboplatin-based regimens			
CarboGem vs. MTX/Carbo/Vinblast (De Santis et al. 2012)	238	41 vs. 30	9.3 vs. 8.1

CaP = carboplatin and paclitaxel; CarboGem = gemcitabine and carboplatin; CD = cisplatin and docetaxel; Cis = cisplatin; CISCA = cisplatin, cyclophosphamide, and doxorubicin; GC = gemcitabine and cisplatin; GCSF = granulocyte colony-stimulating factor; HD = high dose intensity; MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin; ORR = objective response rate; OS = overall survival.

Note: Adapted from [Garcia et al. 2006](#).

1.1.2 Second-Line Treatment for Urothelial Bladder Cancer

Despite the efficacy of first-line regimens for patients with advanced UBC, nearly all patients experience disease progression and will require second line therapy. There are currently no approved second-line therapies for UBC in the United States and only one approved agent (vinflunine) in the European Union. Whereas several chemotherapeutic agents have been studied in the second-line setting over the last two decades, the overall response rates are low and associated with considerable toxicity (see [Table 2](#)). No survival benefit has been demonstrated with second-line chemotherapy. The National Comprehensive Cancer Network (NCCN) guidelines recommend participation in a clinical trial of new agents. If no trials are available, treatment with a single-agent taxane or gemcitabine is preferred for palliation. Additional recommended palliative options include single-agent cisplatin, carboplatin, doxorubicin, 5-fluorouracil (5-FU), ifosfamide, pemetrexed, methotrexate, and vinblastine. European Society of Medical Oncology (ESMO) and European Association of Urology (EAU) clinical practice guidelines recommend vinflunine but also highlight that other agents used in this space may have similar benefit and recommend clinical trials of other treatments ([Bellmunt et al. 2011](#); [Stenzl et al. 2011](#)). The registrational Phase III study of vinflunine as a second-line agent compared vinflunine versus best supportive care (BSC) alone in 370 patients progressing after a platinum-containing therapy. The intent-to-treat (ITT)

analysis showed an improvement in response rate (8.6% vs. 0%) but did not show a statistically significant OS benefit for vinflunine compared with placebo (6.9 vs. 4.6 months, HR=0.88; 95% CI: 0.69, 1.12; p=0.287). Key toxicities included Grade 3 or 4 neutropenia (50%), febrile neutropenia (6%), anemia (19%), fatigue (19%), and constipation (16%). A summary of Randomized Phase II trials of second-line therapy is provided in [Table 2](#).

Table 2 Randomized Phase II Trials of Second-Line Therapy

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

OS= overall survival; PFS= progression-free survival; RR= response rate.

Note: Adapted from [Sonpavde et al. 2010](#).

1.1.3 Targeted Therapy for Urothelial Bladder Cancer

Although there is an increasing understanding of the molecular biology and signaling pathways underlying bladder cancer development and progression (particularly the fibroblast growth factor receptor [FGFR], vascular endothelial growth factor [VEGF], and epidermal growth factor receptor [EGFR]/human epidermal growth factor 2 [HER2]–pathways), no targeted agents currently have a role in the treatment of UBC.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab 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 investigated as a potential therapy against solid tumors and hematologic malignancies in humans.

1.2.1 Summary of Nonclinical Studies

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

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

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

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

Current studies of atezolizumab include an ongoing Phase Ia monotherapy study, three ongoing combination studies, and three Phase II studies in patients with solid tumors (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.

Phase Ib Study GP28328

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 (FOLFOX; Arm B) in patients with advanced solid tumors. Additional cohorts have been included to investigate atezolizumab in combination with carboplatin plus paclitaxel, in combination with carboplatin plus pemetrexed, as well as in combination with carboplatin plus nab-paclitaxel, pemetrexed, and cisplatin in patients with advanced or metastatic non-small cell lung cancer (NSCLC).

Phase Ib Study GP28384

Ongoing Phase Ib Study GP28384 is evaluating the safety and pharmacology of atezolizumab administered in combination with vemurafenib in patients with previously untreated BRAF^{V600} mutation-positive metastatic melanoma.

Phase Ib Study GP28363

Ongoing Phase Ib Study GP28363 is evaluating the safety and pharmacology of atezolizumab administered in combination with cobimetinib (MEK inhibitor) in locally advanced or metastatic solid tumors.

Phase II Study GO28625 (FIR)

Ongoing, single-arm, Phase II Study GO28625 is evaluating the safety and efficacy of atezolizumab monotherapy in PD-L1-positive patients with NSCLC. In particular, this study is evaluating whether archival or fresh tumor tissue is more predictive of response to atezolizumab. Safety and efficacy data are not yet available for this study.

Phase II Study GO28753 (POPLAR)

Ongoing Study GO28753 is a randomized, open-label, Phase II study in patients with locally advanced or metastatic NSCLC who have failed a prior platinum-containing regimen. Patients in the control arm of Study GO28753 will receive docetaxel alone. Eligible patients will be enrolled regardless of PD-L1 status and will be stratified by PD-L1 expression. The primary endpoint is OS for both the PD-L1–positive population and the overall study population.

Phase II Study GO28754 (BIRCH)

Ongoing, single-arm, Phase II Study GO28754 is evaluating the safety and efficacy of atezolizumab monotherapy in PD-L1–positive patients with NSCLC. Safety and efficacy data are not yet available for this study.

Phase III Study GO28915 (OAK)

Ongoing Study GO28915 is a randomized, open-label, Phase III study in patients with locally advanced or metastatic NSCLC who have failed a prior platinum-containing regimen. Patients in the control arm of Study GO28915 will receive docetaxel alone. Eligible patients will be enrolled regardless of PD-L1 status and will be stratified by PD-L1 expression. The primary endpoint is OS for both the PD-L1–positive population and the overall study population.

Phase II Study WO29074

Ongoing Phase II Study WO29074 is evaluating the safety and efficacy of atezolizumab monotherapy or the combination of atezolizumab and bevacizumab versus sunitinib in treatment-naïve patients with renal cell carcinoma (RCC). Safety and efficacy data are not yet available for this study.

Phase II Study GO29293

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 UBC. The co-primary endpoints of this study are independent review facility (IRF)–assessed ORR according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) and investigator-assessed ORR according to modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

1.2.2.2 Clinical Safety

The presented safety data for atezolizumab have been derived from the treatment of patients in Study PCD4989g. As of 1 January 2014, the clinical database contained safety data from 386 safety-evaluable patients, defined as patients who received any amount of atezolizumab at doses between ≤ 0.01 and 20 mg/kg, across multiple tumor types. No dose-limiting toxicities (DLTs) have been observed at any dose level, and no maximum tolerated dose (MTD) was established.

Adverse Events

The most frequently observed adverse events (occurring in $\geq 10\%$ of treated patients) included fatigue, nausea, decreased appetite, pyrexia, dyspnea, diarrhea, constipation, cough, headache, back pain, vomiting, anemia, arthralgia, rash, insomnia, asthenia, abdominal pain, chills, and pruritus. Treatment-related adverse events (per investigator's assessment of causality) were reported in 277 patients (71.8%). Treatment-related adverse events (all grades) occurring in $\geq 10\%$ of patients included fatigue (22%), decreased appetite (12.7%), pyrexia (11.7%), nausea (11.4%), and rash (10.4%) for Study PCD4989g.

Adverse Events in Patients with Urothelial Bladder Cancer

Safety data are available for 68 patients with UBC from Study PCD4989g. In patients with UBC, 62 (91.2%) reported an adverse event regardless of attribution. Adverse events reported in $\geq 10\%$ of patients included decreased appetite (22.1%), pyrexia (17.6%), fatigue (17.6%), nausea (17.6%), anemia (16.2%), urinary tract infection (14.7%), abdominal pain (13.2%), vomiting (13.2%), constipation (13.2%), back pain (11.8%), and asthenia (10.3%). In 57.4% of patients, the adverse events had a maximum severity of either Grade 1 or 2. Adverse events were assessed by the investigator as related to atezolizumab therapy in 39 of 68 (57.4%) treated patients with UBC. The most common events related to study drug that occurred in $\geq 5\%$ of patients were decreased appetite (11.8%), fatigue (11.8%), nausea (11.8%), pyrexia (8.8%), and asthenia (7.4%). Overall, the preliminary safety data from the UBC cohort show a safety profile similar to that of all atezolizumab-treated patients.

Immune-Mediated Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated adverse events have been closely monitored during the atezolizumab clinical program. These include potential dermatologic, hepatic, endocrine, and respiratory events as well as events of hepatitis/elevated liver function tests (LFTs) and influenza-like illness, which are considered potential adverse drug reactions associated with atezolizumab.

See the Atezolizumab Investigator's Brochure for further information regarding safety data from Study PCD4989g.

1.2.2.3 Clinical Activity

As of the data cutoff date of 1 January 2014, efficacy analyses were performed on 362 efficacy-evaluable patients who were defined as those patients with measurable disease at baseline and who were treated by 20 November 2013 in Study PCD4989g. Patients with multiple tumor types were included in the study, with the largest cohorts consisting of patients with NSCLC, RCC, and bladder cancer. In the overall efficacy-evaluable population, the ORR (confirmed and unconfirmed) per RECIST v1.1 was 19.6% (95% CI: 15.6%–23.9%). Objective responses with atezolizumab monotherapy were observed in a broad range of malignancies, including NSCLC, RCC,

melanoma, bladder cancer, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. Altogether, there were 71 patients with responses with a median duration of response of 75.7 weeks (range: 0.1+ to 85.9+ weeks, where “+” denotes censored value). The majority of these responses have been durable, with 73.2% (52 of 71) of responses ongoing as of the clinical cutoff date.

Clinical Activity in Patients with Urothelial Bladder Cancer

As of the clinical cutoff date of 1 January 2014, efficacy analyses have been performed on efficacy-evaluable patients with locally advanced or metastatic UBC who had an immunohistochemistry (IHC) score of PD-L1–positive tumor-infiltrating immune cell (IC)2/3 (30 patients) and in patients with an IHC score of IC0/1 (35 patients) who were dosed by 20 November 2013 in Study PCD4989g (see [Table 3](#)).

In the population of efficacy-evaluable patients with UBC and an IHC score of IC2/3 (n=30), the median follow-up was 4.2 months (range: 1.1+ to 8.5 months). The investigator-assessed ORR per RECIST v1.1 in patients with an IHC score of IC2/3 was 43.3% (95% CI: 25.5%, 62.6%) with two complete responses. Among the efficacy-evaluable patients with UBC and an IHC score of IC2/3, there were 13 responding patients, of which 11 are confirmed responses (two responders did not have follow-up scans to confirm their response prior to the clinical cutoff date). In responding patients (n=13), the median time to first response was 43 days (range: 38–85 days). The median duration of response was not reached (range: 0.1+ to 30.3+ weeks). The majority of these responses have been durable, with 92.3% (12 of 13) of responses still ongoing as of the clinical cutoff date.

Among the population of efficacy-evaluable patients with UBC and an IHC score of IC0/1 (n=35), there are 4 patients with responses, none of which is a confirmed response. The investigator-assessed ORR per RECIST v1.1 in patients with an IHC score of IC0/1 is 11.4% (95% CI: 4.0%, 26.3%). Median duration of follow-up for these patients is 2.7 months (range: 0.7+ to 3.6 months). For these four responses, the median duration of response has not been reached (range: 0.1+, 6.0+ weeks). In patients with an IHC score of IC0/1, all responses were still ongoing as of the clinical cutoff date.

Table 3 Efficacy-Evaluable Patients with UBC Dosed by 20 November 2013 in Study PCD4989g: ORR per RECIST v1.1 by PD-L1 Tumor Expression

IHC Score	ORR (CR or PR)	ORR (CR or PR) of Combined IHC Groups
IHC score of IC3 (IC ≥ 10%)	50% (5 of 10) (95% CI: 22.2%, 77.8%)	43% (13 of 30) (95% CI: 25.5%, 62.6%)
IHC score of IC2 (10% > IC ≥ 5%)	40.0% (8 of 20) (95% CI: 20.9%, 63.9%)	
IHC score of IC1 (5% > IC ≥ 1%)	13% (3 of 23) (95% CI: 3.7%, 31.7%)	11% (4 of 35) (95% CI: 4.0%, 26.3%)
IHC score of IC0 (IC < 1%)	8% (1 of 12) (95% CI: 0.4%, 34.9%)	

CR = complete response; IC = PD-L1–positive tumor-infiltrating immune cell; IHC = immunohistochemistry; ORR = objective response rate; PD-L1 = programmed death–ligand 1; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; UBC = urothelial bladder cancer.

Notes: This table shows efficacy-evaluable patients with UBC dosed by 20 November 2013. Two patients had unknown IHC scores.

ORR covers both confirmed and unconfirmed responses.

See the Atezolizumab Investigator’s Brochure for further information regarding efficacy data from Study PCD4989g.

1.2.2.4 Clinical Pharmacokinetics and Immunogenicity

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

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

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

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

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

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

PD-L1 expression is prevalent in many human tumors, and elevated PD-L1 expression on tumor cells is associated with a poor prognosis in patients with UBC ([Nakanishi et al. 2007](#); [Mu et al. 2011](#)).

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed or refused standard-of-care therapies. As of the data cutoff date of 1 January 2014, efficacy data are available for 362 patients treated in the atezolizumab Phase Ia Study PCD4989g. In the overall efficacy-evaluable population, the ORR per RECIST v1.1 was 15.5%. RECIST v1.1 responses were observed across multiple tumor types, including NSCLC, RCC, melanoma, colorectal cancer, gastric cancer, head and neck cancer, sarcoma, breast cancer, and bladder cancer (see Section [1.2.2.3](#)).

Importantly, preliminary evidence suggests that patients with UBC and high PD-L1–expressing tumors (IHC score of IC2/3) are more likely to benefit from PD-L1 pathway–targeted therapies than are patients with low PD-L1–expressing (IHC score of IC0/1) tumors. Data from the Phase Ia Study PCD4989g showed that patients with UBC and a PD-L1 IHC score of IC2/3 have a numerically higher ORR to atezolizumab than patients with an IHC score of IC 0/1 (43.3% vs. 11.4%; see [Table 3](#)).

In this study, a PD-L1 IHC assay will be used to stratify patients by tumor PD-L1 expression (IHC score of IC0/1 vs. IHC score of IC2/3). Comparisons of OS between the treatment and control arms will be evaluated first in the population of patients with an IHC score of IC2/3 and subsequently in the population of patients with IHC1/2/3, followed by the ITT population in a hierarchical fixed-sequence procedure (see Section 6.5.1).

Study GO29294 will enroll only second- and third-line patients; to date, no therapy has demonstrated a survival benefit in this population. In contrast to the cytotoxic therapies approved for the treatment of UBC, atezolizumab has been generally well tolerated and has not been associated with bone marrow suppression or other systemic toxicities (i.e., neuropathy, peripheral edema, nephrotoxicity, or febrile neutropenia) that may limit the ability to administer subsequent treatments (see Section 1.2.2.2). Therefore, second-line patients enrolled in this study may remain eligible for standard therapies after discontinuation of atezolizumab.

Data from Study PCD4989g have demonstrated a numerically higher RECIST v1.1 response rate in patients with UBC (see Table 3) on atezolizumab when compared with historical response rates of 9%–11% observed in randomized studies of second-line patients who progressed on prior platinum-based chemotherapy (Bellmunt et al. 2009; Choueiri et al. 2012). These responses to atezolizumab have been rapid. Although follow-up in the UBC cohort is limited, when all responders across different tumor types (i.e., NSCLC, RCC, melanoma, colorectal cancer, gastric cancer, head and neck cancer, sarcoma, breast cancer, and bladder cancer) in Study PCD4989g were added up the median duration of response was 75.7 weeks with approximately 73.2% of responses still ongoing as of the data cutoff date of 1 January 2014, suggesting response to atezolizumab could be durable (see Section 1.2.2.3).

Atezolizumab has been generally well tolerated (see Section 1.2.2.2); adverse events with potentially immune-related causes consistent with an immunotherapeutic agent, including rash, hypothyroidism, hepatitis/transaminitis, colitis, and myasthenia gravis, have been observed in ongoing studies of atezolizumab. To date, these events have been monitorable and treatable.

In summary, treatment with atezolizumab offers the potential for clinical benefit in patients with UBC. Because most atezolizumab-related toxicities observed to date have been mild and transient in nature and do not overlap with the adverse effects of chemotherapy, patients who do not respond to study treatment are considered likely to be able to subsequently receive standard therapies for which they would otherwise have been eligible. Patients will be fully informed of the risk of continuing study treatment in spite of apparent radiographic progression, and investigators should make a careful assessment of the potential benefit of doing so, considering radiographic data, biopsy results, and the clinical status of the patient.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

For the primary and secondary efficacy objectives, a comparison of the treatment arms will be performed in different patient subpopulations according to tumor PD-L1 expression as evaluated by IHC. The IHC scores will have three categories (IC0, IC1, and IC2/3), which will also be used for stratification (IHC score of IC0/1 vs. IHC score of IC2/3).

2.1.1 Primary Efficacy Objective

The primary efficacy objective of this study is as follows:

- To evaluate the efficacy of atezolizumab treatment compared with chemotherapy treatment with respect to OS in patients with locally advanced or metastatic UBC who have progressed during or following a platinum-containing regimen

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives of this study are as follows:

- To evaluate the efficacy of atezolizumab compared with chemotherapy with respect to anti-tumor effects as measured by ORR per investigator with use of RECIST v1.1
- To evaluate the efficacy of atezolizumab compared with chemotherapy with respect to anti-tumor effects as measured by PFS per investigator with use of RECIST v1.1
- To evaluate the efficacy of atezolizumab compared with chemotherapy with respect to anti-tumor effects as measured by duration of objective response (DOR) per RECIST v1.1

2.2 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab compared with chemotherapy
- To evaluate the incidence of ATAs against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is as follows:

- To characterize the pharmacokinetics of atezolizumab in patients with locally advanced or metastatic UBC who have progressed during or following a platinum-containing regimen

2.4 PATIENT-REPORTED OUTCOME OBJECTIVE

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

- To evaluate and compare PROs of patient health-related quality of life (HRQoL) between treatment arms as measured by the EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30)

2.5 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab with respect to anti-tumor effects as measured by PFS, ORR, and DOR per modified RECIST
- To evaluate and compare disease control rate (DCR) between the two treatment arms
- To evaluate the relationship between tumor tissue PD-L1 expression and measures of efficacy
- To assess 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
- To assess health status as measured using the EuroQoL 5-Dimension, 3-level version (EQ-5D [3L]) questionnaire for health economic modeling

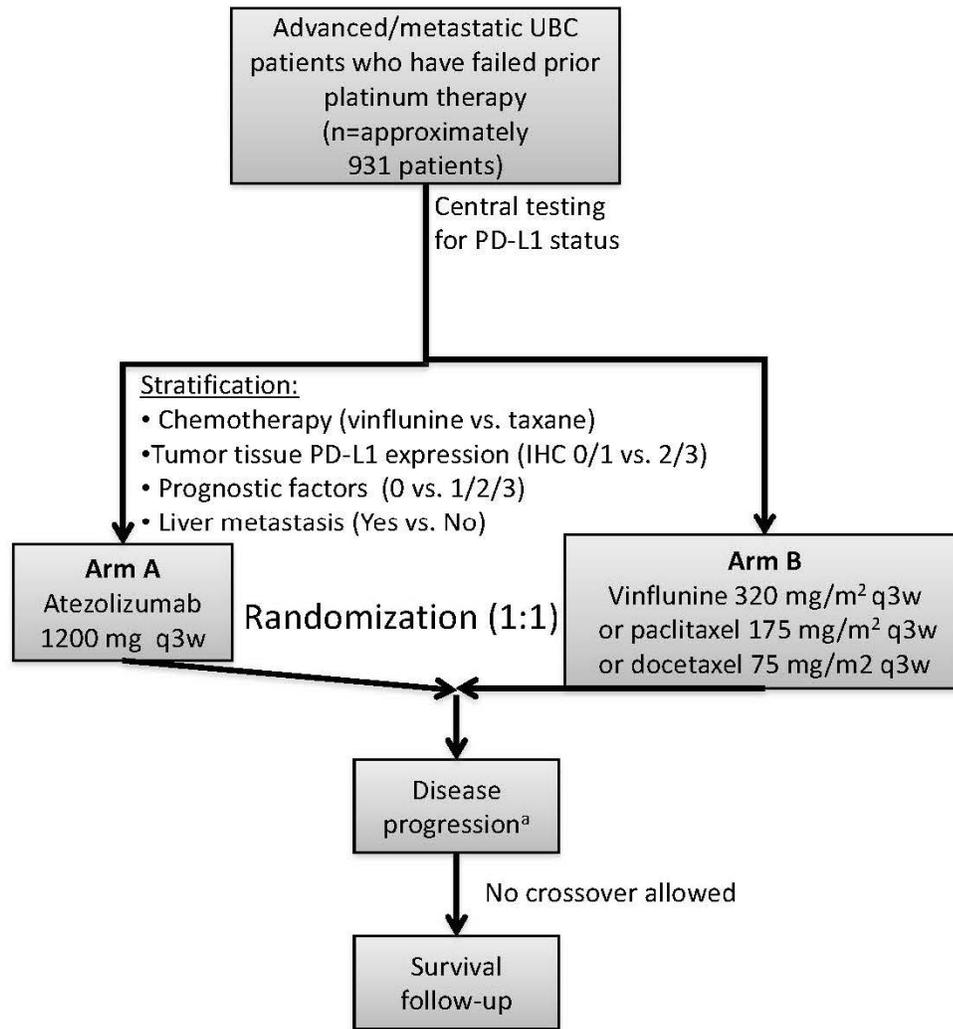
3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a 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 UBC who have progressed during or following a platinum-containing regimen. Within the chemotherapy control arm, the percentage of patients who are treated with a taxane (paclitaxel or docetaxel) will be capped at 40%. Until that cap is reached, the selection of the specific chemotherapy (vinflunine or taxane) for patients who are randomized to the chemotherapy arm will be per investigator's choice.

Figure 1 illustrates the study design.

Figure 1 Study Schema



IHC=immunohistochemistry; PD-L1=programmed death–ligand 1; q3w=every 3 weeks; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; UBC=urothelial bladder cancer.

^a Patients may continue atezolizumab treatment after disease progression according to RECIST v1.1 if they meet criteria specified in Section 4.6.1.1.

Male and female patients aged ≥ 18 years with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 who have histologically or cytologically proven, locally advanced or metastatic UBC and who have experienced disease progression during or following treatment for advanced disease consisting of platinum-based therapy are eligible.

Patients who experience disease progression during or within 12 months following completion of a platinum-based adjuvant or neoadjuvant regimen will also be eligible for enrollment into the study.

Patients must have received at least one platinum-containing regimen (e.g., GC, MVAC, CarboGem, etc.) for locally advanced or metastatic UBC. The maximum number of prior therapies in the locally advanced or metastatic setting is restricted to two.

Tumor specimens from eligible patients will be prospectively tested for PD-L1 expression by a central laboratory. Both patients and investigators will be blind to the PD-L1 expression status. The study will enroll all patients whose tissue is evaluable for expression testing, regardless of PD-L1 expression status.

This study will enroll approximately 931 patients, including a minimum of 230 patients with a PD-L1 IHC score of IC2/3 and a minimum of 537 patients with a PD-L1 IHC score of IC1/2/3 (enrollment of all patients will continue to reach the minimum requirement of patients with a PD-L1 IHC score of IC2/3). Patients will be randomized in a 1:1 ratio to receive either atezolizumab or chemotherapy (vinflunine, paclitaxel, or docetaxel; see Section 4.2 for stratification factors):

- Arm A (experimental arm): Atezolizumab 1200 mg q3w
- Arm B (control arm): Vinflunine 320 mg/m² q3w, paclitaxel 175 mg/m² q3w, or docetaxel 75 mg/m² q3w

Atezolizumab will be administered intravenously at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. Patients will receive atezolizumab as long as they continue to experience clinical benefit in the opinion of the investigator until unacceptable toxicity or symptomatic deterioration attributed to disease progression (i.e., pain secondary to disease or unmanageable ascites, etc.) as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status.

During treatment, patients will be permitted to continue atezolizumab treatment after RECIST v1.1 criteria for progressive disease are met if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed and stabilized by protocol-allowed medical interventions (see Section 4.4.1)

Patients treated with atezolizumab in whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the investigator if they continue to meet the criteria above.

Patients randomized to the chemotherapy arm will receive vinflunine, paclitaxel, or docetaxel per the investigator's choice. Vinflunine 320 mg/m², paclitaxel 175 mg/m², or docetaxel 75 mg/m² will be administered intravenously on Day 1 of each 21-day cycle until disease progression per standard RECIST v1.1 or unacceptable toxicity.

Given the unique characteristics associated with the chemotherapy arm, including toxicities (i.e., mucositis, neutropenia, febrile neutropenia, and alopecia) and the premedications required (i.e., steroid, anti-emetics, and potentially growth factor support), this will be an open-label study.

No crossover will be allowed from the control arm to the experimental arm.

Patients will undergo scheduled tumor assessment at baseline and every 9 weeks thereafter for 54 weeks following randomization. After 54 weeks from randomization, patients will undergo tumor assessment every 12 weeks until disease progression per modified RECIST (see [Appendix 3](#)) or until treatment discontinuation (for patients who continue to receive atezolizumab following disease progression). For patients randomized to the chemotherapy arm, assessments will continue until disease progression per RECIST v1.1 (see [Appendix 4](#)), regardless of whether treatment has been discontinued. 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 Sponsor. 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 Sponsor.

For patients randomized to the atezolizumab arm, response will be assessed by the investigator with use of RECIST v1.1 and modified RECIST. For patients randomized to the chemotherapy arm, response will be assessed by the investigator with use of RECIST v1.1 only.

Primary imaging data used for tumor assessment may be collected by the Sponsor to enable centralized, independent review of response endpoints if needed.

Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (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 and plasma and whole 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 (see Section 3.1.1).

3.1.1 Independent Data Monitoring Committee

An iDMC will be set up to evaluate safety data during the study. The iDMC will evaluate study safety data on a periodic basis, approximately every 6 months from the point of first patient in (FPI). Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. The Sponsor will remain blind to the results until the primary analysis.

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

3.2 END OF STUDY

The end of the study is defined as the date when all patients have one of the following:

- Experienced an OS event
- Been lost to follow-up
- Withdrawn consent

In addition, the Sponsor may decide to terminate the study at any time (see Section 4.6.2).

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Study Design

This Phase III study design is based on the assumption that, in patients with UBC who have failed prior platinum therapy, treatment with atezolizumab may prolong OS compared with treatment with single-agent chemotherapy. Prospective evaluation of PD-L1 expression in tumor tissue will allow for the estimation of treatment benefit according to different levels of PD-L1 expression.

3.3.2 Rationale for Primary and Secondary Endpoints

Improvement in OS is generally accepted as the best measure of clinical benefit for patients with advanced/unresectable or metastatic UBC. The assumption that treatment with atezolizumab will prolong OS compared with treatment with single-agent chemotherapy is based on the durable response rates observed in multiple tumor types in Phase I Study PCD4989g with atezolizumab. Comparisons of OS between the

treatment and control arms will be evaluated in a hierarchical fixed-sequence testing procedure in the population of patients with an IHC score of IC2/3, the population of patients with an IHC score of IC1/2/3, and in the ITT population.

The secondary efficacy endpoints of PFS and ORR will allow the evaluation of differences in response and progression patterns between the two treatment arms. Patients will be evaluated for disease progression at predefined, standard intervals to minimize evaluation-time biases and will be followed off-treatment for continued safety monitoring and date of death. Safety and tolerability of study treatments will be assessed. Atezolizumab pharmacokinetics will be characterized and exploratory biomarker analyses performed. The atezolizumab concentration results may be compared with available data from other atezolizumab clinical studies and correlated with efficacy endpoints and safety events as appropriate. PRO data will allow further evaluation of the relative tolerability of treatment and the impact of therapy on disease symptoms between the two treatment groups.

3.3.3 Rationale for Inclusion of All Patients (All Levels of PD-L1 Expression by Immunohistochemistry) in the Study

Responses to atezolizumab have been observed in both PD-L1–positive (defined by IHC score of IC2 or IC3) and PD-L1–negative patients (defined by IHC score of IC0 or IC1), although the response rate in patients with PD-L1–positive UBC has been higher than that observed for the PD-L1–negative patients in Phase I Study PCD4989g. As indicated in Section 1.2.2.3, PD-L1–negative patients had a response rate of 11.4%, which is comparable to the historical response rates of 9% to 11% observed in randomized studies of second-line patients who progressed on prior platinum-based chemotherapy (Bellmunt et al. 2009; Choueiri et al. 2012). The inclusion of patients with all levels of PD-L1 expression by IHC will also enable a robust assessment of the hypothesis that PD-L1–positive status is predictive of increased efficacy with atezolizumab treatment relative to PD-L1–negative status and will also allow for the evaluation of OS benefit in the overall population with atezolizumab treatment relative to chemotherapy treatment irrespective of PD-L1 status.

3.3.4 Rationale for Testing Atezolizumab in Patients with UBC Who Have Failed Prior Platinum Therapy

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

3.3.5 Rationale for Control Arm Therapy

Since a single, global standard of care is lacking for the second-line treatment of patients with UBC, three single-agent chemotherapy regimens were chosen to reflect the most commonly used therapies worldwide in this patient population.

3.3.5.1 Vinflunine

Vinflunine is the only second-line agent approved in the European Union only for the treatment of patients with UBC. This regimen is recommended by the ESMO and EUA clinical practice guidelines.

3.3.5.2 Paclitaxel or Docetaxel

Single-agent taxane therapy is recommended by the NCCN guidelines as one of the preferred palliation options for the second-line treatment of patients with UBC. In one study, patients were administered paclitaxel 175 to 250 mg/m² by 24-hour infusion and one PR was reported among 3 patients who failed first-line therapy (Dreicer et al. 1996). Dose modifications were required because of myelosuppression or neurotoxicity for most patients dosed at 200 or 250 mg/m². Weekly paclitaxel given at a dose of 80 mg/m² has been tested in patients with previously treated UBC and has demonstrated a modest 10% ORR (Vaughn et al. 2002). Since there are no data in this disease setting suggesting weekly paclitaxel to have advantages in terms of tolerability and/or efficacy compared with q3w paclitaxel, the paclitaxel 175 mg/m² q3w regimen has been chosen for this study so patients randomized to either arm will be dosed with a q3w schedule.

Docetaxel has demonstrated similar survival benefit relative to vinflunine in patients with UBC. In the randomized Phase II CONSORT study (n=142), docetaxel plus vandetanib was compared with docetaxel plus placebo in patients with platinum-pretreated metastatic UBC (Choueiri et al. 2012). OS was similar in both arms (HR=1.21; 95% CI: 0.81, 1.79). Median OS in the docetaxel plus placebo arm was 7.39 months.

3.3.6 Rationale for Stratification Factors

In order to balance the disease-related risk factors between the treatment arms, patients will be stratified at study entry. A permuted-block randomization scheme will be used to ensure an approximately equal sample size and a similar distribution of stratification factors for the two treatment arms.

Chemotherapy (i.e., vinflunine vs. taxane) is included as a stratification factor because the second-line standards of care treatment for UBC, which may impact the final OS endpoint, differ among geographic regions.

The PD-L1 IHC status (i.e., IHC score of IC0/1 vs. IHC score of IC2/3) is included as a stratification factor because the primary efficacy analysis for OS will be conducted in a hierarchical procedure for which the comparison between the treatment and control arms will be tested in the group of patients with IHC score of IC2/3 first followed by patients with an IHC score of IC1/2/3 and then in the overall population (ITT population).

In the second-line setting of UBC, OS differs on the basis of the presence of certain risk factors: time from prior chemotherapy (TFPC) < 3 months, ECOG performance status > 0, hemoglobin < 10 g/dL, and liver metastasis. The median OS of four groups based on 0, 1, 2, and 3/4 risk factors demonstrated significant divergence: 12.2, 6.7, 5.1, and 3.0 months, respectively (Bellmunt et al. 2010; Pond et al. 2013). In the only randomized Phase III study in second-line UBC comparing vinflunine with BSC, which examined 16 potential prognostic factors for their association with survival, patients with liver metastasis had the worst OS outcome (Bellmunt et al. 2009). Considering this observation, patients in this study will first be stratified on the basis of the number of risk factors (0 vs. 1/2/3): TFPC < 3 months, ECOG performance status > 0, hemoglobin < 10 g/dL, and liver metastasis (yes vs. no) will be selected as a stand-alone stratification factor.

3.3.7 Rationale for Atezolizumab Dosage

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

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

The atezolizumab dose is also informed by available clinical activity, safety, PK, and immunogenicity data. Anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg. The MTD of atezolizumab was not reached, and no DLTs have been observed at any dose in Study PCD4989g. Available preliminary PK data (0.03–20 mg/kg) from Study PCD4989g suggest that for doses ≥ 1 mg/kg, overall atezolizumab exhibits pharmacokinetics that are both linear and consistent with typical IgG1 antibodies. Detectable ATAs were observed in patients at all dose levels but were associated with changes in pharmacokinetics for some patients in only the lower dose cohorts (0.3, 1, and 3 mg/kg). It is unclear from currently available data in these lower dose cohorts 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 from 10 to 20 mg/kg in most patients. Correspondingly, patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained target trough levels of drug despite the detection of 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 $C_{\text{trough}} \geq 6 \mu\text{g/mL}$ 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. 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.

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

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 enrolling patients 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.

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

3.3.9 Rationale for Blood Sampling for Biomarkers and for Collection of Optional Tumor Specimens

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

In addition, potential correlations of these pharmacodynamic markers with the dose, safety, and anti-tumor activity of atezolizumab will be explored. Anti-tumor immune responses such as those associated with atezolizumab may result in objective responses that are delayed and that can be preceded by initial apparent radiological progression. This initial apparent progression may occur as a result of either delayed anti-tumor activity and/or robust tumor immune cell infiltration with a concomitant increase in tumor size. In addition, lesions that might otherwise be undetectable with conventional imaging may increase in size as a result of these processes and be recorded as new lesions (Hales et al. 2010). Furthermore, patients agreeing to optional tumor biopsies will undergo tissue collection, if clinically feasible, at pre-treatment and at the first evidence of early radiographic disease progression. These optional biopsy samples will be placed in the Roche Clinical Repository (RCR) (see Section 4.5.6).

3.3.10 Rationale for Patient-Reported Outcome Assessments

PROs provide an understanding of the impact a treatment has on a patient. Currently, there are no fully validated PRO instruments to measure symptoms and HRQoL specifically among patients with advanced/metastatic UBC. The EORTC QLQ-C30 is a validated instrument that has been widely used in assessing quality of life in patients with cancer. The core instrument assesses global health status/quality of life, functions (physical, role, emotional, cognitive, and social), and general cancer symptoms.

3.3.11 Rationale for Allowing Patients to Continue Atezolizumab Treatment beyond Initial Progression per RECIST v1.1

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure (see Section 3.3.9). Because of the potential for pseudoprogression/tumor immune infiltration, this study will allow patients randomized to receive atezolizumab to remain on study treatment after apparent radiographic progression, provided the benefit-risk ratio is judged to be favorable. In Study PCD4989g, several patients with NSCLC who progressed by RECIST v1.1 criteria continued on atezolizumab treatment and demonstrated durable anti-tumor activity. In addition, in some responding patients, the growth of known lesions or the appearance of new radiographic lesions were shown to contain immune cells and no viable cancer cells on biopsy. Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by

the investigator after an integrated assessment of radiographic data and clinical status (see Section 4.6.2).

Although secondary endpoint measures of efficacy (ORR, PFS) comparing the atezolizumab and chemotherapy arms will use RECIST v1.1 criteria, noncomparative analyses of these measures with use of modified RECIST criteria (see Appendix 3) will be performed for patients randomized to receive atezolizumab. Modified RECIST criteria allow the incorporation of new lesions into the calculation of total tumor burden after baseline. Similar to the immune-related response criteria (Wolchok et al. 2009), it is recommended that radiological progression be confirmed at a subsequent tumor assessment to take into account the potential for pseudoprogression/tumor immune infiltration. In addition, it is highly recommended that evidence of progressive disease in responding patients be confirmed by a biopsy of the growing or new lesion when feasible.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

3.4.1.1 Primary Efficacy Outcome Measure

- OS, defined as the time between the date of randomization and death due to any cause

3.4.1.2 Secondary Efficacy Outcome Measures

- ORR, defined as the proportion of patients with an objective response (either a CR or PR) as determined by the investigator with use of RECIST v1.1
- PFS, defined as the time between the date of randomization and the date of first documented disease progression as determined by the investigator with use of RECIST v1.1 or death due to any cause, whichever occurs first
- DOR, defined as the time between the date of first documented response and the date of first documented disease progression as determined by the investigator with use of RECIST v1.1 or death due to any cause, whichever occurs first

3.4.2 Safety Outcome Measures

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

3.4.3 Pharmacokinetic Outcome Measures

- Maximum observed serum atezolizumab concentration (C_{max}) after infusion on Day 1 of Cycle 1
- Minimum observed serum atezolizumab concentration (C_{min}) prior to infusion on Day 1 of Cycles 1, 2, 3, 4, 8, and 16, at treatment discontinuation, and at 120 days (± 30 days) after the last dose of atezolizumab

3.4.4 Patient-Reported Outcome Measure

- UBC cancer symptoms, patient functioning, and HRQoL as measured by the EORTC QLQ-C30

3.4.5 Exploratory Outcome Measures

- PFS, ORR, and DOR with use of modified RECIST (see [Appendix 3](#)) for patients randomized to atezolizumab
- DCR, defined as the rate of patients with complete or partial response as best response or stable disease maintained for ≥ 18 weeks per RECIST v1.1
- Status of tumor immune-related or disease type-related exploratory biomarkers in archival and/or freshly obtained tumor tissues and association with disease status and/or response to atezolizumab
- Status of exploratory biomarkers in plasma, whole blood, or serum (including but not limited to cytokines such as interleukin 6 [IL-6]) collected before or during treatment with atezolizumab or at progression and association with disease status and/or response to atezolizumab
- Utility scores of the EQ-5D (3L) for use in economic models
- Items from the EORTC QLQ-C30 that are not included in the main PRO outcome measure

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry:

- Signed Informed Consent Form
- Ability to comply with protocol
- Age ≥ 18 years
- Histologically or cytologically documented locally advanced (T4b, any N; or any T, N2–3) or metastatic (M1, Stage IV) UBC (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).

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

Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)

No ongoing requirement for corticosteroids as therapy for CNS disease

No stereotactic radiation within 7 days

No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases.

Following treatment, these patients may then be eligible without the need for an additional brain scan prior to enrollment [or randomization], if all other criteria are met.

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

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

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 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 meeting 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 having additional tissue samples from procedures performed at different times during the course of their UBC will be requested (but not required) to also submit these samples for central testing. Tissue samples obtained at multiple times for individual patients will greatly contribute to an improved understanding of the dynamics of PD-L1 expression and relationship with intervening anti-cancer therapy. In situations where multiple specimens were received from different sites or at different times, the highest score will be used for both primary and secondary analyses.

- Disease progression during or following treatment with at least one platinum-containing regimen (e.g., GC, MVAC, CarboGem, etc.) for inoperable, locally advanced or metastatic UBC or disease recurrence

A regimen is defined as patients receiving at least two cycles of a platinum-containing regimen.

Patients who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment with a platinum-containing adjuvant/neoadjuvant regimen will be considered as second-line patients.

Patients may have received no more than two prior regimens of treatment (including the required platinum-based regimen) for their advanced UBC. Patients must have demonstrated disease progression during or following all prior regimen(s).

Patients who have received one cycle of a platinum-containing regimen but discontinued because of a Grade 4 hematologic toxicity or a Grade 3/4 non-hematologic toxicity may also be eligible.

Patients with disease progression following chemoradiotherapy must demonstrate progression outside the prior radiotherapy port.

- ECOG performance status of 0 or 1 (see [Appendix 8](#)).
- Life expectancy ≥ 12 weeks
- Measurable disease, as defined by RECIST v1.1

Previously irradiated lesions should not be counted as target lesions.

- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment:

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

WBC counts $> 2500/\mu$ L

Lymphocyte count $\geq 500/\mu$ L

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

Hemoglobin ≥ 9.0 g/dL

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

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

Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN

Patients with documented liver or bone metastases: alkaline phosphatase $\leq 5 \times$ ULN

Serum bilirubin $\leq 1.0 \times \text{ULN}$

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

INR and aPTT $\leq 1.5 \times \text{ULN}$

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

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

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 5 months after the last dose of atezolizumab, 3 months after the last dose of vinflunine and 6 months from the last dose of paclitaxel or docetaxel.

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

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

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

- 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 3 months after the last dose of vinflunine and 6 months from the last dose of paclitaxel or docetaxel. Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 28 days after the last dose of vinflunine, paclitaxel, or docetaxel.

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

4.1.2 Exclusion Criteria

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

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 trial with therapeutic intent within 28 days prior to enrollment
- Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) 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, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)

No history of intracranial or spinal cord hemorrhage

No ongoing requirement for dexamethasone 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 with 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 requiring 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 > 12 mg/dL
 - Corrected serum calcium > ULN (if serum albumin < 4.0 g/dL)
 - 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.

Patients who are receiving denosumab prior to enrollment must be willing and eligible to discontinue its use and replace it with a bisphosphonate instead while on study.
- Malignancies other than UBC within 5 years prior to Cycle 1, Day 1

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

Patients with low risk prostate cancer (defined as Stage T1/T2a, Gleason score \leq 6, and PSA \leq 10 ng/mL) who are treatment-naïve and undergoing active surveillance are eligible.

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

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

4.1.2.2 General Medical Exclusions

- Pregnant and lactating
- Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina
- Patients with a known left ventricular ejection fraction (LVEF) <40% will be excluded.

Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF < 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.

- Severe infections within 4 weeks prior to randomization including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received 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) 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
- Inability to understand the local language(s) for which the EORTC QLQ-C30 and EQ-5D (3L) questionnaires are available (see [Appendix 5](#) for English versions)

4.1.2.3 Exclusion Criteria Related to Paclitaxel

- Prior treatment with paclitaxel for assignment of paclitaxel in the chemotherapy control arm prior to randomization
- History of severe hypersensitivity to paclitaxel or to other drugs formulated with polyoxyethylated castor oil

4.1.2.4 Exclusion Criteria Related to Docetaxel

- Prior treatment with docetaxel for assignment of docetaxel in the chemotherapy control arm prior to randomization
- History of severe hypersensitivity to docetaxel or to other drugs formulated with polysorbate 80
- Grade ≥ 2 peripheral neuropathy as defined by NCI CTCAE v4.0 criteria
- Inability to discontinue use of strong cytochrome P450 (CYP)3A4 inhibitors including but not limited to ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, or voriconazole

4.1.2.5 Exclusion Criteria Related to Vinflunine

- Prior treatment with vinflunine for assignment of vinflunine in the chemotherapy control arm prior to randomization
- History of severe hypersensitivity to vinflunine or other vinca alkaloids

4.1.2.6 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, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see [Appendix 6](#) for a more comprehensive list of autoimmune diseases)

Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study.

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.

- Serum albumin <2.5 g/dL
- Positive test for HIV

- Patients with active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C
 - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.
 - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Active tuberculosis (TB)
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study
 - Influenza vaccination should be given during influenza season only (approximately October through March in the Northern Hemisphere and approximately April through September in the Southern Hemisphere). Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist[®]) 28 days prior to randomization, during treatment or within 5 months following the last dose of atezolizumab (for patients randomized to atezolizumab).
- Prior treatment with CD137 agonists, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents
 - Patients who have had prior anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) may be enrolled, provided the following requirements are met:
 - Minimum of 12 weeks from the first dose of anti-CTLA-4 and >6 weeks from the last dose
 - No history of severe immune-related adverse effects from anti-CTLA-4 (NCI CTCAE Grade 3 and 4)
- Treatment with systemic immunostimulatory agents (including but not limited to interferons or IL-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to randomization
- 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 randomization or anticipated requirement for systemic immunosuppressive medications during the trial
 - Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.
 - The use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e., for adrenal insufficiency), and mineralocorticoids (e.g., fludrocortisone) is allowed.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study.

After written informed consent has been obtained and eligibility has been established (including determination of tumor PD-L1 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 randomization number and treatment assignment from the IxRS. Randomization to the treatment and control arms will occur in a 1:1 ratio with use of a permuted-block randomization method. Prior to the randomization, the investigator will have the option of choosing one of three chemotherapy regimens (vinflunine, paclitaxel, or docetaxel) for each patient. Randomization will be stratified by the following factors:

- Chemotherapy (vinflunine vs. taxane)
- PD-L1 IHC status (IHC score of IC0/1 vs. IHC score of IC2/3)
- Number of risk factors (0 vs. 1/2/3)
 - TFPC < 3 months
 - ECOG performance status > 0
 - Hemoglobin < 10 g/dL
- Liver metastasis (yes vs. no)

Patients should receive their first dose of study treatment on the day of randomization if possible. If this is not possible, the first dose should occur no later than 3 days after randomization.

4.3 STUDY TREATMENT

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

Vinflunine, paclitaxel, and docetaxel are considered non-IMPs in this study. Depending on local legislation, vinflunine, paclitaxel, and docetaxel may be considered IMPs. If considered an IMP, then appropriate information on formulation, packaging, handling, and administration will be provided.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 **Atezolizumab**

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

4.3.1.2 Vinflunine, Paclitaxel, and Docetaxel

See the local prescribing information for details on drug formulation, packaging, and handling. Vinflunine, paclitaxel, or docetaxel will be provided by the Sponsor (F. Hoffmann-La Roche Ltd) where it is considered an IMP by local regulations.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Atezolizumab

The dose level of atezolizumab proposed to be tested in this study is 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) administered by IV infusion q3w (21 [\pm 3] days).

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. For more detailed information on drug preparation, storage, and administration, refer to the Atezolizumab Investigator’s Brochure and Pharmacy Manual.

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

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

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) infusion-related event, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should continue to deliver the infusion at the reduced rate for 30 minutes. If tolerated, the infusion rate may then be increased to the original rate.
- In the event that a patient experiences a moderate infusion-related event (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the patient should have his or her infusion immediately interrupted and should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to the baseline grade. The infusion rate at restart should be half of the rate that was in progress at the time of the onset of the infusion-related event.

- For severe or life-threatening infusion-related events (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening infusion-related events will not receive further infusion and will be further managed as clinically indicated until the event resolves.

For anaphylaxis precautions, see [Appendix 7](#).

Guidelines for dosage modification, treatment interruption, or discontinuation and the management of specific adverse events are provided in [Appendix 9](#).

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF (see Section [5.3.5.10](#)).

4.3.2.2 Paclitaxel

Paclitaxel will be administered according to the local prescribing information. The starting dose level of paclitaxel in this study will be 175 mg/m² q3w administered via IV infusion over 3 hours. Pretreatment with corticosteroids, diphenhydramine, and H2 antagonists will be required to prevent severe hypersensitivity reactions. Dose modifications should be performed according to Section [5.1.6](#).

Vital signs will be collected for paclitaxel infusions according to Section [4.5.2.3](#).

4.3.2.3 Docetaxel

Docetaxel will be administered according to the local prescribing information. The starting dose of docetaxel will be 75 mg/m² q3w. Dose modifications should be performed Section [5.1.7](#).

All patients randomized to receive docetaxel should be premedicated with oral corticosteroids, such as dexamethasone at 16 mg/day (e.g., 8 mg twice daily), for 3 days starting a day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

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

Vital signs will be collected for docetaxel infusions according to Section [4.5.2.3](#).

4.3.2.4 Vinflunine

Vinflunine will be administered according to the locally approved label. The starting dose of vinflunine will be 320 mg/m² q3w in patients aged <75 years with an ECOG performance status of 0; 280 mg/m² q3w in patients aged between 75 and <80 years, with an ECOG performance status of 1, moderate renal impairment (CRCL ≥40 to

≤ 60 mL/min), or previous pelvic radiation; or 250 mg/m² q3w in patients aged ≥ 80 years or with severe renal impairment (CRCL ≥ 30 to < 40 mL/min). In order to prevent constipation, laxatives and dietary measures including oral hydration are recommended from Day 1 to Days 5 or 7 after each vinflunine administration.

For patients with ECOG performance status of 1 or prior pelvic radiation, the starting dose of vinflunine will be 280 mg/m². In the absence of any hematological toxicity during the first cycle causing treatment delay or dose reduction, the dose will be increased to 320 mg/m² for the subsequent cycles.

See local prescribing information/institutional guidelines for detailed guidelines on administration or dose adjustments for special populations. Dose modifications for toxicities should be performed according to Section 5.1.8.

Vital signs will be collected for vinflunine infusions according to Section 4.5.2.3.

4.3.3 Investigational Medicinal Product Accountability

As an IMP, atezolizumab will be provided by the Sponsor. Vinflunine, paclitaxel, and docetaxel will be provided by the Sponsor if considered an IMP by local regulations. The investigational site will acknowledge receipt of atezolizumab, vinflunine, paclitaxel, and docetaxel (if provided by the Sponsor) with use of 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-Trial Access to Atezolizumab

The Sponsor will offer post-trial 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 UBC
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for locally advanced or metastatic UBC
- 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

4.4.1 Permitted Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the date of informed consent and the date of clinical or radiographic progression or study discontinuation.

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

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 specific recommendations, see [Appendix 9](#)). For patients randomized to atezolizumab, alternatives to corticosteroids should be considered if feasible, but premedication may be administered for Cycles ≥ 2 . The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed. Megestrol administered as an appetite stimulant is acceptable while the patient is enrolled in the study.

Patients who use hormonal therapy such as 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 ongoing therapies or medications (see Section 4.1.2) should continue their use. Female patients of reproductive potential should use a highly effective means of contraception.

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

4.4.2 Excluded Therapy

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

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

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. Study drug should be suspended for patients being treated with vinflunine, paclitaxel, or docetaxel per institutional guidelines.

Patients experiencing a mixed response requiring local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) for control of three or fewer lesions may still be eligible to continue study treatment, at the discretion of the investigator. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression. Such cases should be discussed with the Medical Monitor.

4.4.2.1 Excluded and Cautionary Therapy for Atezolizumab-Treated Patients

The following guidance applies only to patients randomized to receive atezolizumab. The following medications are excluded while the patient is receiving study treatment:

- Traditional herbal medicines; these therapies are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound the assessment of toxicity.
- RANKL inhibitor (denosumab)
- Immunomodulatory agents, including but not limited to interferons or IL-2, during the entire study; these agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab.
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab.

Influenza vaccinations (inactivated forms only) should be given during influenza season only (approximately October to March in the Northern hemisphere; April to September in the Southern Hemisphere). Patients must agree not to receive live, attenuated influenza vaccines (such as FluMist[®]) 28 days prior to randomization, during treatment or within 5 months following the last dose of atezolizumab (for patients randomized to atezolizumab).

Initiation or increased dose of granulocyte colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is prohibited.

Systemic corticosteroids and anti-TNF- α agents may also attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to these agents should be considered.

In addition, patients treated with atezolizumab (including those who discontinue the study early) should not receive other immunomodulatory agents for 10 weeks after study treatment discontinuation.

4.4.3 Concomitant Medications with Paclitaxel

The metabolism of paclitaxel is catalyzed by CYP isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) and inducers (e.g., rifampin and carbamazepine) of CYP3A4.

Granulocyte colony-stimulating factor treatment is permitted for patients in the paclitaxel arm. The primary prophylaxis should be administered per the American Society of Clinical Oncology (ASCO), EORTC, and ESMO guidelines; namely, in patients who are ≥ 60 years of age and/or with comorbidities ([Smith et al. 2006](#); [Crawford et al. 2009](#); [Aapro et al. 2011](#)).

Anti-emetics, anti-allergic measures, and other treatments for concomitant paclitaxel toxicities may be used at the discretion of the investigator, taking into account precautions from the Summary of Product Characteristics.

See the Summary of Product Characteristics (Package Insert) for paclitaxel for all boxed warnings and contraindications.

4.4.4 Concomitant Medications with Docetaxel

Docetaxel is a CYP3A4 substrate. Patients randomized to receive docetaxel must avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors.

In addition, concomitant treatment with CYP3A4 inducers may decrease plasma concentrations of docetaxel. Therefore, concomitant medications that are CYP3A4 inducers should be used with caution.

Granulocyte colony-stimulating factor treatment is permitted for patients in the docetaxel arm. The primary prophylaxis should be administered per the ASCO, EORTC, and ESMO guidelines; namely, in patients who are ≥ 60 years of age and/or with comorbidities ([Smith et al. 2006](#); [Crawford et al. 2009](#); [Aapro et al. 2011](#)).

Anti-emetics, anti-allergic measures, and other treatments for concomitant docetaxel toxicities may be used at the discretion of the investigator, taking into account precautions from the Summary of Product Characteristics.

See the Summary of Product Characteristics (Package Insert) for docetaxel for all boxed warnings and contraindications.

4.4.5 Concomitant Medications with Vinflunine

Patients randomized to receive vinflunine must avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) or inducers (e.g., rifampicin, St John's wort) since they may increase or decrease plasma concentration of vinflunine and its metabolite 4Odeacetyl-vinflunine, respectively.

In addition, the concomitant use of vinflunine with other QT/QTc interval–prolonging drugs should be avoided.

Laxatives and dietary measures including oral hydration for concomitant vinflunine toxicities may be used at the discretion of the investigator, taking into account precautions from the Summary of Product Characteristics.

See the Summary of Product Characteristics (Package Insert) for vinflunine for all boxed warnings and contraindications.

4.5 STUDY ASSESSMENTS

Flowcharts of scheduled study assessments are provided in [Appendix 1](#) and [Appendix 2](#). Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

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

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

4.5.1 Informed Consent Forms and Screening Log

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

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

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

4.5.2 Description of Study Assessments

4.5.2.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the date of informed consent.

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

4.5.2.2 Physical Examinations

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

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

4.5.2.3 Vital Signs

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

For patients assigned to both treatment arms, at all infusions, vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before and 30 (\pm 10) minutes after the infusion. For the atezolizumab arm, vital signs will also be collected during the first infusion (every 15 [\pm 5] minutes). Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

4.5.2.4 Tumor and Response Evaluations

Measurable and nonmeasurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Tumor assessments are to be performed at the timepoints specified in [Appendix 1](#), \pm 3 business days regardless of drug delays or interruptions.

Results of standard of care tests or examinations performed prior to obtaining Informed Consent and \leq 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/IV contrast unless contraindicated) or MRI of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. 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 active or untreated CNS metastases are not eligible for this study (see Section [4.1.2.1](#) for CNS-related exclusions).

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

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

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

For subsequent tumor assessments, procedures for tumor assessment should be performed as clinically indicated. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation. For patients randomized to the atezolizumab arm, response will be assessed by the investigator with use of RECIST v1.1 and modified RECIST (see [Appendix 3](#) and [Appendix 4](#)). For patients randomized to the chemotherapy arm, response will be assessed by the investigator with use of RECIST v1.1 only. Assessments should be performed by the same evaluator if possible to ensure internal consistency across visits.

Patients assigned to atezolizumab who continue treatment beyond radiographic disease progression (see Section [4.6.1](#)) will be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 9 weeks. If the scan frequency is every 12 weeks (see [Appendix 1](#)), the follow-up scan must be performed at 9 (± 2) weeks as an unscheduled tumor assessment, or earlier if clinically indicated.

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

Primary imaging data used for tumor assessment may be collected by the Sponsor to enable centralized, independent review of response endpoints if needed.

4.5.2.5 Laboratory, Biomarker, and Other Biological Samples

Samples for hematology, serum chemistries, coagulation, urinalysis, and the pregnancy test will be analyzed at the study site's local laboratory. Central laboratories will coordinate the collection of archival tumor, fresh tumor, and leftover tumor tissue and blood samples for the assessment of atezolizumab pharmacokinetics and pharmacodynamic biomarkers, ATA assays, Epstein-Barr virus (EBV) testing, 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 (aPTT and 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)
- All patients will be tested for HIV within 3 months prior to the inclusion into the study, and HIV-positive patients will be excluded from the clinical trial.
- All patients will have a tuberculin (PPD) skin test or IGRA performed locally within 3 months prior to the inclusion into the study, and patients with active TB will be excluded from the clinical trial.
- HBV serology (HBsAg, antibody to HBsAg [anti-HBs], anti-HBc)
 - HBV DNA is required on or before Cycle 1, Day 1 if patient has negative serology for HBsAg and positive serology for anti-HBc.
- HCV serology (anti-HCV)

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

- EBV serology (screening sample collection only; serology tests to be performed on the screening sample only in patients who experience an acute inflammatory event such as systemic inflammatory response syndrome while receiving study treatment)
- CRP
- ATA assays (patients assigned to atezolizumab only)
 - Serum samples will be assayed for the presence of ATAs to atezolizumab with use of validated immunoassays.
- PK assays (patients assigned to atezolizumab only)
 - Serum samples will be assayed for atezolizumab concentration with use of a validated immunoassay.
 - Any remaining samples collected for PK and ATAs may be used for exploratory biomarker profiling, identification, and pharmacodynamic assay development purposes and additional safety assessments (e.g., ATA assay) as appropriate.
- Vitamin D assays
 - 25(OH)D
- Auto-antibody testing (patients assigned to atezolizumab only); baseline sample to be collected on Cycle 1, Day 1 prior to the first dose of study drug. For patients who show evidence of immune-mediated toxicity, additional samples may be collected and all samples will be analyzed centrally.
 - Anti-nuclear antibody

Anti-double-stranded DNA

Circulating anti-neutrophil cytoplasmic antibody

Perinuclear anti-neutrophil cytoplasmic antibody

- Biomarker assays

Blood samples will be obtained for biomarker evaluation (including but not limited to biomarkers that are related to bladder or tumor immune biology) from all eligible patients according to the schedule in [Appendix 2](#). Samples will be processed to obtain plasma and serum for the determination of changes in blood-based biomarkers. Whole blood samples may be processed to obtain peripheral blood mononuclear cells (PBMCs) and their derivatives (e.g., RNA).

- Archival or fresh 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 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.

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

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

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

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.

- Optional biopsies

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

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

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

The remaining samples obtained for study-related procedures will be destroyed no later than 5 years after the end of the study or earlier depending on local regulations. If the patient provides optional consent for storing samples into the RCR for future research (see Section 4.5.6), the samples will be destroyed no later than 15 years after the date of final closure of the clinical database.

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

4.5.3 Anti-Therapeutic Antibody Testing (Atezolizumab-Treated Patients Only)

Atezolizumab may elicit an immune response. Patients with signs of any potential immune response to atezolizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect ATAs at multiple timepoints before, during, and after treatment with atezolizumab (see [Appendix 2](#) for the schedule). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy ([Rosenberg 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.

4.5.4 Cardiac and Pulmonary Function Tests

4.5.4.1 Electrocardiograms

A 12-lead ECG is required at screening and 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.

4.5.5 Patient-Reported Outcomes

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

The EQ-5D (3L) is generic preference-based HRQoL questionnaire that provides a single index value for health status (see Appendix 5 and is used to inform pharmacoeconomic evaluations. The EQ-5D (3L) consists of two parts; the first part, health state classification, contains five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. From these five items, a utility measure is obtained for each patient. The second part, consisting of a visual analog scale, will not be used in this study.

A paper instrument or electronic PRO (ePRO) data collection modality may be employed. The PRO questionnaires, translated as required in the local language, will be distributed by the investigator's staff and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigational site prior to the completion of other study assessments and the administration of study treatment. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. Hard copy originals of the questionnaires must be maintained as part of the patient's medical record at the site for source data verification. These originals should have the respondent's initials on each page in compliance with good clinical practices.

The PRO questionnaires (EORTC QLQ-C30 and EQ-5D [3L]) will be completed on Cycle 1, Day 1 (prior to any health care interaction), on Day 1 of each subsequent cycle, and at the treatment discontinuation visit, which is within 30 days after the last treatment dose. In addition, the EQ-5D (3L) only will be collected at 6, 12, and 24 weeks after the CT/MRI scan date from which disease progression per RECIST v1.1 is determined. The EQ-5D (3L) post-disease progression will be collected via telephone interview by trained site staff and in compliance with best practices and recommendations by EuroQoL. Study personnel will record patient responses on a paper copy of the EQ-5D (3L) during the telephone interview as record of source documentation. For patients assigned to atezolizumab who continue treatment beyond radiographic disease progression (see

Section 4.6.1), only EQ-5D (3L) will be collected on Day 1 of each subsequent cycle and after eventual treatment discontinuation until collection at 6, 12, and 24 weeks after disease progression is fulfilled.

4.5.6 Optional Biopsies and Samples for RCR (Optional Future Research)

4.5.6.1 Overview of the Roche Clinical Repository

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

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

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

4.5.6.2 Approval by the Institutional Review Board or Ethics Committee

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

4.5.6.3 Optional Samples for Roche Clinical Repository

The following samples will be collected for the identification of dynamic (non-inherited) biomarkers:

- Remaining blood derivatives (serum, plasma, PBMCs and their derivatives) after study-related tests have been performed
- Remaining FFPE tissue (with the exception of archival FFPE blocks, which will be returned to sites) after study-related tests have been performed
- Optional tissue samples collected for biopsy during the study (preferably before treatment and at the time of radiographic progression)

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

- Whole blood sample for DNA isolation

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

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

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

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

4.5.6.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

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

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

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

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

4.5.6.5 Consent to Participate in the Roche Clinical Repository

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

The investigator should document whether the patient has given consent to participate by completing the Informed Consent eCRF.

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

4.5.6.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. 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 with use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the appropriate Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GO29294 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study GO29294.

4.5.6.7 Monitoring and Oversight

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

4.5.7 Timing of Study Assessments

4.5.7.1 Screening and Pre-Treatment Assessments

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

Written informed consent can be obtained up to 42 days prior to randomization. Tumor tissue may be submitted up to 42 days prior to randomization. Screening tests and evaluations will be performed within 28 days prior to randomization, unless otherwise specified. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days (or as otherwise specified) prior to randomization may be used; such tests do not need to be repeated for screening. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

See [Appendix 1](#) for the schedule of screening and pre-treatment assessments.

4.5.7.2 Assessments during Treatment

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

See the table provided in [Appendix 1](#) for the schedule of treatment period assessments.

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

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

After 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.

Blood samples for pharmacodynamic biomarker analysis and pharmacokinetics will be obtained according to the schedules in [Appendix 2](#).

4.5.7.3 Assessments at Treatment Discontinuation Visit

Patients who discontinue from treatment will be asked to return to the clinic not more than 30 days after the last treatment for a treatment discontinuation visit. The visit at which the decision is made to discontinue treatment (e.g., disease progression is determined or confirmed) may be used as the treatment discontinuation visit.

See [Appendix 1](#) and [Appendix 2](#) for the schedule of activities performed at the treatment discontinuation visit.

4.5.7.4 Follow-Up Assessments Ongoing Tumor Assessments

Patients who discontinue study drug for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments at the same frequency as would have been followed if the patient had remained on study drug until death, disease progression (see exceptions for atezolizumab arm in [Section 3.1](#) and [Appendix 1](#), withdrawal of consent, or until the study is terminated by Sponsor, whichever occurs first. Patients who start a new anti-cancer therapy in the absence of disease progression should continue to undergo tumor assessments according to the protocol schedule until disease progression, withdrawal of consent, study termination by Sponsor, or death whichever occurs first.

4.5.7.5 Adverse Events

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. All adverse events regardless of relationship to study drug will be reported until 30 days after the last dose of study drug.

After the treatment discontinuation visit, adverse events should be followed as outlined in [Appendix 9](#).

4.5.7.6 Anti-Therapeutic Antibody and Pharmacokinetic Assessments

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

See the schedules of assessments provided in [Appendix 1](#) and [Appendix 2](#) for specified follow-up assessments.

4.5.7.7 Survival and Subsequent Anti-Cancer Therapy

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

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. 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 noncompliance

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

4.6.1.1 Discontinuation from Study Drug

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

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

Exception: Patients will be permitted to continue atezolizumab after RECIST v1.1 criteria for progressive disease are met if they meet all of the following criteria (see Figure 2 for schematic representation):

Evidence of clinical benefit (defined as the stabilization or improvement of disease-related symptoms) as assessed by the investigator

Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease

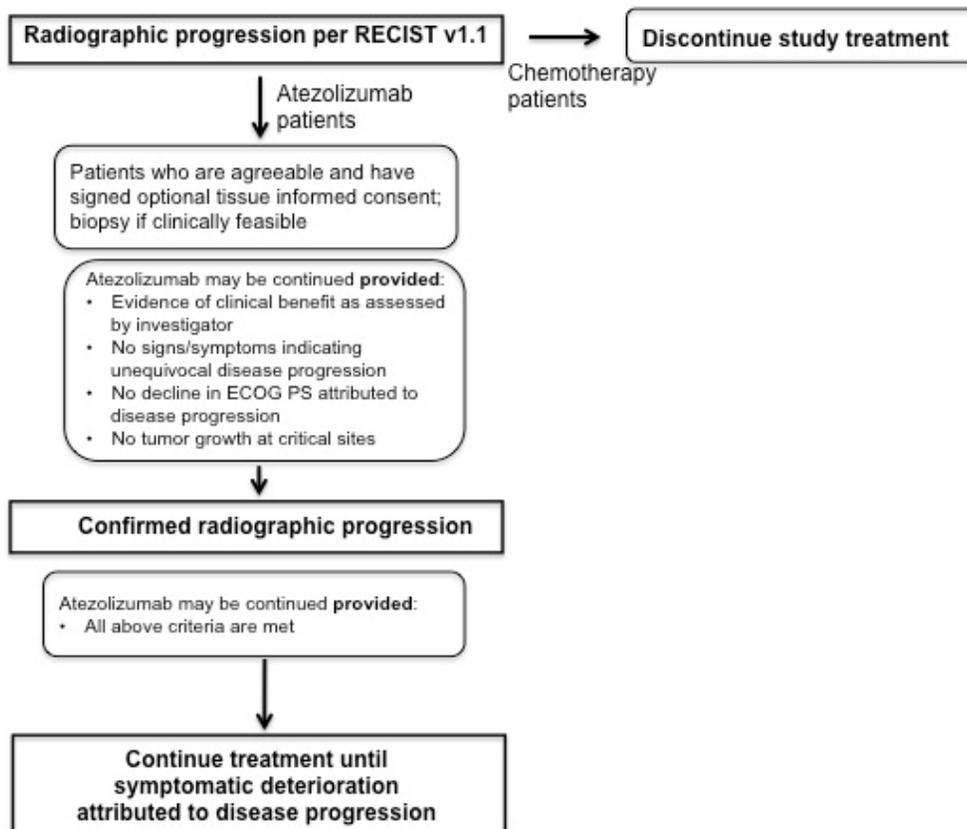
No decline in ECOG performance status that can be attributed to disease progression

Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing

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

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

Figure 2 Conditions for Continuing Atezolizumab in the Presence of Increased Radiographic Tumor Size



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

4.6.2 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 study is placed on hold or if the Sponsor decides to discontinue the study or development program.

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

- Excessively slow recruitment

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Noncompliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice

5. ASSESSMENT OF SAFETY

Atezolizumab is approved in the United States for the treatment of locally advanced or metastatic urothelial carcinoma. Clinical studies are currently ongoing and the entire safety profile is not known at this time. The following information is based on results from nonclinical and clinical studies and published data on similar molecules.

5.1 SAFETY PLAN

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

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. *Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Appendix 9. Refer to Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.*

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, and myocarditis. In addition, systemic immune activation is a potential risk when atezolizumab is given in combination with other immunomodulating agents. Refer to Appendix 9 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with Vinflunine, Paclitaxel, and Docetaxel

For adverse reactions, warnings, and precautions for vinflunine, paclitaxel, and docetaxel see local prescribing information. Other specific instructions can be found in Sections 4.4.3 and 5.1.6 for paclitaxel, Sections 4.4.4 and 5.1.7 for docetaxel, and Sections 4.4.5 and 5.1.8 for vinflunine.

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 trial. Results from the nonclinical toxicology studies with atezolizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were taken into account. Specifically, patients at risk for study-emergent autoimmune conditions or with a prior diagnosis of autoimmune disease, patients with evidence of acute infections, and patients who have received a live, attenuated viral vaccine within 4 weeks of randomization are excluded from the study (see Section 4.1 for additional details).

5.1.3.2 Monitoring

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

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see [Appendix 1](#) and [Appendix 2](#) for the list and timing of study assessments).

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

All serious adverse events and protocol-defined events of special interest (see Section 5.2.3) will be reported in an expedited fashion (see Section 5.4.2). In addition, the iDMC and investigators will review and evaluate observed adverse events on a regular basis.

Patients will be followed for safety for 90 days following their last dose of study drug.

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

5.1.4 Atezolizumab Dose Modification

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment for up to 42 days beyond the last dose if they experience adverse events that require a dose to be withheld. If atezolizumab is withheld because of adverse events for >42 days beyond the last dose, then the patient will be discontinued from atezolizumab and will be followed up for safety and efficacy as specified in Section 4.5.7.4.

If, in the judgment of the investigator, the patient is likely to derive clinical benefit from atezolizumab after a hold of >42 days, study drug may be restarted with the approval of the Medical Monitor.

If a patient must be tapered off steroids used to treat adverse events, atezolizumab may be held for additional time beyond 42 days from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤ 10 mg/day. The acceptable length of interruption will depend on an agreement between the investigator and the Medical Monitor.

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

Management of atezolizumab-specific adverse events is presented below (Section 5.1.5) and in [Appendix 9](#).

5.1.5 Management of Atezolizumab-Specific Adverse Events

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

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

The primary approach to Grade 1–2 immune-mediated adverse events is supportive and symptomatic care with continued treatment with atezolizumab; for higher grade immune-mediated adverse events, atezolizumab should be held and oral/parenteral steroids administered. Recurrent Grade 2 immune-mediated adverse events may also mandate holding atezolizumab or the use of steroids. Consideration for benefit-risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening immune-mediated adverse events.

Management of systemic immune activation is presented below. See [Appendix 9](#) for details on management of *infusion-related reactions*, gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, *neurologic disorders*, potential pancreatic

or eye toxicity, and other immune-mediated adverse events. See [Appendix 7](#) for precautions for anaphylaxis.

5.1.5.1 Systemic Immune Activation

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

Language regarding early identification and management of systemic immune activation may be found in the Atezolizumab Investigator's Brochure. If systemic immune activation is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations.

5.1.6 Paclitaxel Dose Modification and Management of Specific Adverse Events

Paclitaxel should be held for any Grade 3–4 toxicity attributable to paclitaxel (e.g., neutropenia, anemia, thrombocytopenia, peripheral neuropathy, myalgia/arthralgia, and nausea/vomiting) until symptoms resolve to Grade ≤ 1 or baseline grade. When treatment is resumed, the paclitaxel dose may be reduced to 135 mg/m² (see [Table 4](#)). No dose re-escalation will be allowed. Subsequent Grade 3–4 toxicities at the reduced dose will result in discontinuation of paclitaxel. If Grade ≥ 3 toxicities persist for more than 21 days after the last administered dose or recur after dose reduction, the patient will be permanently discontinued from paclitaxel treatment.

See the local prescribing information/institution guidelines for paclitaxel for further guidance on adverse event management and dose modifications.

Table 4 Dose Levels for Paclitaxel

	Starting Dose	First Dose-Level Reduction	Indication for Further Dose-Level Reduction
Paclitaxel	175 mg/m ²	135 mg/m ²	Discontinue

5.1.7 Docetaxel Dose Modification and Management of Specific Adverse Events

Guidelines for docetaxel dose modifications to manage general toxicities are shown in [Table 5](#). Guidelines for the management of hepatotoxicity for docetaxel-treated patients are shown in [Table 6](#). Guidelines for the management of edema for docetaxel-treated patients are shown in [Table 7](#).

Patients who are dosed initially at 75 mg/m² and who experience either febrile neutropenia, neutrophils < 500 cells/ mm³ for more than 1 week, severe or cumulative cutaneous reactions, or other Grade 3–4 non-hematological toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity and then have treatment resumed at 55 mg/m². Patients who develop Grade > 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

Table 5 Guidelines for Management of Specific Docetaxel-Related Adverse Events

Adverse Event (Worst Grade in Previous Cycle)	Action to Be Taken
<ul style="list-style-type: none"> • Febrile neutropenia/Grade 4 AGC ≥ 7 days 	<ul style="list-style-type: none"> • Hold docetaxel until symptoms resolve ^a • Reduce docetaxel to 75% of previous dose (e.g., from 75 mg/m² to 55 mg/m²)
<ul style="list-style-type: none"> • Grade 3 skin/neuropathy/major organ/non-hematologic toxicity 	<ul style="list-style-type: none"> • Hold docetaxel until symptoms resolve • Reduce docetaxel to 75% of previous dose
<ul style="list-style-type: none"> • Grade 4 skin/neuropathy/major organ/non-hematologic toxicity OR <ul style="list-style-type: none"> • Recurrence of Grade 3 toxicity after prior dose reduction 	<ul style="list-style-type: none"> • Discontinue docetaxel treatment

AGC = absolute granulocyte count.

^a Do not retreat until AGC ≥ 1.5 × 10⁹/L, platelets ≥ 100 × 10⁹/L, and toxicity Grade ≤ 2.

Table 6 Guidelines for Management of Hepatotoxicity in Docetaxel-Treated Patients

	AST/ALT		Alkaline Phosphatase		Bilirubin	Docetaxel Dose
Mild to moderate	> 1.5 × ULN	AND	> 2.5 × ULN			75%
Severe	> 3.5 × ULN	AND	> 6 × ULN	OR	> ULN	Do not treat. Discontinue if treatment already started.

ULN = upper limit of normal.

5.1.7.1 Other Specific Toxicities Not Requiring Dose Adjustment Hypersensitivity Reactions

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension, and/or bronchospasm, or very rarely, fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be rechallenged with docetaxel.

Hypersensitivity reactions may occur within a few minutes following initiation of docetaxel infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required.

Fluid Retention

Severe fluid retention has been reported following docetaxel therapy. Patients should be pre-medicated with oral corticosteroids prior to each docetaxel infusion to reduce the incidence and severity of fluid retention (see Section 4.3.2.3). Patients with preexisting effusions should be closely monitored from the first dose for the possible exacerbation of the effusions. See Table 7 for the management of edema.

Table 7 Guidelines for the Management of Edema in Docetaxel-Treated Patients

Edema	Severity	Effusion
Asymptomatic	Mild, Grade 1	Asymptomatic, no intervention needed
Symptomatic	Moderate, Grade 2	Symptomatic, may require intervention
Symptomatic, resulting in interruption of treatment	Severe, Grade 2	Symptomatic, urgent intervention required

5.1.8 Vinflunine Dose Modification and Management of Specific Adverse Events

Criteria for vinflunine dose delay and dose reduction are listed in [Table 8](#) and [Table 9](#), respectively. Criteria for dose reduction in patients with renal impairment or elderly patients are listed in [Table 10](#). See local prescribing information/institution guidelines for vinflunine for further guidance on adverse event management and dose modifications.

Table 8 Dose Delay Guidelines for Vinflunine

Toxicity	Day 1 Treatment Administration
Neutropenia (ANC < 1000/mm ³) OR Thrombocytopenia (platelets < 100,000/mm ³)	Delay until recovery (ANC ≥ 1000/mm ³ and platelets ≥ 100,000 cells/mm ³) and adjust the dose if necessary (see Table 9). Discontinuation if recovery has not occurred within 2 weeks.
Organ toxicity: moderate, severe, or life-threatening	Delay until recovery to mild toxicity or none, or to initial baseline status and adjust the dose if necessary (see Table 9). Discontinuation if recovery has not occurred within 2 weeks.
Cardiac ischemia in patients with prior history of myocardial infarction or angina pectoris	Discontinuation

Table 9 Dose Modification Guidelines for Vinflunine

Toxicity	Dose Modification				
	Vinflunine Initial Dose of 320 mg/m ²			Vinflunine Initial Dose of 280 mg/m ²	
	First Event	Second Consecutive Event	Third Consecutive Event	First Event	Second Consecutive Event
Neutropenia Grade 4 (ANC < 500/mm ³) > 7 days Febrile neutropenia (ANC < 1000/mm ³ and fever ≥ 38.5°C) Mucositis or constipation Grade 2 ≥ 5 days or Grade ≥ 3 any duration Any other toxicity Grade ≥ 3 (severe or life-threatening; except Grade ≥ 3 vomiting or nausea)	280 mg/m ²	250 mg/m ²	Definitive treatment discontinuation	250 mg/m ²	Definitive treatment discontinuation

Table 10 Dose Modification Guidelines for Vinflunine in Patients with Renal Impairment or Elderly Patients

Toxicity	Dose Modification			
	Vinflunine Initial Dose of 280 mg/m ²		Vinflunine Initial Dose of 250 mg/m ²	
	First Event	Second Consecutive Event	First Event	Second Consecutive Event
Neutropenia Grade 4 (ANC < 500/mm ³) > 7 days				
Febrile neutropenia (ANC < 1000/mm ³ and fever ≥ 38.5°C)				
Mucositis or constipation Grade 2 ≥ 5 days or Grade ≥ 3 any duration	250 mg/m ²	Definitive treatment discontinuation	225 mg/m ²	Definitive treatment discontinuation
Any other toxicity Grade ≥ 3 (severe or life threatening; except Grade ≥ 3 vomiting or nausea)				

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of the monitoring and recording of 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 considered related to the medicinal product or not
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.8
- 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 5.3.5.9)

- 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 (rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

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

- The following conditions which may be suggestive of an autoimmune disorder:
 - Pneumonitis
 - Hypoxia or dyspnea Grade ≥ 3
 - Colitis
 - Endocrinopathies: diabetes mellitus, pancreatitis, or adrenal insufficiency
 - Vasculitis
 - Hepatitis
 - Transaminitis: Grade ≥ 2 (AST or ALT $> 3 \times$ ULN and bilirubin $> 2 \times$ ULN) OR AST/ALT $> 10 \times$ ULN
 - Systemic lupus erythematosus
 - Guillain-Barré syndrome
 - Myasthenia gravis
 - Skin reactions: vitiligo, pemphigoid

- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome, or infusion reaction syndromes
- 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
- 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.

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, 5.5, and 5.6.

For each adverse event, 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) on the Adverse Event eCRF.

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 should be reported (e.g., serious adverse events related to invasive procedures such as biopsies).

After initiation of study drug, any serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug. All adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug. After this period, investigators should only report any serious adverse events or other adverse events of concern that are believed to be related to prior treatment with study drug (see Section 5.3.5.6 for reporting of deaths).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of nondirective questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of nondirective 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 11 will be used for assessing the severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 11 Adverse Event Severity Grading Scale

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

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

Note: Based on the NCI CTCAE (Version 4.0), which can be found at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered 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 (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

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; colloquialisms and abbreviations should be avoided.

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.

5.3.5.1.1 Infusion-Related Reactions

An exception to the above is symptoms that occur during or within 24 hours after an atezolizumab infusion. These may be part of an acute infusion reaction and should not be recorded under the diagnosis of “infusion-related reaction.” Rather, non-serious symptoms should be recorded as separate adverse events on the Adverse Event eCRF.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if chest pain is known to have resulted in myocardial infarction, it is sufficient to record only myocardial infarction as an adverse event on the eCRF.

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

5.3.5.3 Persistent or Recurrent Adverse Events

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

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

5.3.5.4 Abnormal Laboratory Values

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

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

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

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).

5.3.5.4.1 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3 \times \text{ULN}$ in combination with total bilirubin $>2 \times \text{ULN}$

- Treatment-emergent ALT or AST $>3 \times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or, if a diagnosis cannot be established, the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.5 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:

- Worsened from baseline
- 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 if 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).

5.3.5.6 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 UBC should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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

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. The term “**sudden death**” should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. 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.

During survival follow-up, deaths attributed to progression of UBC should be recorded only on the Survival eCRF.

5.3.5.7 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”).

5.3.5.8 Worsening of Urothelial Bladder Cancer

The term disease progression (i.e., worsening and/or progression of UBC) should not be recorded as an adverse event. The underlying symptoms should be captured as adverse events and assessed accordingly for seriousness, severity, and causality. Data for disease progression will be captured as efficacy assessment data only.

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST 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 with use of objective criteria.

5.3.5.9 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization 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.

The following hospitalization scenarios are not considered to be serious adverse events:

- 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.

The following hospitalization scenarios are not considered to be serious adverse events but should be reported as adverse events instead:

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

5.3.5.10 Adverse Events Associated with an Overdoses or Error in Drug Administration

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

5.3.5.11 Patient-Reported Outcome Data

The PRO measurements are described in Section [3.4.4](#). The methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Because of these differences, PRO data will not be reported as adverse events and no attempt will be made to resolve any noticeable discrepancies between PRO data and observed or volunteered adverse events. The PRO data will be presented in separate tables, figures, and data listings from the adverse event data, and will be included in the appropriate section of the final study report.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Adverse events of special interest
- Pregnancies

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 on the basis of 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 (Roche Medical Responsible) Contact Information

Medical Monitor: [REDACTED], M.D.
E-mail: [REDACTED]
Telephone Nos.: + [REDACTED] (mobile)
+ [REDACTED] (office)

Back-up Medical Monitor: [REDACTED], M.D.
E-mail: [REDACTED] m
Telephone Nos.: + [REDACTED] (mobile)
+ [REDACTED] (office)

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

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

5.4.2.1 Events that Occur prior to Study Drug Initiation

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

The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to Roche 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 with use of 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. All adverse events regardless of relationship to study drug will be reported until 30 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the 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, a paper Serious Adverse Event/Adverse Event of Special Interest Case Report Form (CRF) and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), with use of the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab, 3 months after the last dose of vinflunine, and 6 months after the last dose of docetaxel or paclitaxel. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancies 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 the conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to Roche 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 with use of the fax number or

email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Pregnancies in Female Partners of Male Patients

There are no known reproductive risks to the female partner of a male patient receiving atezolizumab. 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 3 months after the last dose of vinflunine, and 6 months after the last dose of docetaxel or paclitaxel. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. 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. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. 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.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section [5.4.3.1](#).

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), 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](#)).

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, new anti-cancer treatment is initiated, the patient is lost to follow-up, or the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event. Every effort should be made to follow all serious adverse events considered related to study drug or trial-related procedures until a final outcome can be reported.

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

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (see Section 5.3.1), all deaths, regardless of cause, should be reported through use of the Survival Follow-Up eCRF. In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior study drug treatment or study procedure, the event should be reported through use of the Adverse Event eCRF (see Section 5.3.5.6 for reporting of deaths).

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 on the basis of applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events with use of the Atezolizumab IB as a reference and with the use of vinflunine, paclitaxel or docetaxel local label as a reference.

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

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a Phase III, global, multicenter, open-label, randomized, two-arm, controlled study designed to evaluate the efficacy and safety of atezolizumab compared with chemotherapy in patients with locally advanced or metastatic UBC who have progressed during or following a platinum-containing regimen. Within the chemotherapy control arm, the percentage of patients who are treated with a taxane (paclitaxel or docetaxel) will be capped at 40%. Until that cap is reached, the selection of the specific chemotherapy (vinflunine or taxane) for patients who are randomized to the chemotherapy arm will be per investigator's choice.

Primary efficacy analysis of OS and PFS will be performed on randomized patients, irrespective of whether the assigned treatment was actually received. ORR analyses will be performed on all randomized patients who have measureable disease at baseline. DOR analyses will be performed on the subset of patients who achieve an objective response. For all efficacy analyses, patients will be grouped according to the treatment assigned at randomization.

Safety analyses will be performed on all randomized patients who received any amount of study treatment (i.e., atezolizumab or chemotherapy), with patients grouped according to whether any amount of atezolizumab was received including the case when atezolizumab was received in error.

6.1 DETERMINATION OF SAMPLE SIZE

This study will enroll approximately 931 patients, including a minimum of 230 patients with a PD-L1 IHC score of IC2/3 and a minimum of 537 patients with a PD-L1 IHC score of IC1/2/3.

The numbers of events required to demonstrate efficacy of the atezolizumab experimental arm over the chemotherapy arm (i.e., vinflunine, paclitaxel, or docetaxel) with regard to OS are estimated based on the following assumptions:

- Two-sided significance level of 5%
- 94% for the primary analysis of OS in the population of patients with an IHC score of IC2/3 with an HR of 0.57, corresponding to an improvement in median OS from 7.5 months to 13.2 months
- 98% power for the primary analysis of OS in the population of patients with an IHC score of IC1/2/3 with an HR of 0.68, corresponding to an improvement in median OS from 7.5 months to 11 months

- 97% power for the primary analysis of OS in the ITT population with an HR of 0.74, corresponding to an improvement in median OS from 7.5 months to 10.1 months
- 1:1 randomization ratio
- Dropout rate of 5% per year over 24 months

6.2 ANALYSES TIMING

The primary analyses of OS will occur when approximately 152, 403, and 652 deaths have been observed in the following populations: patients with an IHC score of IC2/3, patients with an IHC score of IC1/2/3, and ITT populations, respectively, whichever occurs later. This is expected to occur approximately 25 months after FPI. No interim analysis is planned for this study.

The timing of the primary analyses of OS will depend on the actual accrual rate and will be driven by the occurrence of number of deaths as indicated above.

6.3 SUMMARIES OF CONDUCT OF STUDY

Study enrollment, study drug administration, reasons for discontinuation from study drug, and reasons for study termination will be summarized by treatment arm for the following populations: patients with an IHC score of IC2/3, patients with an IHC score of IC1/2/3, and overall ITT population. Major protocol violations will be reported and summarized by treatment arm for the overall ITT population.

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic characteristics, such as age, sex, race/ethnicity, baseline disease characteristics (e.g., ECOG performance status), and number of prior cancer treatments, will be summarized by treatment arm for the following populations: patients with an IHC score of IC2/3, patients with an IHC score of IC1/2/3, and the overall ITT population individually. Descriptive statistics (mean, median, SD, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

Baseline measurements are the last available data obtained prior to the patient receiving the first dose of study drug.

6.5 EFFICACY ANALYSES

6.5.1 Primary Efficacy Endpoint

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

The primary analysis will occur when approximately 152, 403, and 652 deaths have been observed in the following populations: patients with an IHC score of IC2/3, patients with an IHC score of IC1/2/3, and ITT populations respectively, whichever occurs later.

Comparisons with respect to OS between the treatment and control arms will be tested using a hierarchical fixed-sequence procedure based on a stratified log-rank test at two-sided level of 5% significance within the following populations: patients with an IHC score of IC2/3, patients with an IHC score of IC1/2/3, and in the ITT population as follows:

1. Test to reject the null hypothesis of no difference in OS between the two arms in the population of patients with an IHC score of IC2/3. If the estimate of the HR is < 1 and the two-sided p-value corresponding to the stratified log-rank test is < 0.05 , the null hypothesis will be rejected and it will be concluded that atezolizumab prolongs OS relative to chemotherapy (i.e., vinflunine, paclitaxel, or docetaxel) in the population of patients with an IHC score of IC2/3.
2. If the null hypothesis from Step 1 is rejected, then test to reject the null hypothesis of no difference in OS between the two arms in the population of patients with an IHC score of IC1/2/3. If the estimate of the HR is < 1 and the two-sided p-value corresponding to the stratified log-rank test is < 0.05 , the null hypothesis will be rejected and it will be concluded that atezolizumab prolongs OS relative to chemotherapy (i.e., vinflunine, paclitaxel, or docetaxel) in the population of patients with an IHC score of IC1/2/3.
3. If the null hypothesis from Step 2 is rejected, then test to reject the null hypothesis of no difference in OS between the two arms in the ITT population. If the estimate of the HR is < 1 and the two-sided p-value corresponding to the stratified log-rank test is < 0.05 , the null hypothesis will be rejected and it will be concluded that atezolizumab prolongs OS relative to chemotherapy (i.e., vinflunine, paclitaxel, or docetaxel) in the ITT population.

The stratification factors will be those specified for randomization (i.e., chemotherapy, PD-L1 IHC status, prognostic factors, and liver metastases). Results from an unstratified analysis will also be presented.

Kaplan–Meier methodology will be used to estimate median OS for each treatment arm and to construct survival curves for the visual description of the difference between the treatment arms. Brookmeyer–Crowley methodology will be used to construct the 95% CI for the median OS for each treatment arm ([Brookmeyer and Crowley 1982](#)).

6.5.2 Secondary Efficacy Endpoints

If the primary endpoint of OS is statistically significant in the population of patients with an IHC score of IC2/3, the population of patients with an IHC score of IC1/2/3, and in the ITT population, the secondary endpoints of ORR and PFS will be tested in order (i.e., ORR followed by PFS), each at the two-sided 5% significance level in each respective population (i.e., test for an ORR difference between the two arms in the population of

patients with an IHC score of IC2/3, and if the preceding null hypothesis is rejected, test for an ORR difference in the population of patients with an IHC score of IC1/2/3. If the preceding null hypothesis is rejected, test for an ORR difference in the ITT population, and if the preceding null hypothesis is rejected, test for a PFS difference between the two arms in the population of patients with an IHC score of IC2/3, and if the preceding null hypothesis is rejected, test for a PFS difference between the two arms in the population of patients with an IHC score of IC1/2/3, and if the preceding null hypothesis is rejected, test for a PFS difference in the ITT population).

6.5.2.1 Objective Response Rate

An objective response is defined as either a CR or PR, as determined by the investigator with use of RECIST v1.1. Objective response in this study does not need to be a confirmed response. Patients not meeting these criteria including patients including patients without any post-baseline tumor assessment will be considered non-responders.

ORR is defined as the proportion of patients who had an objective response. The analysis population for ORR will be all randomized patients with measurable disease at baseline. An estimate of ORR and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms will be determined using the normal approximation to the binomial distribution. The ORR will be compared between the two arms with use of the stratified Cochran-Mantel-Haenszel test.

6.5.2.2 Progression-Free Survival

PFS is defined as the time between the date of randomization and the date of first documented disease progression or death, whichever occurs first. Disease progression will be determined on the basis of investigator assessment with use of RECIST v1.1. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

The analyses that will be performed for OS as described in Section 6.5.1 will also be applied to PFS.

6.5.2.3 Duration of Objective Response

DOR is defined as the time between the date of the first occurrence of a complete or partial response (whichever status is recorded first) and the date of first documented progressive disease or death is documented, whichever occurs first. Disease progression will be determined on the basis of investigator assessment with use of RECIST v1.1. DOR based on the investigator assessment will be analyzed for the subset of patients who achieve an objective response as determined by the investigator with use of RECIST v1.1.

Patients who have not progressed or who have not died by the data cutoff date for analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after date of the first occurrence of a complete or partial response, DOR will be censored at the date of the first occurrence of a complete or partial response plus 1 day.

The secondary endpoint of DOR as well as the exploratory efficacy endpoints will be analyzed but will not be part of the endpoints in the hierarchical fixed sequence.

DOR analysis is based on a non-randomized subset of patients (specifically, patients who achieve an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. DOR will be estimated using Kaplan-Meier methodology. Comparisons between treatment arms will be made for descriptive purposes only.

Further details on the analysis plan of secondary endpoints can be found in the Statistical Analysis Plan (SAP).

6.5.3 Handling of Missing Data

For OS, patients who are not reported as having died will be analyzed as censored observations on the date when 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 a post-baseline assessment will be considered non-responders.

For PFS, patients without a date of disease progression and death will be analyzed as censored observations on the date of last tumor assessment. If no post-baseline tumor assessment is available, PFS will be censored at the date of randomization plus 1 day.

For DOR, patients who have not progressed or 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 date of the first occurrence of a complete or partial response, DOR will be censored at the date of the first occurrence of a complete or partial response plus 1 day.

6.6 SAFETY ANALYSES

Safety analyses will be performed on safety-evaluable population, defined as all randomized patients who receive any amount of the study drug, with patients grouped according to whether any amount of atezolizumab was received, including the case when atezolizumab was received in error. Summaries will be presented for the safety-evaluable populations by treatment arm.

Drug exposure will be summarized to include treatment duration, number of doses, and dose intensity.

Verbatim description of adverse events will be mapped to MedDRA thesaurus terms 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, severe adverse events (Grade ≥ 3), adverse events of special interest, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. The proportion of patients experiencing at least one adverse event will be reported by toxicity term and treatment arm.

Laboratory data with values outside the normal ranges will be identified. In addition, selected laboratory data will be summarized by treatment arm and grade.

Changes in vital signs will be summarized by treatment arm and grade.

Deaths reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation will be summarized by treatment arm.

6.7 PHARMACOKINETIC ANALYSES

Atezolizumab serum concentration data (C_{\min} and C_{\max}) will be tabulated and summarized for each cycle at which pharmacokinetics are to be measured (C_{\max} will be reported for Cycle 1 only; C_{\min} will be evaluated at Cycles 1, 2, 3, 4, 8, and 16 and both at treatment discontinuation and at 120 days [± 30 days] after the last dose of atezolizumab). Descriptive statistics will include means, medians, ranges, and SDs, as appropriate.

Additional PK and pharmacodynamic analyses will be conducted as appropriate.

6.8 OUTCOME ANALYSES

The EORTC 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 pro-rated 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. All PRO data analyses will be performed on patients with baseline assessments and at least one post-baseline assessment by treatment arm for the following populations (individually): patients with an IHC score of IC2/3, patients with an IHC score of IC1/2/3, and the ITT population.

HRQoL will be summarized using items from the EORTC QLQ-C30. A responder analysis will be used to assess improvement in function between treatment arms. Responders are defined as patients with a ≥ 10 -point improvement in mean scale score

from baseline and will be assessed in the fatigue and physical function scales. Patient-reported bothersomeness of treatment-related symptoms, including constipation, nausea and vomiting, diarrhea, and pain, will be summarized descriptively as absolute mean scores and change from baseline for each post-baseline assessment.

6.9 EXPLORATORY ANALYSES

Analyses using modified RECIST criteria (atezolizumab arm only with no comparison to the chemotherapy arm for PFS, ORR, and DOR) will also be performed (see [Appendix 3](#)). The investigator-assessed ORR is defined as the proportion of patients whose best overall response is either a PR or CR per modified RECIST.

DCR is defined as the rate of patients with complete or partial response as best response or stable disease maintained for ≥ 18 weeks per RECIST v1.1. The analysis methods for DCR will be the same as those for the analysis of ORR.

Exploratory biomarker analyses will be performed in order to understand the association of these markers with study drug response, including efficacy and/or adverse events. Exploratory biomarker analyses will include assessments of biomarkers in both tumor tissue and blood. Changes in biomarkers will be listed by cohort and response status.

The pharmacodynamic biomarker analyses will include patients with at least one predose and one postdose biomarker assessment, with patients grouped according to the treatment actually received. Blood samples for biomarker assessments will be assayed using analytically qualified methods (e.g., enzyme-linked immunosorbent assay, quantitative real-time polymerase chain reaction).

EQ-5D (3L) health status data will be used for obtaining utility measures for economic modeling. For the EQ-5D (3L), further scoring and analysis may be reported in a separate document.

All items from the EORTC QLQ-C30 that are not included in the main PRO outcomes analyses will be summarized descriptively with summary statistics (mean, SD, median, 25th and 75th percentiles, and range) of absolute scores of the EORTC QLQ-C30 scales and their changes from baseline at each assessment timepoint for both treatment arms.

6.10 SENSITIVITY ANALYSES

6.10.1 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 survival in either treatment arm, a sensitivity analysis (“worst-case” analysis) will be performed 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.

6.10.2 Subsequent Anti-Cancer Therapy

The impact of non-protocol specified anti-cancer therapy use on OS will also be assessed.

6.11 SUBGROUP ANALYSIS

To assess the consistency of the study results in subgroups defined by demographics (e.g., age, sex, and race/ethnicity) and baseline prognostic characteristics (e.g., PD-L1 IHC status, ECOG performance status, number of risk factors, hemoglobin, vinflunine vs. taxane, visceral involvement, liver metastasis, etc.), OS in these subgroups will be examined. It is expected that accrual in subgroups defined by these baseline characteristics may not be large enough for definitive treatment comparisons to be made between these subgroups.

Summaries of survival, including unstratified hazard ratios 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.

6.12 INTERIM ANALYSES

No interim efficacy analyses are planned for this study.

An iDMC will be set up to evaluate safety results approximately every 6 months after FPI. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an external iDCC. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.

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 with use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

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

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

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

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

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

Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in

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

7.5 RETENTION OF RECORDS

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

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

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 application (IND) will comply with U.S. Food and Drug Administration (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 Caregiver's 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.

The Informed Consent Form will contain a separate section that addresses the collection of optional samples and the use of remaining mandatory samples (plasma, serum, whole

blood, and tissue) for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. 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 allow the collection of optional samples and to use any remaining specimens for exploratory research. Patients who decline to participate will not provide a separate signature.

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

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 250 sites globally will participate in the study and approximately 931 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.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results.

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

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

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

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

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

9.6 PROTOCOL AMENDMENT SECTIONS

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

- Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer* 2011;47:8–32.
- 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.
- American Cancer Society. Cancer facts and figures. 2013. Available from: <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-031941.pdf>.
- 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.
- Bamias A, Aravantinos G, Deliveliotis C, et al. Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the hellenic cooperative oncology group. *J Clin Oncol* 2004;22:220–8.
- Bellmunt J, Choueiri TK, Fougeray R, et al. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. *J Clin Oncol*. 2010;28:1850–5.
- Bellmunt J, Orsola A, Wiegel T, et al. Bladder cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol* 2011;22:vi45–9.
- Bellmunt J, Théodore 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.
- 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.
- Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics* 1982;38:29–41.
- Butte MJ, Keir ME, Phamduy TB, et al. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. *Immunity* 2007;27:111–22.

- Chalasan V, Chin JL, Izawa JI. Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. *Can Urol Assoc* 2009;3:S193–8.
- Chen DS, Irving BA, Hodi FS, et al. Molecular pathways: next-generation immunotherapy—inhibiting programmed death–ligand 1 and programmed death-1. *Clin Cancer Res* 2012;18:6580–7.
- Choueiri TK, Ross RW, Jacobus S, et al. Double-blind, randomized trial of docetaxel plus vandetanib versus docetaxel plus placebo in platinum-pretreated metastatic urothelial cancer. *J Clin Oncol* 2012;30:507–12.
- Crawford J, Caserta C, Roila F, et al., on behalf of the ESMO Guidelines Working Group. Hematopoietic growth factors: ESMO recommendations for the applications. *Ann Oncol* 2009;20:162–5.
- De Santis M, Bellmunt J, Mead J. 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.
- Di Giacomo AM, Biagioli M, Maio M. The emerging toxicity profiles of anti–CTLA-4 antibodies across clinical indications. *Semin Oncol* 2010;37:499–507.
- Dogliotti L, Carteni G, Siena S, et al. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. *Eur Urol* 2007;52:134–41.
- Dreicer R, Gustin DM, See Wa, et al. Paclitaxel in advanced urothelial carcinoma: its role in patients with renal insufficiency and as salvage therapy. *J Urol* 1996;156:1606–8.
- Dreicer R, Manola J, Roth BJ, et al. Phase III trial of methotrexate, vinblastine, doxorubicin, and cisplatin versus carboplatin and paclitaxel in patients with advanced carcinoma of the urothelium. *Cancer*. 2004;100:1639–45.
- Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:22–47.
- Fayers PM, Aaronson NK, Bjordal K, et al. On behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.
- Garcia JA, Dreicer R. Systemic chemotherapy for advanced bladder cancer: update and controversies. *J Clin Oncol* 2006;24:5545–51.
- GLOBOCAN 2008. Estimated cancer incidence: mortality, prevalence and disability-adjusted life years (DALYs) Worldwide in 2008. Available at: <http://globocan.iarc.fr/factsheets/cancers/lung.asp>.
- Hales RK, Banchereau J, Ribas A, et al. Assessing oncologic benefit in clinical trials of immunotherapy agents. *Ann Oncol* 2010;21:1944–51.

- Herbst RS, Gordon MS, Fine GD, et al. A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumors. *J Clin Oncol* 2013;31:abstract 3000.
- 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.
- Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711–23.
- Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363:411–22.
- Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. *Annual Rev Immunol* 2008;26:677–704.
- 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.
- Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124:188–95.
- 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.
- Logothetis CJ, Dexeus FH, Finn L, et al. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. *J Clin Oncol* 1990;8:1050–5.
- Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer J*. 2014;20(2):119–22.
- 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. *Medical Oncology* 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 Cancer Institute. Surveillance, Epidemiology, and End Results Program (SEER) Stat Facts Sheets: bladder cancer. 2013 Nov. Available from: <http://seer.cancer.gov/statfacts/html/urinb.html>.
- Nishino M, Gargano M, Suda M, et al. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab. *J Immunother Can* 2014;2:17.

- Nishino M, Giobbie-Hurder A, Gargano M, et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. *Clin Can Res* 2013;19:3936–43.
- 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 Life Res* 1997;6:103–8.
- Pond GR, Agarwal N, Bellmunt J, et al. A nomogram including baseline prognostic factors to estimate the activity of second-line therapy for advanced urothelial carcinoma. *BJU Int*. 2013 Nov 13. doi: 10.1111/bju.12564. [Epub ahead of print].
- Rosenberg AS, Worobec AS. A risk-based approach to immunogenicity concerns of therapeutic protein products. *BioPharm Intl* 2004;Nov:22–26;Dec:34–42.
- Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006;3187–205.
- Sonpavde G, Sternberg CN, Rosenberg JE, et al. Second-line systemic therapy and emerging drugs for metastatic transitional-cell carcinoma of the urothelium. *Lancet Oncol* 2010;11:861–70.
- Stenzl A, Cowan NC, De Santis M, et al. Treatment of muscle-invasive and metastatic bladder cancer: update of the EAU guidelines. *Eur Urol* 2011;59(6);1009–18.
- 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.
- Teachey DT, Rheingold SR, Maude SL, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. *Blood*. 2013;121:5154–7.
- 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.
- Vaughn DJ, Broome CM, Hussain M, et al. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. *J Clin Oncol* 2002;20:937–40.
- 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.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Can Res* 2009;15:7412–20.

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.

Appendix 1 Schedule of Assessments

Assessment Window (Days)	Screening ^a	All Cycles	Treatment Discontinuation ^b	Follow-Up
	Days –28 to –1	Day 1 (±3 Days for Cycles ≥2)	≤30 Days after Last Dose	
Signed Informed Consent Form(s) ^a	x			
Review of eligibility criteria	x			
Medical, surgical, and cancer histories, including demographic information ^c	x			
HIV, HBV, HCV, EBV serology ^d	x			
TB test ^e	x			
Concomitant medications ^f	x	x	x	
Tumor assessment ^g	x	Every 9 weeks ±3 business days for 54 weeks and every 12 weeks ±6 business days thereafter until disease progression, death, or loss of follow-up		
Patient-reported outcomes ^h		x	x	x
Complete physical examination ⁱ	x		x	
Limited physical examination ⁱ		x ^j		x
ECOG performance status	x	x ^j	x	
Vital signs ^k	x	x	x	
12-lead ECG ^l	x	x ^l	x ^l	
Weight	x	x	x	
Height	x			
Hematology ^m	x	x ^j	x	
Serum chemistry ⁿ	x	x ^j	x	

Appendix 1 Schedule of Assessments (cont.)

Assessment Window (Days)	Screening ^a	All Cycles	Treatment Discontinuation ^b	Follow-Up
	Days -28 to -1	Day 1 (±3 Days for Cycles ≥2)	≤30 Days after Last Dose	
Coagulation panel (aPTT, INR) ⁿ	x		x	
Vitamin D assay	x			
C-reactive protein testing	x	x ^o		
Urinalysis ^p	x	x ^q	x	
Serum pregnancy test ^r	x			
TSH, free T3, free T4	x	x ^s	x	
Auto-antibody testing (atezolizumab patients only) ^t		x		
Serum sample for ATA assessment (atezolizumab patients only) ^u		x	x	
Serum sample for PK sampling (atezolizumab patients only) ^u		x	x	
Blood samples for pharmacodynamics biomarkers ^v		x	x	
Optional whole blood sample for RCR DNA ^w	x			
Adverse events ^x		x	x	x
Study drug infusion ^y		x		
Archival/screening FFPE tumor tissue specimen or 15 unstained slides ^z	x			

Appendix 1 Schedule of Assessments (cont.)

Assessment Window (Days)	Screening ^a	All Cycles	Treatment Discontinuation ^b	Follow-Up
	Days –28 to –1	Day 1 (±3 Days for Cycles ≥2)	≤30 Days after Last Dose	
Fresh biopsy (optional RCR)	x ^{aa}		Per investigator discretion, biopsy(ies) to be performed preferably at the time of radiographic progression (atezolizumab-treated patients only) ^z	
Survival and anti-cancer therapy follow-up ^{bb}				x

anti-HBc=antibody against hepatitis B core antigen; ATA=anti-therapeutic antibody; EBV=Epstein-Barr virus; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D (3L)=EuroQoL 5 Dimensions; FFPE=formalin fixed paraffin embedded; HBV=hepatitis B virus; HCV=hepatitis C virus; MUGA=multiple-gated acquisition; PD-L1=programmed death-ligand 1; PK=pharmacokinetic; PRO=patient-reported outcome; QLQ-C30=Quality-of-life Questionnaire Core 30; RCR=Roche Clinical Repository; RECIST=Response Evaluation Criteria in Solid Tumors; 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.
- ^b Patients will be asked to return to the clinic not more than 30 days after the last treatment for a treatment discontinuation visit.
- ^c 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.
- ^d 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 trial. Hepatitis B surface antigen, 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 prior to Cycle 1, Day 1. EBV serology tests will be performed centrally on the samples collected during screening only in patients who experience an acute inflammatory event such as systemic inflammatory response syndrome while receiving study treatment.

Appendix 1 Schedule of Assessments (cont.)

-
- ^e All patients will have a tuberculin (PPD) skin test or IGRA done locally prior to the inclusion into the study, and patients with active TB will be excluded from the clinical trial.
- ^f 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 the date of informed consent should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.
- ^g 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. For patients randomized to vinflunine or taxane, assessments will continue until disease progression per RECIST v1.1 (see [Appendix 4](#)), regardless of whether treatment has been discontinued. Patients randomized to atezolizumab will undergo assessments until disease progression or until treatment discontinuation (for patients who continue to receive atezolizumab following disease progression). Tumor assessments should continue regardless of whether patients start new anti-cancer therapy in the absence of disease progression unless they withdraw consent. 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. Patients assigned to atezolizumab who continue treatment beyond radiographic disease progression (see [Section 4.6.1.1](#)) will be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 9 weeks. If the scan frequency is every 12 weeks, the follow-up scan must be performed at 9 weeks (± 2 weeks) as an unscheduled tumor assessment, or earlier if clinically indicated. Investigators may perform additional scans or more frequent assessments if clinically indicated.
- ^h The PRO questionnaires (EORTC QLQ-C30, and EQ-5D [3L]) will be completed by the patients at the investigational site. All PRO questionnaires are required to be administered prior to administration of study treatment and/or prior to any other study assessment(s) to ensure that the validity of the instrument is not compromised and to ensure that data quality meets regulatory requirements. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site, and the hard copy originals of the questionnaires must be maintained as part of the patient's medical record when relevant at the site for source data verification. In addition, the EQ-5D only will be collected at 6, 12, and 24 weeks after disease progression per RECIST 1.1 through telephone interview by trained site staff and in compliance with best practices and recommendations by EuroQoL. Study personnel will record patient responses on a paper copy of the EQ-5D (3L) during the telephone interview as record of source documentation.
- ⁱ Complete and limited physical examinations are defined in [Section 4.5.2.2](#).

Appendix 1 Schedule of Assessments (cont.)

-
- ^j ECOG performance status, limited physical examination, local laboratory assessments, and C-reactive protein assessment may be obtained ≤ 96 hours before Day 1 of each cycle (including Cycle 1).
 - ^k Vital signs include heart rate, respiratory rate, blood pressures, and temperature. At all infusions of study drug (atezolizumab, vinflunine, paclitaxel, or docetaxel), the patient's vital signs should be determined up to 60 minutes before and 30 (± 10) minutes after the infusion. For the atezolizumab arm, vital signs will also be collected during the first infusion (every 15 [± 5] minutes).
 - ^l ECG recordings will be obtained during screening and when clinically indicated. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.
 - ^m Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. See Section 4.1.1 for a list of laboratory results obtained within 14 days prior to the first study treatment.
 - ⁿ Serum chemistry includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin. See Section 4.1.1 for a list of laboratory results obtained within 14 days prior to the first study treatment.
 - ^o On Day 1 of Cycle 4 and every four cycles thereafter until Cycle 16.
 - ^p Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood).
 - ^q On Day 1 of Cycle 3 and every two cycles thereafter.
 - ^r Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Day 1. Starting from Cycle 3, either serum or urine pregnancy test (positive urine test results will be confirmed with a serum pregnancy test) must be performed every two cycles during the study treatment, and as clinically indicated thereafter.
 - ^s On Day 1 of Cycle 5 and every four cycles thereafter.
 - ^t For patients assigned to atezolizumab only. Baseline sample to be collected on Cycle 1, Day 1 prior to the first dose of study treatment. For patients who show evidence of immune-mediated toxicity, additional samples will be collected, and all samples will be analyzed centrally. Includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.
 - ^u For patients assigned to atezolizumab only. See Appendix 2 for details of the ATA and PK collection schedule. Blood samples should be processed to obtain serum. A post-treatment ATA and PK sample should be collected 120 (± 30) days after the last dose of atezolizumab unless the patient withdraws consent or the study closes.
 - ^v See Appendix 2 for details of the pharmacodynamic sampling schedule.

Appendix 1 Schedule of Assessments (cont.)

-
- ^w Whole blood for DNA isolation will be collected from patients who have consented to optional RCR sampling at baseline. If, however, the RCR genetic blood sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study.
- ^x 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, any serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug. All adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug. After this period, investigators should only report any serious adverse events or other adverse events of concern that are believed to be related to prior treatment with study drug (see Section 5.3.5.6 for reporting of deaths). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.
- ^y Patients should receive their first dose of study drug the day of randomization if possible. If this is not possible, the first dose should occur no later than 3 days after randomization. For atezolizumab, the will be delivered over 60 (± 15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. Atezolizumab treatment may be continued as long as the patient continues to experience clinical benefit in the opinion of the investigator until unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status. For vinflunine, paclitaxel, and docetaxel, study drug will be administered according to the local prescribing information, including premedication for paclitaxel (see Section 4.3.2) and docetaxel. Vinflunine, paclitaxel, and docetaxel treatment will continue until disease progression per standard RECIST v1.1 or unacceptable toxicity.
- ^z 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 of the Informed Consent Form, retrieval and submission of archival tumor sample can occur outside the 28-day screening period.
- ^{aa} For patients who have consented to collection of optional biopsies on the Optional Collection of Samples for RCR Informed Consent Form, optional tumor biopsy samples may be collected by core needle or excisional/punch biopsy per investigator discretion. Preferably, growing lesions should be selected, and samples collected at the time of radiographic progression. Optional biopsy tissue will be stored in the RCR. Not applicable for a site that has not been granted approval for RCR sampling.

Appendix 1 Schedule of Assessments (cont.)

^{db} Starting from treatment discontinuation visit, survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by Roche. 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 study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 2 Anti-Therapeutic Antibody, Pharmacodynamic, and Pharmacokinetic Sampling Schedule

Study Visit	Time	Sample	
		Patients Randomized to Vinflunine, Paclitaxel, or Docetaxel	Patients Randomized to Atezolizumab
Cycle 1, Day 1	Predose	Pharmacodynamics ^a	ATA Atezolizumab pharmacokinetics and pharmacodynamics. ^a
	30 (± 10) minutes after end of atezolizumab infusion		Atezolizumab pharmacokinetics
Cycles 2, 3, and 4, Day 1	Predose	Pharmacodynamics ^a	ATA Atezolizumab pharmacokinetics and pharmacodynamics. ^a
Cycles ≥ 8, Day 1	Predose		ATA (every 8 cycles). Atezolizumab pharmacokinetics (every 8 cycles).
At time of fresh biopsy (before treatment, on treatment, or at progression)		Pharmacodynamics ^a	Pharmacodynamics ^a
Treatment discontinuation visit	At visit	Pharmacodynamics ^a	ATA Atezolizumab pharmacokinetics and pharmacodynamics. ^a
120 (± 30) days after last dose of atezolizumab	At visit		ATA Atezolizumab pharmacokinetics and pharmacodynamics. ^a

ATA= anti-therapeutic antibody.

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

Appendix 3 Modified Response Evaluation Criteria in Solid Tumors

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

Modified Response Evaluation Criteria in Solid Tumors (RECIST) is derived from RECIST, Version 1.1 (RECIST v1.1) conventions^{1,2,3} and immune-related response criteria^{3,4,5} (irRC). When not otherwise specified, RECIST v1.1 conventions will apply.

Modified RECIST and RECIST, Version 1.1: Summary of Changes

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

RECIST = Response Evaluation Criteria in Solid Tumors.

-
- ¹ Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
 - ² Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443–54.
 - ³ Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Can Res* 2009;15:7412–20.
 - ⁴ Nishino M, Gargano M, Suda M, et al. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab. *J Immunother Can* 2014;2:17.
 - ⁵ Nishino M, Giobbie-Hurder A, Gargano M, et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. *Clin Can Res* 2013;19:3936–43.

Appendix 3

Modified Response Evaluation Criteria in Solid Tumors (cont.)

DEFINITIONS OF MEASURABLE/NONMEASURABLE LESIONS

All measurable and nonmeasurable lesions should be assessed at screening and at the protocol-specified tumor assessment timepoints. Additional assessments may be performed, as clinically indicated for suspicion of progression. The investigator will evaluate response to treatment with use of modified RECIST.

MEASURABLE LESIONS

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

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

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

NONMEASURABLE LESIONS

Nonmeasurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm), as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

BONE LESIONS

Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Appendix 3

Modified Response Evaluation Criteria in Solid Tumors (cont.)

Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are nonmeasurable.

CYSTIC LESIONS

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

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

LESIONS WITH PRIOR LOCAL TREATMENT

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

TUMOR RESPONSE EVALUATION

DEFINITIONS OF TARGET/NONTARGET LESIONS

Target Lesions

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

Appendix 3

Modified Response Evaluation Criteria in Solid Tumors (cont.)

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

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

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

Nontarget Lesions

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

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

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

Appendix 3

Modified Response Evaluation Criteria in Solid Tumors (cont.)

New Lesions

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

New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint may be measured from that point forward and contribute to the tumor response evaluation.

CALCULATION OF SUM OF THE DIAMETERS

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

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

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

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

Note: In the case of new lymph nodes, RECIST v1.1 for measurability (equivalent to baseline target lesion selection) will be followed. That is, if at first appearance the short axis of a new lymph node lesion is ≥ 15 mm, it will be considered a measurable new lesion and will be tracked and included in the sum of diameters. Thereafter, the lymph node lesion will be measured at subsequent timepoints and measurements will be included in the sum of diameters, even if the short axis diameter decreases to < 15 mm (or even < 10 mm). However, if it subsequently decreases to < 10 mm and all other

Appendix 3

Modified Response Evaluation Criteria in Solid Tumors (cont.)

lesions (including nontarget lesions) are no longer detectable (or have also decreased to a short axis diameter of < 10 mm if lymph nodes) then a response assessment of CR may be assigned.

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

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

RESPONSE CRITERIA

Evaluation of Target Lesions

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

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

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

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

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

Impact of New Lesions on Modified RECIST

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

Appendix 3 Modified Response Evaluation Criteria in Solid Tumors (cont.)

EVALUATION OF BEST OVERALL RESPONSE USING MODIFIED RECIST

TIMEPOINT RESPONSE

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

MISSING ASSESSMENTS AND INEVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned 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 at follow-up only two lesions were assessed but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Table 1 Modified RECIST Timepoint Response Definitions

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

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

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

Appendix 3

Modified Response Evaluation Criteria in Solid Tumors (cont.)

BEST OVERALL RESPONSE: ALL TIMEPOINTS

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

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

- **CR:** Complete disappearance of all tumor lesions (target and nontarget) and no new measurable or unmeasurable lesions, confirmed by a consecutive assessment ≥ 4 weeks from the date first documented. All lymph nodes short axes must be < 10 mm.
- **PR:** Decrease in the sum of the diameters of all target and all new measurable lesions $\geq 30\%$ relative to baseline, in the absence of CR, confirmed by a consecutive assessment ≥ 4 weeks from the date first documented.
- **SD:** Criteria for CR, PR, and PD are not met.
- **PD:** Increase in the sum of the diameters of all target and all new measurable lesions $\geq 20\%$ relative to the nadir, which may be confirmed by a consecutive assessment ≥ 4 weeks from the date first documented as follows:

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

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

Appendix 4

Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1¹ are presented below, with slight modifications and the addition of explanatory text as needed for clarity.²

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

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

Measurable Tumor Lesions

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

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

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

Nonmeasurable Tumor Lesions

Nonmeasurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal 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 4

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 nonmeasurable.

Cystic lesions:

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

Lesions with prior local treatment:

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

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of Lesions

All measurements should be recorded in metric notation, with use of calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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 4

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

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

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

Appendix 4

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 NONTARGET LESIONS

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

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

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

Appendix 4

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 nontarget lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal progression.”

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

RESPONSE CRITERIA

Evaluation of Target Lesions

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

- **Complete response (CR):** disappearance of all target lesions
Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
- **Partial response (PR):** at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- **Progressive disease (PD):** at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline
In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
The appearance of one or more new lesions is also considered progression.
- **Stable disease (SD):** neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Appendix 4

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 on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on the CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the 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.

Evaluation of Nontarget Lesions

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

Appendix 4

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

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

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

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

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

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

Special Notes on Assessment of Progression of Nontarget Disease

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

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

Appendix 4

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

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

New Lesions

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

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

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

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

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

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

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

Appendix 4 Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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

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

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

Table 2 Timepoint Response: Patients with Nontarget Lesions Only

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

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

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

Missing Assessments and Not-Evaluable Designation

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

Appendix 4

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

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

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

Appendix 4 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.

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

Appendix 4

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

progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and nontarget disease as shown in [Table 1](#), [Table 2](#), and [Table 3](#).

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

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

Appendix 5 Patient-Reported Outcomes Instruments

ENGLISH



EORTC QLQ-C30 (version 3)

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

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year):

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> 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 5 Patient-Reported Outcomes Instruments (Cont.)

ENGLISH

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

© Copyright 1995 EORTC Quality of Life Group. All rights reserved. Version 3.0

Appendix 5
Patient-Reported Outcomes Instruments (Cont.)



Health Questionnaire

English version for the US

Appendix 5 Patient-Reported Outcomes Instruments (Cont.)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-Care

- I have no problems with self-care
- I have some 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 with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

Appendix 6 Preexisting Autoimmune Diseases

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Please contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Acute disseminated encephalomyelitis	Dysautonomia	Ord's thyroiditis
Addison's disease	Epidermolysis bullosa acqvista	Pemphigus
Ankylosing spondylitis	Gestational pemphigoid	Pernicious anemia
Antiphospholipid antibody syndrome	Giant cell arteritis	Polyarteritis nodosa
Aplastic anemia	Goodpasture's syndrome	Polyarthritis
Autoimmune hemolytic anemia	Graves' disease	Polyglandular autoimmune syndrome
Autoimmune hepatitis	Guillain-Barre syndrome	Primary biliary cirrhosis
Autoimmune hypoparathyroidism	Hashimoto's disease	Psoriasis
Autoimmune hypophysitis	IgA nephropathy	Reiter's syndrome
Autoimmune myocarditis	Inflammatory bowel disease	Rheumatoid arthritis
Autoimmune oophoritis	Interstitial cystitis	Sarcoidosis
Autoimmune orchitis	Kawasaki's disease	Scleroderma
Autoimmune thrombocytopenic purpura	Lambert-Eaton myasthenia syndrome	Sjögren's syndrome
Behcet's disease	Lupus erythematosus	Stiff-Person syndrome
Bullous pemphigoid	Lyme disease – chronic	Takayasu's arteritis
Chronic fatigue syndrome	Mooren's ulcer	Ulcerative colitis
Chronic inflammatory demyelinating polyneuropathy	Morphea	Vitiligo
Chung-Strauss syndrome	Multiple sclerosis	Vogt-Kovanagi-Harada disease
Crohn's disease	Myasthenia gravis	Wegener's granulomatosis
Dermatomyositis	Neuromyotonia	
	Opsoclonus myoclonus syndrome	
	Optic neuritis	

Appendix 7 Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

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

Appendix 8

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 9

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

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

Although most immune-related 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-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

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

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 42 days after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 42 days to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 42 days if the Medical Monitor agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

MANAGEMENT GUIDELINES

PULMONARY EVENTS

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

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

<i>Event</i>	<i>Management</i>
<i>Pulmonary event, Grade 1</i>	<ul style="list-style-type: none"> • Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
<i>Pulmonary event, Grade 2</i>	<ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset. ^a • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. ^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. ^c • For recurrent events, treat as a Grade 3 or 4 event.
<i>Pulmonary event, Grade 3 or 4</i>	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^c • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL = bronchoscopic alveolar lavage.

^a Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

HEPATIC EVENTS

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

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

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

Table 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	<ul style="list-style-type: none"> • Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	<p>All events:</p> <ul style="list-style-type: none"> • Monitor LFTs more frequently until return to baseline values. <p>Events of > 5 days' duration:</p> <ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset. ^a • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. ^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. ^c

LFT = liver function tests.

^a Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
<i>Hepatic event, Grade 3 or 4</i>	<ul style="list-style-type: none"> • <i>Permanently discontinue atezolizumab and contact Medical Monitor. ^c</i> • <i>Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury.</i> • <i>Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.</i> • <i>If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</i> • <i>If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.</i>

LFT = liver function tests.

^a Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

GASTROINTESTINAL EVENTS

Immune-related colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in [Table 3](#).

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

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

<i>Event</i>	<i>Management</i>
<i>Diarrhea or colitis, Grade 1</i>	<ul style="list-style-type: none"> • Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
<i>Diarrhea or colitis, Grade 2</i>	<ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset.^a • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c
<i>Diarrhea or colitis, Grade 3</i>	<ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset.^a • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c

GI = gastrointestinal.

^a Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

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

<i>Event</i>	<i>Management</i>
<i>Diarrhea or colitis, Grade 4</i>	<ul style="list-style-type: none"> • <i>Permanently discontinue atezolizumab and contact Medical Monitor. ^c</i> • <i>Refer patient to GI specialist for evaluation and confirmation biopsy.</i> • <i>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.</i> • <i>If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</i> • <i>If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.</i>

GI = gastrointestinal.

^a Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

ENDOCRINE EVENTS

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

Table 4 Management Guidelines for Endocrine Events

<i>Event</i>	<i>Management</i>
<i>Asymptomatic hypothyroidism</i>	<ul style="list-style-type: none"> • Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
<i>Symptomatic hypothyroidism</i>	<ul style="list-style-type: none"> • Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
<i>Asymptomatic hyperthyroidism</i>	<p>TSH ≥ 0.1 mU/L and < 0.5 mU/L:</p> <ul style="list-style-type: none"> • Continue atezolizumab. • Monitor TSH every 4 weeks. <p>TSH < 0.1 mU/L:</p> <ul style="list-style-type: none"> • Follow guidelines for symptomatic hyperthyroidism.
<i>Symptomatic hyperthyroidism</i>	<ul style="list-style-type: none"> • 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-related hyperthyroidism.^c

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

^a Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	<ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset. ^a • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. ^b • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. ^c
Hyperglycemia, Grade 1 or 2	<ul style="list-style-type: none"> • Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	<ul style="list-style-type: none"> • Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

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

^a Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

<i>Event</i>	<i>Management</i>
<i>Hypophysitis (pan-hypopituitarism), Grade 2 or 3</i>	<ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset. ^a • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. ^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. ^c • For recurrent hypophysitis, treat as a Grade 4 event.
<i>Hypophysitis (pan-hypopituitarism), Grade 4</i>	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^c • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

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

^a Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in [Table 5](#).

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^c • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

^a Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

IMMUNE-RELATED MYOCARDITIS

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

Table 6 Management Guidelines for Immune-Related Myocarditis

Event	Management
<i>Immune-related myocarditis, Grade 1</i>	<ul style="list-style-type: none"> • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.
<i>Immune-related myocarditis, Grade 2</i>	<ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset ^a and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. ^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. ^c
<i>Immune-related myocarditis, Grade 3-4</i>	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^c • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

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

^a Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

INFUSION-RELATED REACTIONS

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

Guidelines for medical management of IRRs during Cycle 1 are provided in [Table 7](#). For subsequent cycles, IRRs should be managed according to institutional guidelines.

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

Table 7 Management Guidelines for Infusion-Related Reactions

<i>Event</i>	<i>Management</i>
<i>IRR, Grade 1</i>	<ul style="list-style-type: none"> • <i>Reduce infusion rate to half the rate being given at the time of event onset.</i> • <i>After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate.</i> • <i>If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.</i>
<i>IRR, Grade 2</i>	<ul style="list-style-type: none"> • <i>Interrupt atezolizumab infusion.</i> • <i>Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen).</i> • <i>After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset.</i> • <i>For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs.</i>
<i>IRR, Grade 3 or 4</i>	<ul style="list-style-type: none"> • <i>Stop infusion.</i> • <i>Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen).</i> • <i>Permanently discontinue atezolizumab and contact Medical Monitor.^a</i>

IRR = infusion-related reaction.

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

PANCREATIC EVENTS

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

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
<i>Amylase and/or lipase elevation, Grade 2</i>	<ul style="list-style-type: none"> • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
<i>Amylase and/or lipase elevation, Grade 3 or 4</i>	<ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset.^a • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.^c

GI = gastrointestinal.

^a Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

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

Event	Management
<i>Immune-related pancreatitis, Grade 2 or 3</i>	<ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset.^a • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.^c
<i>Immune-related pancreatitis, Grade 4</i>	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor.^c • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

^a Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

DERMATOLOGIC EVENTS

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

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	<ul style="list-style-type: none"> • Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	<ul style="list-style-type: none"> • Continue atezolizumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	<ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset.^a • Refer patient to dermatologist. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c
Dermatologic event, Grade 4	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor.^c

^a Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
<i>Immune-related neuropathy, Grade 1</i>	<ul style="list-style-type: none"> • Continue atezolizumab. • Investigate etiology.
<i>Immune-related neuropathy, Grade 2</i>	<ul style="list-style-type: none"> • Withhold atezolizumab for up to 12 weeks after event onset. ^a • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. ^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. ^c
<i>Immune-related neuropathy, Grade 3 or 4</i>	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^c • Initiate treatment as per institutional guidelines.
<i>Myasthenia gravis and Guillain-Barré syndrome (any grade)</i>	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor. ^c • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

^a Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

Appendix 9

Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (Cont.)

IMMUNE-RELATED MENINGOENCEPHALITIS

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

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 11](#).

Table 11 Management Guidelines for Immune-Related Meningoencephalitis

<i>Event</i>	<i>Management</i>
<i>Immune-related meningoencephalitis, all grades</i>	<ul style="list-style-type: none"> • <i>Permanently discontinue atezolizumab and contact Medical Monitor.^a</i> • <i>Refer patient to neurologist.</i> • <i>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.</i> • <i>If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</i> • <i>If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.</i>

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

STATISTICAL ANALYSIS PLAN

TITLE: A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (MPDL3280A) (ANTI-PD-L1 ANTIBODY) COMPARED WITH CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC UROTHELIAL BLADDER CANCER AFTER FAILURE WITH PLATINUM-CONTAINING CHEMOTHERAPY

PROTOCOL NUMBER: GO29294

STUDY DRUG: Atezolizumab (MPDL3280A; RO5541267)

VERSION NUMBER 1

IND NUMBER: 120827

EUDRACT NUMBER 2014-003231-19

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [REDACTED], Ph.D.

DATE FINAL See electronic date stamp below.

STATISTICAL ANALYSIS PLAN APPROVAL

Name	Reason for Signing	Date and Time (UTC)
[REDACTED]	[REDACTED]	03-Aug-2016 17:59:31

CONFIDENTIAL

This is an F. Hoffmann-La Roche Ltd document that contains confidential information. Nothing herein is to be disclosed without written consent from F. Hoffmann-La Roche Ltd.

TABLE OF CONTENTS

1.	BACKGROUND	5
2.	STUDY DESIGN	5
2.1	Protocol Synopsis	8
2.2	Outcome Measures	8
2.2.1	Efficacy Outcome Measures	8
2.2.1.1	Primary Efficacy Outcome Measure	8
2.2.1.2	Secondary Efficacy Outcome Measures	8
2.2.2	Safety Outcome Measures	8
2.2.3	Pharmacokinetic Outcome Measures	8
2.2.4	Patient-Reported Outcome Measure	9
2.2.5	Exploratory Outcome Measures	9
2.3	Determination of Sample Size	9
2.4	Analyses Timing	10
2.5	Interim Analyses	10
3.	STUDY CONDUCT	10
3.1	Randomization Issues	10
3.2	Data Monitoring	10
4.	STATISTICAL METHODS	11
4.1	Analysis Populations	11
4.1.1	Intent-to-Treat Population	11
4.1.2	Pharmacokinetic-Evaluable Population	11
4.1.3	Safety Population	11
4.2	Analysis of Study Conduct	11
4.3	Analysis of Treatment Group Comparability	11
4.4	Efficacy Analyses	12
4.4.1	Primary Efficacy Endpoint	12
4.4.2	Secondary Efficacy Endpoints	13
4.4.2.1	Objective Response Rate	13
4.4.2.2	Progression-Free Survival	13
4.4.2.3	Duration of Objective Response	14

4.4.3	Exploratory Efficacy Endpoints	14
4.4.3.1	Objective Response Rate, Progression-Free Survival, and Duration of Objective Response per Modified RECIST	14
4.4.3.2	Disease Control Rate	15
4.4.3.3	Assessment of Tumor Burden	15
4.4.3.4	Exploratory Analyses on Primary Efficacy Endpoint	15
4.4.3.5	Exploratory Analyses on Secondary Efficacy Endpoints.....	17
4.4.3.6	Biomarker Analyses.....	17
4.5	Patient-Reported Outcome Analyses	17
4.6	Pharmacokinetic and Pharmacodynamic Analyses	18
4.7	Safety Analyses	18
4.7.1	Exposure to Study Medication	18
4.7.2	Adverse Events	19
4.7.3	Laboratory Data	19
4.7.4	Vital Signs.....	19
4.7.5	Anti-Therapeutic Antibodies.....	19
4.8	Missing Data.....	20
5.	REFERENCES	21

LIST OF FIGURES

Figure 1	Study Schema.....	6
----------	-------------------	---

LIST OF APPENDICES

Appendix 1	Protocol Synopsis	22
Appendix 2	Schedule of Assessments.....	35

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ATA	anti-therapeutic antibody
CR	complete response
DCR	disease control rate
DOR	duration of objective response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30
EQ-5D-3L	Euro QoL 5 Dimension 3 Level
FDA	U.S. Food and Drug Administration
FPI	first patient in
GC	gemcitabine and cisplatin
HR	hazard ratio
HRQoL	health-related quality of life
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
ITT	intent-to-treat
MVAC	methotrexate, vinblastine, doxorubicin, and cisplatin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO(s)	patient-reported outcome(s)
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SLD	sum of longest diameter
TCC	transitional cell carcinoma
UBC	urothelial bladder cancer

1. **BACKGROUND**

Urothelial bladder cancer (UBC, also termed transitional cell carcinoma [TCC] or urothelial cell carcinoma [UCC] of the urinary tract) is the most common cancer of the urinary system worldwide with UBC of the bladder being the predominant histologic type and location. Although less common, urothelial cancers may originate in the renal pelvis, ureter, or urethra. The overall 5-year survival rate for metastatic UBC is approximately 5.4%. Although several chemotherapeutic agents have been studied in the second-line setting over the last two decades, the overall response rates are low and associated with considerable toxicity. No survival benefit has been demonstrated with second-line chemotherapy.

Atezolizumab 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 investigated as a potential therapy against solid tumors and hematologic malignancies in humans. On 18 May 2016, atezolizumab was granted accelerated approval by the US Food and Drug Administration (FDA) for the treatment of metastatic urothelial carcinoma in patients who had progressed following prior platinum-containing chemotherapy.

The Ventana anti–PD-L1 (SP142) immunohistochemistry (IHC) assay will be used to determine programmed death–ligand 1 (PD-L1) expression. Using this assay, the PD-L1 IHC score will have three categories: IC0, IC1, and IC2/3 which are defined as PD-L1 stained tumor-infiltrating immune cells (ICs) covering < 1%, ≥ 1% to < 5%, and ≥ 5% of the tumor area, respectively.

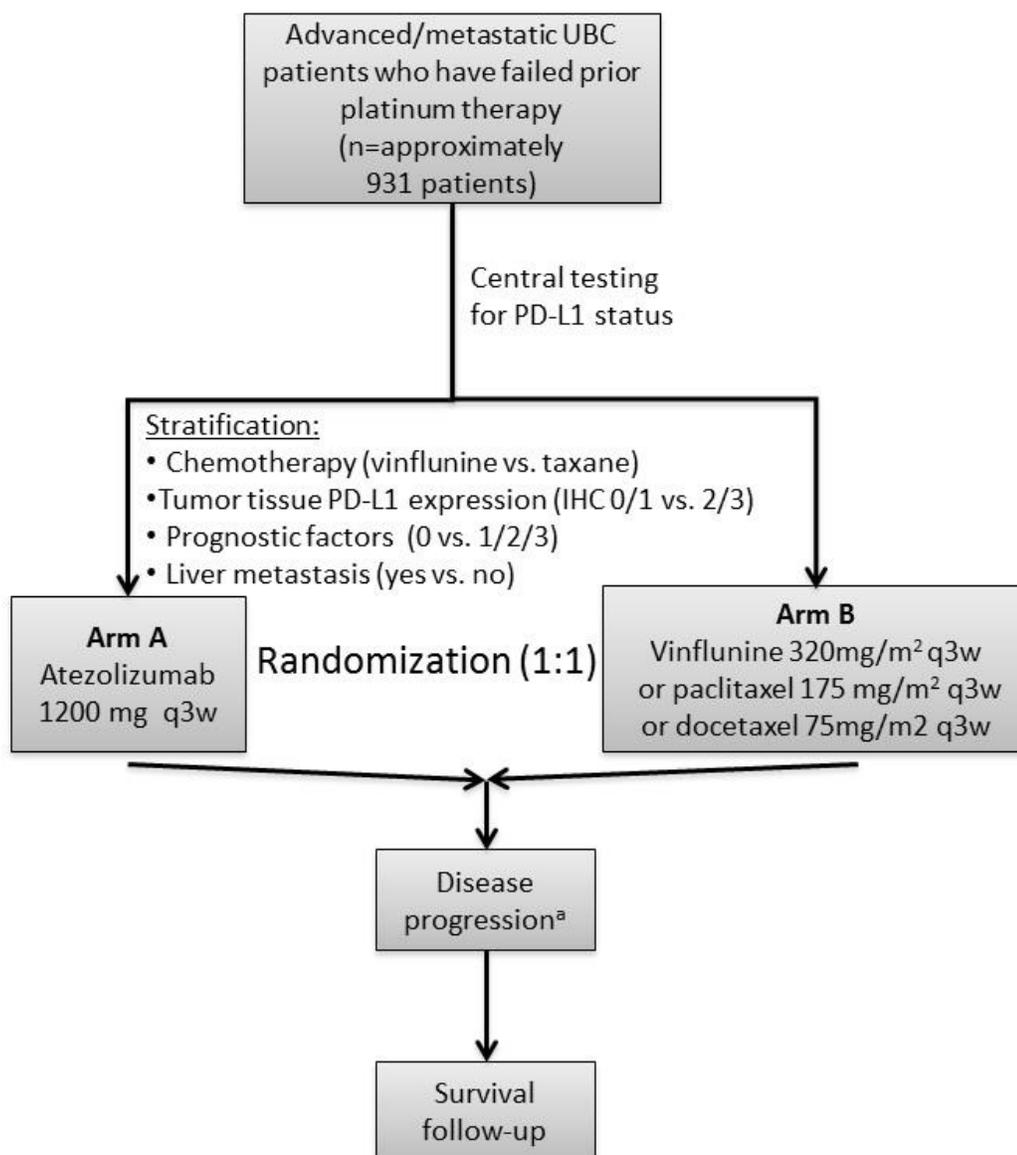
This Statistical Analysis Plan (SAP) specifies the planned analyses and statistical methods used for Study GO29294, and will supersede those specified in study protocol.

2. **STUDY DESIGN**

Study GO29294 is a 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 UBC who have progressed during or following a platinum-containing regimen. Prior to randomization, the investigator will have the option of choosing one of three chemotherapy regimens (vinflunine, paclitaxel, or docetaxel) for each patient. [Figure 1](#) illustrates the study design.

Atezolizumab—F. Hoffmann-La Roche Ltd
5/Statistical Analysis Plan GO29294

Figure 1 Study Schema



IHC=immunohistochemistry; PD-L1=programmed death–ligand 1; q3w=every 3 weeks; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; UBC=urothelial bladder cancer.

^a Patients randomized to Arm A may continue atezolizumab treatment after disease progression according to RECIST v1.1 if they meet criteria specified in Protocol Section 4.6.1.1.

The primary endpoint of this study is overall survival (OS). Secondary endpoints of the study include objective response rate (ORR), progression-free survival (PFS), and duration of objective response (DOR). Other endpoints include safety, pharmacokinetic (PK), patient-reported outcome (PRO), and exploratory outcome measures (see Section 2.2).

Male and female patients aged ≥ 18 years with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 who have histologically or cytologically proven locally advanced or metastatic UBC and who have experienced disease progression during or following treatment for advanced disease consisting of platinum-based therapy are eligible. Patients who experience disease progression during or within 12 months following completion of a platinum-based adjuvant or neoadjuvant regimen will also be eligible for enrollment into the study. Patients must have received at least one platinum-containing regimen (e.g., gemcitabine and cisplatin [GC], methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC], carboplatin and gemcitabine [CarboGem], etc.) for locally advanced or metastatic UBC. The maximum number of prior therapies in the locally advanced or metastatic setting is restricted to two. Tumor specimens from eligible patients will be prospectively tested for PD-L1 expression by a central laboratory. Patients, investigators and Sponsor will be blinded to the PD-L1 expression status. The study will enroll all patients whose tissue is evaluable for expression testing, regardless of PD-L1 expression status.

Eligible patients will be randomized in a 1:1 ratio to receive either atezolizumab or chemotherapy (vinflunine, paclitaxel, or docetaxel) and stratified by the following criteria:

- Chemotherapy (vinflunine vs. taxane [paclitaxel or docetaxel])
- PD-L1 immunohistochemistry (IHC) status (IC0/1 vs. IC2/3)
- Number of baseline prognostic risk factors (0 vs. 1/2/3)
 - Time from prior chemotherapy (TFPC) < 3 months
 - ECOG performance status > 0
 - Hemoglobin < 10 g/dL
- Liver metastasis (yes vs. no)

Atezolizumab will be administered intravenously at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. Patients will receive atezolizumab as long as they continue to experience clinical benefit in the opinion of the investigator until unacceptable toxicity or symptomatic deterioration attributed to disease progression (i.e., pain secondary to disease or unmanageable ascites, etc.) as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status.

No crossover will be allowed from the control arm to the experimental arm.

Atezolizumab—F. Hoffmann-La Roche Ltd
7/Statistical Analysis Plan GO29294

Clinical Study Report: RO5541267 - F. Hoffmann-La Roche Ltd
Protocol GO29294 Report Number 1074426

An external independent Data Monitoring Committee (iDMC) will evaluate study safety data approximately every 6 months after first-patient-in (FPI) in accordance with the iDMC Charter.

A total of approximately 931 patients will be enrolled into the study, including a minimum of 230 patients with a PD-L1 IHC score of IC2/3 and a minimum of 537 patients with a PD-L1 IHC score of IC1/2/3. The primary analyses of OS will occur when approximately 152, 403, and 652 deaths have been observed in the following populations: patients with an IHC score of IC2/3, patients with an IHC score of IC1/2/3, and intent-to-treat (ITT) populations, respectively, whichever occurs later.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in [Appendix 1](#). For additional details, see the Schedule of Assessments in [Appendix 2](#).

2.2 OUTCOME MEASURES

2.2.1 Efficacy Outcome Measures

2.2.1.1 Primary Efficacy Outcome Measure

- OS, defined as the time between the date of randomization and death due to any cause

2.2.1.2 Secondary Efficacy Outcome Measures

- ORR, defined as the proportion of patients with an objective response (either a complete response [CR] or partial response [PR]) as determined by the investigator with use of Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
- PFS, defined as the time between the date of randomization and the date of first documented disease progression as determined by the investigator with use of RECIST v1.1 or death due to any cause, whichever occurs first
- DOR, defined as the time between the date of first documented response and the date of first documented disease progression as determined by the investigator with use of RECIST v1.1 or death due to any cause, whichever occurs first

2.2.2 Safety Outcome Measures

- Incidence, nature, and severity of adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0
- Changes in selected vital signs, physical findings, and clinical laboratory results
- Incidence of anti-therapeutic antibody (ATA) response to MPDL3280A and potential correlation with PK, pharmacodynamic, safety, and efficacy parameters

2.2.3 Pharmacokinetic Outcome Measures

- Maximum observed serum atezolizumab concentration (C_{\max}) after infusion on Day 1 of Cycle 1

Atezolizumab—F. Hoffmann-La Roche Ltd
8/Statistical Analysis Plan GO29294

Clinical Study Report: RO5541267 - F. Hoffmann-La Roche Ltd
Protocol GO29294 Report Number 1074426

- Minimum observed serum atezolizumab concentration (C_{min}) prior to infusion on Day 1 of Cycles 1, 2, 3, 4, 8, and 16, at treatment discontinuation, and at 120 days (± 30 days) after the last dose of atezolizumab

2.2.4 Patient-Reported Outcome Measure

- UBC cancer symptoms, patient functioning, and health-related quality of life (HRQoL) as measured by the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30)

2.2.5 Exploratory Outcome Measures

- ORR, PFS, and DOR with use of modified RECIST for patients randomized to atezolizumab
- Disease control rate (DCR), defined as the rate of patients with CR or PR as best response or stable disease maintained for ≥ 24 weeks per RECIST v1.1
- Tumor burden: change over time in the sum of the longest diameters (SLD) computed from RECIST-defined target lesions identified at baseline
- Status of tumor immune-related or disease type-related exploratory biomarkers in archival and/or freshly obtained tumor tissues and association with disease status and/or response to atezolizumab
- Status of exploratory biomarkers in plasma, whole blood, or serum (including but not limited to cytokines such as interleukin 6 [IL-6]) collected before or during treatment with atezolizumab or at progression and association with disease status and/or response to atezolizumab
- Utility scores of the EuroQoL 5 Dimension 3 Level (EQ-5D-3L) questionnaire for use in economic models
- Items from the EORTC QLQ-C30 that are not included in the main PRO outcome measure

2.3 DETERMINATION OF SAMPLE SIZE

This study will enroll approximately 931 patients, including a minimum of 230 patients with a PD-L1 IHC score of IC2/3 and a minimum of 537 patients with a PD-L1 IHC score of IC1/2/3 (enrollment of all patients will continue until the minimum requirement of patients with PD-L1 IC2/3 and IC1/2/3 are reached).

The number of events required to demonstrate efficacy of the atezolizumab treatment arm over the chemotherapy arm (i.e., vinflunine, paclitaxel, or docetaxel) with regard to OS (see Section 4.4.1) are estimated on the basis of the following assumptions:

- Two-sided significance level of 5%
- 94% power for the primary analysis of OS in the IC2/3 population with an HR of 0.57, corresponding to an improvement in median OS from 7.5 months to 13.2 months
- 98% power for the primary analysis of OS in the IC1/2/3 population with an HR of 0.68, corresponding to an improvement in median OS from 7.5 months to

Atezolizumab—F. Hoffmann-La Roche Ltd
9/Statistical Analysis Plan GO29294

11 months

- 97% power for the primary analysis of OS in the ITT population with an HR of 0.74, corresponding to an improvement in median OS from 7.5 months to 10.1 months
- 1:1 randomization ratio
- Dropout rate of 5% per year over 24 months

2.4 ANALYSES TIMING

The primary analyses of OS will occur when approximately 152, 403, and 652 deaths have been observed in the following populations: patients with an IHC score of IC2/3, patients with an IHC score of IC1/2/3, and ITT populations, respectively, whichever occurs later. This is expected to occur approximately 25 months after FPI.

The timing of the primary analyses of OS will depend on the actual accrual rate and will be driven by the occurrence of number of deaths as indicated above.

2.5 INTERIM ANALYSES

No interim analyses of efficacy are planned for this study.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Eligible patients will be randomized in a 1:1 ratio to receive either atezolizumab or chemotherapy (vinflunine, paclitaxel, or docetaxel) on a 21-day cycle. A permuted-block randomization scheme will be used to ensure balanced assignments to each treatment arm with respect to the following stratification factors:

- Chemotherapy (vinflunine vs. taxane)
- PD-L1 IHC status (IC0/1 vs. IC2/3)
- Number of baseline prognostic risk factors (0 vs. 1/2/3)
 - TFPC <3 months
 - ECOG performance status >0
 - Hemoglobin <10 g/dL
- Liver metastasis (yes vs. no)

3.2 DATA MONITORING

The iDMC, consisting of independent, external experts, will monitor all accumulated patient safety data approximately every 6 months during the course of the study after FPI. All summaries and analyses by treatment arm for the iDMC review will be prepared by an external independent Data Coordinating Center (iDCC). Members of the iDMC will follow a charter that outlines their roles and responsibilities. Additional details will be provided in the iDMC Charter.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

The intent-to-treat (ITT) population is defined as all randomized patients, irrespective of whether the assigned treatment was actually received. The IC2/3 population for efficacy analyses is defined as ITT patients with a PD-L1 IHC score of IC2/3 at the time of randomization, and the IC1/2/3 population for efficacy analyses is defined as ITT patients with a PD-L1 IHC score of IC1 or IC2/3 at the time of randomization. For each patient, the sample(s) with highest IC score prior to the start of study drug treatment will be used to determine the PD-L1 IC score for the patient.

For all efficacy analyses, patients will be grouped according to the treatment assigned at randomization by the interactive voice/web response system (IxRS).

4.1.2 Pharmacokinetic-Evaluable Population

The PK-evaluable population will include all randomized patients who received atezolizumab.

4.1.3 Safety Population

The safety population will include all randomized patients who received any amount of study drug, with patients grouped according to whether any amount of atezolizumab was received, including the case when atezolizumab was received in error. Patients who are randomized into the study but do not receive any amount of study drug will not be included in the safety population.

4.2 ANALYSIS OF STUDY CONDUCT

Study enrollment, major protocol violations and reasons for discontinuation from the study will be summarized overall and by treatment arm for the IC2/3, IC1/2/3 and overall ITT populations. Study drug administration and reasons for discontinuation from the study drug will be summarized for the Safety Population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic characteristics, such as age, sex, race/ethnicity, and baseline disease characteristics (e.g., ECOG performance status), number of Bellmunt risk factors (ECOG performance status ≥ 1 , liver metastases [yes vs. no], and hemoglobin < 10 g/dL) and number of prior cancer treatments will be summarized by treatment arm for the IC2/3, IC1/2/3 and overall ITT populations individually. Descriptive statistics (mean, median, SD, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

Baseline measurements are the last available data obtained prior to the patient receiving the first dose of study drug on Cycle 1, Day 1.

4.4 EFFICACY ANALYSES

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is OS. OS is defined as the time between the date of randomization and death due to any cause. Patients who are not reported as having died by the date of data cutoff for primary analysis will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization plus one day.

Comparisons with respect to OS between the treatment and control arms within the IC2/3, IC1/2/3 and ITT populations will be tested using a hierarchical fixed-sequence procedure based on a stratified log-rank test at two-sided level of 5% significance:

- Step 1. Test to reject the null hypothesis of no difference in OS between the two arms in the IC2/3 population. If the estimate of the HR is < 1 and the two-sided p-value corresponding to the stratified log-rank test is < 0.05 , the null hypothesis will be rejected and it will be concluded that atezolizumab prolongs OS relative to chemotherapy (i.e., vinflunine, paclitaxel, or docetaxel) in the IC2/3 population.
- Step 2. If the null hypothesis from Step 1 is rejected, then test to reject the null hypothesis of no difference in OS between the two arms in the IC1/2/3 population. If the estimate of the HR is < 1 and the two-sided p-value corresponding to the stratified log-rank test is < 0.05 , the null hypothesis will be rejected and it will be concluded that atezolizumab prolongs OS relative to chemotherapy (i.e., vinflunine, paclitaxel, or docetaxel) in the IC1/2/3 population.
- Step 3. If the null hypothesis from Step 2 is rejected, then test to reject the null hypothesis of no difference in OS between the two arms in the ITT population. If the estimate of the HR is < 1 and the two-sided p-value corresponding to the stratified log-rank test is < 0.05 , the null hypothesis will be rejected and it will be concluded that atezolizumab prolongs OS relative to chemotherapy (i.e., vinflunine, paclitaxel, or docetaxel) in the ITT population.

The null and alternative hypotheses for OS analysis can be phrased in terms of the survival functions $S_A(t)$ and $S_B(t)$ in the atezolizumab arm (Arm A) and chemotherapy arm (Arm B), respectively:

$$H_0: S_A(t) = S_B(t) \text{ versus } H_1: S_A(t) \neq S_B(t)$$

Kaplan-Meier methodology will be used to estimate the median OS for each treatment arm and to construct survival curves for the visual description of the difference between the treatment arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS for each treatment arm ([Brookmeyer and Crowley 1982](#)).

The hazard ratio, λ_A/λ_B , where λ_A and λ_B represent the hazard of death in Arm A and Arm B, respectively, will be estimated using a stratified Cox regression model with the

same stratification variables used in the stratified log-rank test, including 95% CIs. The stratification factors will be those specified for randomization (i.e., chemotherapy, prognostic factors, and liver metastases as recorded on the electronic Case Report Forms [eCRFs), and PD-L1 IHC status as recorded on the central laboratory form). Results from an unstratified analysis will also be presented.

4.4.2 Secondary Efficacy Endpoints

If the primary endpoint of OS is statistically significant in all the IC2/3, IC1/2/3 and ITT populations, the secondary endpoints of ORR and PFS will be tested in order (i.e., ORR followed by PFS), each at 5% significance level in the IC2/3, IC1/2/3 and ITT populations individually as follows. First, test for an ORR difference between the two arms (i.e., $H_0: ORR_A = ORR_B$ versus $H_1: ORR_A \neq ORR_B$) in the IC2/3 population. If the null hypothesis is rejected, test for an ORR difference in the IC1/2/3 population. If the preceding null hypothesis is rejected, test for an ORR difference in the ITT population. If the preceding null hypothesis is rejected, test for a PFS difference between the two arms (i.e., the null hypothesis of no difference in PFS between the two arms) in the IC2/3 population. If the preceding null hypothesis is rejected, test for a PFS difference in the IC1/2/3 population, and if the preceding null hypothesis is rejected, test for a PFS difference in the ITT population.

4.4.2.1 Objective Response Rate

An objective response is defined as either a CR or PR, as determined by the investigator with use of RECIST v1.1. Objective response in this study does not need to be a confirmed response. Patients not meeting these criteria, including patients without any post-baseline tumor assessment, will be considered non-responders.

ORR is defined as the proportion of patients who had an objective response. The analysis population for ORR will be all randomized patients with measurable disease at baseline per investigator assessment using RECIST v1.1. An estimate of ORR and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms will be determined using the normal approximation to the binomial distribution. The ORR will be compared between the two arms with use of the stratified Cochran-Mantel-Haenszel test without using the continuation correction factor.

4.4.2.2 Progression-Free Survival

PFS is defined as the time between the date of randomization and the date of first documented disease progression or death, whichever occurs first. Disease progression will be determined on the basis of investigator assessment with use of RECIST v1.1. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization plus one day.

For U.S. registrational purposes, PFS will be defined as described above with an additional censoring rule for missed visits. Patients with a PFS event who missed two or more consecutive assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits.

PFS will be analyzed using the same methods as OS.

4.4.2.3 Duration of Objective Response

DOR is defined as the period measured from the date of the first occurrence of a CR or PR (whichever status is recorded first) to the date that progressive disease or death is first documented. Disease progression will be determined on the basis of investigator assessment with use of RECIST v1.1. DOR based on the investigator assessment will be analyzed for the subset of patients who achieve an objective response as determined by the investigator with use of RECIST v1.1. Patients who have not progressed or who have not died by the data cutoff date for 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 one day.

DOR analysis is on the basis of a non-randomized subset of patients (specifically, patients who achieve an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. DOR will be estimated using Kaplan-Meier methodology.

4.4.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints will be analyzed using the same methodology specified in Section 4.4.2 for their respective endpoints. The exploratory efficacy endpoints are not part of the endpoints tested in the hierarchical fixed sequence specified in Section 4.4.1.

ORR, PFS, and DOR analyses using modified RECIST criteria (see Protocol) will be performed on patients in the MPDL3280A arm only, with no comparison with the chemotherapy arm.

4.4.3.1 Objective Response Rate, Progression-Free Survival, and Duration of Objective Response per Modified RECIST

ORR, PFS, and DOR per modified RECIST have the same definitions as the secondary efficacy endpoints except that disease progression is determined by the modified RECIST criteria as described below.

ORR per modified RECIST is defined as either a CR or PR, as determined by the investigator with use of modified RECIST.

PFS per modified RECIST is defined as the time between the date of randomization and the date of first documented disease progression per modified RECIST or death, whichever occurs first. A patient is considered to have disease progression by modified RECIST if either of the following conditions is met:

- (a) Modified RECIST criteria for progression were met at a tumor assessment and no subsequent tumor assessment was performed.
- (b) Modified RECIST criteria for progression were met at a tumor assessment and at the subsequent tumor assessment the criteria for confirmed progression by modified RECIST were also met.

For patients who meet criterion (a), the date of progression is the date of the tumor assessment that met the criteria for modified RECIST. For patients who meet criterion (b), the date of progression is the date of the tumor assessment at which the modified RECIST criteria for progression were first met. Patients who do not meet either of the above criteria are not considered to have had disease progression by modified RECIST.

DOR per modified RECIST is defined as the period measured from the date of the first occurrence of a CR or PR (whichever status is recorded first) until the first date that progressive disease per modified RECIST or death is documented. Analysis methodology for ORR, PFS, and DOR per modified RECIST are the same as those used for these endpoints per RECIST v1.1.

4.4.3.2 Disease Control Rate

DCR is defined as the proportion of patients with CR or PR as best response or stable disease maintained for ≥ 24 weeks per RECIST v1.1. The analysis methods for DCR will be the same as those for the analysis of ORR.

4.4.3.3 Assessment of Tumor Burden

The change in the sum of longest diameter (SLD) computed from the RECIST-defined target lesions identified at baseline will be plotted for each patient by visit. Per RECIST v1.1, up to five target lesions, not more than two per organ, will be designated as target lesions at baseline and followed at subsequent tumor assessments.

4.4.3.4 Exploratory Analyses on Primary Efficacy Endpoint Overall Survival Rate at Landmark Timepoints

The OS rate at various timepoints (i.e., 6, 12, 18, and 24 months after randomization) within the IC2/3, IC1/2/3, and ITT populations will be estimated with use of the Kaplan-Meier methodology for each treatment arm with 95% CIs calculated using Greenwood's formula. The 95% CI for the difference in OS rates between the two treatment arms will be estimated using the normal approximation method with the standard errors computed using Greenwood's formula.

Sensitivity Analyses

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 survival in either treatment arm, a sensitivity analysis (“worst case” analysis) will be performed in which patients who are lost to follow-up will be considered to have died at the last date they were known to be alive. Kaplan-Meier methods will be used to estimate median OS. OS between the two treatment arms will be compared using unstratified and stratified log-rank tests within the IC2/3, IC1/2/3 and ITT populations individually. Stratified and unstratified Cox models will be used to estimate the HR for OS between the two treatment arms.

Subsequent Anti-Cancer Therapy: The impact of non-protocol specified anti-cancer therapy use on OS will be assessed depending on the number of patients who receive non-protocol anti-cancer therapy before an OS event. If >10% of patients have received a non-protocol anti-cancer therapy before an OS event in any treatment arm, one sensitivity analysis will be performed for the comparisons between atezolizumab and chemotherapy in which patients who have received non-protocol therapy before an OS event will be censored on the date they were last alive before receipt of non-protocol anti-cancer therapy.

Stratification Factors: A sensitivity analysis of OS will be performed using the stratification factors (i.e., chemotherapy, PD-L1 IHC status, prognostic factors, and liver metastases) as recorded on IxRS.

Subgroup Analyses

The consistency of OS results in subgroups defined by demographics (e.g., age [<65 , ≥ 65], sex, and race/ethnicity, etc.) and baseline characteristics including PD-L1 IHC status (IC0/1, IC2/3, IC1/2/3, IC0, IC1), ECOG performance status, number of Bellmunt risk factors, hemoglobin (<10 g/dL vs. ≥ 10 g/dL), chemotherapy (vinflunine vs. taxane), visceral metastasis, and liver metastasis, etc., will be examined. It is expected that accrual in subgroups defined by these baseline characteristics may not be large enough for definitive treatment comparisons to be made between these subgroups.

Within each IHC subpopulations (IC2/3, IC1/2/3 and ITT populations), descriptive summaries of survival, 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 listed above and displayed on a forest plot (Lewis and Clarke 2001).

Multivariate Modeling

The impact of each of the baseline variables and potential interaction on the estimate of treatment effect for OS will be assessed using the Cox proportional hazards model. For each variable, the Cox model will include factors for treatment and the individual variable. An initial multivariate model that includes the effects of treatment and all variables that

were individually significant will be examined. The final multivariate model will exclude variables that are not significant at a 0.05 significance level in the initial multivariate model, and the final model will contain only significant variables.

4.4.3.5 Exploratory Analyses on Secondary Efficacy Endpoints Objective Response Rate

Exploratory analyses of ORR based on confirmed CR or PR per RECIST v1.1 will be performed using the same analysis methods described for the unconfirmed ORR analyses in Section [4.4.2.1](#).

Duration of Objective Response

Exploratory analyses of DOR based on confirmed CR or PR per RECIST v1.1 will be performed using the same analysis methods described for the DOR based on unconfirmed CR or PR in Section [4.4.2.3](#).

4.4.3.6 Biomarker Analyses

Efficacy analyses, including OS, PFS, and ORR, will be performed in subgroups defined by gene or gene signature expression in tumor tissue and/or in peripheral blood mononuclear cells. The analyses will include a comparison of the atezolizumab arm to the chemotherapy arm. The gene or gene signatures used for the analyses may include PD-L1, IFNG, T-effector, and/or a combination thereof.

The association between efficacy and other predictive biomarkers in blood and tumor tissue (e.g., tumor mutation status and burden, T-cell markers, plasma cytokines) may also be analyzed.

The exploratory biomarker analyses may not be included in the Clinical Study Report (CSR).

4.5 PATIENT-REPORTED OUTCOME ANALYSES

The EORTC QLQ-C30 data will be scored according to the EORTC scoring manual ([Fayers et al. 2001](#)). For all questionnaire subscales, if >50% of the constituent items are completed, a pro-rated score will be computed consistent with the scoring manuals and validation papers. For subscales with <50% of the items completed, the subscale will be considered missing. All PRO data analyses will be performed on randomized patients with non-missing baseline assessments and at least one non-missing post-baseline assessment by treatment arm for the IC2/3, IC1/2/3 and ITT populations individually unless otherwise stated.

EORTC QLQ-C30 standardized scores at each visit and change from baseline will be summarized with descriptive statistics (mean, median, SD, and range). In addition, the standardized scores will be displayed in a shift table for each response category (0 to 24, 25 to 49, 50 to 74, and 75 to 100).

Compliance with EORTC QLQ-C30 assessment, defined as the proportion of the number of forms received to the number of forms expected, will be documented at each visit by treatment arm. When available, reasons for non-completion will be provided.

A responder analysis will be used to assess improvement in the physical function score, the fatigue scale, and the global health status scores between treatment arms at each visit and at time of progression. Responders are defined as patients with a ≥ 10 -point improvement in mean scale score from baseline.

Time to deterioration (TTD) on the EORTC scale (the physical function score, the fatigue scale, and the global health status scores) is defined as the time from baseline to the first time the patient's score shows a ≥ 10 -point increase above baseline. In order for the symptom to be considered "deteriorated," a score increase of ≥ 10 points above baseline must be held for at least two consecutive cycles or an initial score increase of ≥ 10 points is followed by death within 3 weeks from the last assessment. A ≥ 10 -point change in the score is perceived by patients as clinically significant (Osoba et al. 1998). Patients who have not deteriorated before the last PRO assessment is completed will be censored at this timepoint. Patients with no assessment post-baseline will be censored at randomization date plus one day. TTD analyses will be performed in the IC2/3, IC1/2/3 and ITT populations with non-missing baseline measurement.

4.6 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

The PK analyses will be performed on the PK-evaluable population (see Section 4.1.2). Atezolizumab serum concentration data (C_{\min} and C_{\max}) will be tabulated and summarized for each cycle for which pharmacokinetics are to be measured (C_{\max} will be reported for Cycle 1 only; C_{\min} will be evaluated at Cycles 1, 2, 3, 4, 8, and 16, and both at treatment discontinuation and at 120 days [± 30 days] after the last dose of atezolizumab). Descriptive statistics will include means, medians, ranges, and SDs, as appropriate.

Additional PK and PD analyses will be conducted as appropriate and may not be included in the CSR.

4.7 SAFETY ANALYSES

Safety analyses will be performed on the safety population (see Section 4.1.3). Summaries will be presented for the safety-evaluable populations by treatment arm.

4.7.1 Exposure to Study Medication

Study drug exposure, including treatment duration, number of doses, and dose intensity, will be summarized for each treatment arm using descriptive statistics.

4.7.2 Adverse Events

Verbatim description of adverse events will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded according to NCI CTCAE v4.0. Adverse events will be summarized by treatment arm and NCI CTCAE grade. Multiple occurrences of the same event will be counted once at the maximum severity.

Safety summaries for adverse events, except for summaries of treatment-related serious adverse events, adverse events of special interest, and adverse events requiring the use of systemic corticosteroids with no clear alternate etiology (immune-mediated adverse events), will include all treatment-emergent adverse events defined as adverse events occurring on or after the first dose of study drug until the earliest of the following:

- 30 days after the last administration of study drug
- Initiation of another non-protocol anti-cancer therapy after the last administration of study drug
- Clinical cutoff date

Summaries of treatment-related serious adverse events, adverse events of special interest, immune-mediated adverse events, and all listings of adverse events will include adverse events with an onset date on or after the date of the first dose of study drug up to the data cutoff date. The adverse events of special interest will be derived from Sponsor-defined adverse event group terms consisting of preferred terms representing immune-mediated reactions.

In addition, serious adverse events, severe adverse events (Grade ≥ 3), adverse events of special interest, immune-mediated adverse events, and adverse events leading to study drug discontinuation or interruption will be summarized separately.

Deaths reported during the study treatment period and those reported during the follow-up period after treatment completion or discontinuation and causes of death will be summarized by treatment arm.

4.7.3 Laboratory Data

Laboratory data during study treatment and for 30 days after the last dose of study drug with values outside the normal ranges will be identified. In addition, selected laboratory data will be summarized by treatment arm and grade.

4.7.4 Vital Signs

Changes in vital signs will be summarized by treatment arm and grade.

4.7.5 Anti-Therapeutic Antibodies

The number and percentage of patients with positive serum antibodies to atezolizumab at baseline and post-baseline during the study period will be summarized. Adverse events occurring in patients with positive serum antibodies to atezolizumab will be

reviewed. The relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy may also be evaluated when appropriate.

4.8 MISSING DATA

For OS, patients who are not reported as having died will be analyzed as censored observations on the date when they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization plus one day.

For PFS, patients without a date of disease progression and death will be analyzed as censored observations on the date of last tumor assessment. If no post-baseline tumor assessment is available, PFS will be censored at the date of randomization plus one day. In the analysis of PFS for U.S. registrational 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.

For objective response, patients without any post-baseline assessment will be considered non-responders.

For DOR, patients who have not progressed or 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 date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a complete or partial response plus one day.

5. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics* 1982;38:29–41.

Fayers PM, Aaronson NK, Bjordal K, et al. On behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16:139–44.

Lewis S, Clarke M. Forest plots: trying to see the wood and the trees. *BMJ* 2001;322:1479–80.

Appendix 1

Protocol Synopsis

TITLE: A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) COMPARED WITH CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC UROTHELIAL BLADDER CANCER AFTER FAILURE WITH PLATINUM-CONTAINING CHEMOTHERAPY

PROTOCOL NUMBER: GO29294

VERSION NUMBER: 6

EUDRACT NUMBER: 2014-003231-19

IND NUMBER: 120827

TEST PRODUCT: Atezolizumab (RO5541267)

PHASE: III

INDICATION: Urothelial bladder cancer

SPONSOR: F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

For the primary and secondary efficacy objectives, a comparison of the treatment arms will be performed in different patient subpopulations according to tumor PD-L1 expression as evaluated by IHC. The IHC scores will have three categories (IC0, IC1, and IC2/3), which will also be used for stratification (IHC score of IC0/1 vs. IHC score of IC2/3).

Primary Efficacy Objective

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of atezolizumab treatment compared with chemotherapy treatment with respect to overall survival (OS) in patients with locally advanced or metastatic urothelial bladder cancer (UBC) who have progressed during or following a platinum-containing regimen

Secondary Efficacy Objectives

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab compared with chemotherapy with respect to anti-tumor effects as measured by objective response rate (ORR) per investigator with use of Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
- To evaluate the efficacy of atezolizumab compared with chemotherapy with respect to anti-tumor effects as measured by progression-free survival (PFS) per investigator with use of RECIST v1.1
- To evaluate the efficacy of atezolizumab compared with chemotherapy with respect to anti-tumor effects as measured by duration of objective response (DOR) per RECIST v1.1

Atezolizumab—F. Hoffmann-La Roche Ltd
22/Statistical Analysis Plan GO29294

Clinical Study Report: RO5541267 - F. Hoffmann-La Roche Ltd
Protocol GO29294 Report Number 1074426

Appendix 1

Protocol Synopsis (cont.)

Safety Objectives

The safety objectives for this study are as follows:

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

Pharmacokinetic Objective

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

- To characterize the pharmacokinetics of atezolizumab in patients with locally advanced or metastatic UBC who have progressed during or following a platinum-containing regimen

Patient-Reported Outcome Objective

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

- To evaluate and compare PROs of patient health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab with respect to anti-tumor effects as measured by PFS, ORR, and DOR per modified RECIST
- To evaluate and compare disease control rate (DCR) between the two treatment arms
- To evaluate the relationship between tumor tissue programmed death–ligand 1 (PD-L1) expression and measures of efficacy
- To assess 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
- To assess health status as measured using the EuroQol 5-Dimension, 3-level version (EQ-5D [3L]) questionnaire for health economic modeling

Study Design

Description of Study

This is a 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 UBC who have progressed during or following a platinum-containing regimen. Within the chemotherapy control arm, the percentage of patients who are treated with a taxane (paclitaxel or docetaxel) will be capped at 40%. Until that cap is reached, the selection of the specific chemotherapy (vinflunine or taxane) for patients who are randomized to the chemotherapy arm will be per investigator's choice.

Male and female patients aged ≥ 18 years with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 who have histologically or cytologically proven, locally advanced or metastatic UBC and who have experienced disease progression during or following treatment for advanced disease consisting of platinum-based therapy are eligible.

Patients who experience disease progression during or within 12 months following completion of a platinum-based adjuvant or neoadjuvant regimen will also be eligible for enrollment into the study.

Appendix 1 Protocol Synopsis (cont.)

Patients must have received at least one platinum containing regimen (e.g., gemcitabine and cisplatin [GC], methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC], carboplatin and gemcitabine [CarboGem], etc.) for locally advanced or metastatic UBC. The maximum number of prior therapies in the locally advanced or metastatic setting is restricted to two.

Tumor specimens from eligible patients will be prospectively tested for PD-L1 expression by a central laboratory. Both patients and investigators will be blind to the PD-L1 expression status. The study will enroll all patients whose tissue is evaluable for expression testing, regardless of PD-L1 expression status.

This study will enroll approximately 931 patients, including a minimum of 230 patients with a PD-L1 IHC score of IC2/3 and a minimum of 537 patients with a PD-L1 IHC score of IC1/2/3 (enrollment of all patients will continue to reach the minimum requirement of patients with a PD-L1 IHC score of IC2/3). Patients will be randomized in a 1:1 ratio to receive either atezolizumab or chemotherapy (vinflunine, paclitaxel, or docetaxel; see protocol for stratification factors):

- Arm A (experimental arm): Atezolizumab 1200 mg every 3 weeks (q3w)
- Arm B (control arm): Vinflunine 320 mg/m² q3w, paclitaxel 175 mg/m² q3w, or docetaxel 75 mg/m² q3w

Atezolizumab will be administered intravenously at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. Patients will receive atezolizumab as long as they continue to experience clinical benefit in the opinion of the investigator until unacceptable toxicity or symptomatic deterioration attributed to disease progression (i.e., pain secondary to disease or unmanageable ascites, etc.) as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status.

During treatment, patients will be permitted to continue atezolizumab treatment after RECIST v1.1 criteria for progressive disease are met if they meet all of the following criteria:

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

Patients treated with atezolizumab for whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the investigator if they continue to meet the criteria above.

Patients randomized to the chemotherapy arm will receive vinflunine, paclitaxel, or docetaxel per the investigator's choice. Vinflunine 320 mg/m², paclitaxel 175 mg/m², or docetaxel 75 mg/m² will be administered intravenously on Day 1 of each 21-day cycle until disease progression per standard RECIST v1.1 or unacceptable toxicity.

Given the unique characteristics associated with the chemotherapy arm, including toxicities (i.e., mucositis, neutropenia, febrile neutropenia, and alopecia) and the premedications required (i.e., steroid, anti-emetics, and potentially growth factor support), this will be an open-label study.

No crossover will be allowed from the control arm to the experimental arm.

Patients will undergo scheduled tumor assessment at baseline and every 9 weeks thereafter for 54 weeks following randomization. After 54 weeks from randomization, patients will undergo tumor assessment every 12 weeks until disease progression per modified RECIST (see protocol) or until treatment discontinuation (for patients who continue to receive atezolizumab following disease progression). For patients randomized to the chemotherapy arm, assessments will continue until disease progression per RECIST v1.1 (see protocol), regardless of whether treatment has been discontinued. In the absence of disease progression, tumor

Atezolizumab—F. Hoffmann-La Roche Ltd
24/Statistical Analysis Plan GO29294

Clinical Study Report: RO5541267 - F. Hoffmann-La Roche Ltd
Protocol GO29294 Report Number 1074426

Appendix 1 Protocol Synopsis (cont.)

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 Sponsor. 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 Sponsor.

For patients randomized to the atezolizumab arm, response will be assessed by the investigator with use of RECIST v1.1 and modified RECIST. For patients randomized to the chemotherapy arm, response will be assessed by the investigator with use of RECIST v1.1 only.

Primary imaging data used for tumor assessment may be collected by the Sponsor to enable centralized, independent review of response endpoints if needed.

Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (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 and plasma and whole 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 (see protocol).

Number of Patients

This study will enroll approximately 931 patients, including a minimum of 230 patients with a PD-L1 IHC score of IC2/3 and a minimum of 537 patients with a PD-L1 IHC score of IC1/2/3.

Target Population

Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry:

- Signed Informed Consent Form
- Ability to comply with protocol
- Age \geq 18 years
- Histologically or cytologically documented locally advanced (T4b, any N; or any T, N 2–3) or metastatic (M1, Stage IV) UBC (also termed transitional cell carcinoma [TCC] or urothelial cell carcinoma [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).

- Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:
 - Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)
 - No ongoing requirement for corticosteroids as therapy for CNS disease
 - No stereotactic radiation within 7 days
 - No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
 - Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to enrollment [or randomization], if all other criteria are met.

Appendix 1 Protocol Synopsis (cont.)

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

Tumor tissue should be of good quality on the basis of 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.

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 or nephroureterectomy 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 meeting 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 having additional tissue samples from procedures performed at different times during the course of their UBC will be requested (but not required) to also submit these samples for central testing. Tissue samples obtained at multiple times for individual patients will greatly contribute to an improved understanding of the dynamics of PD-L1 expression and relationship with intervening anti-cancer therapy. In situations where multiple specimens were received from different sites or at different times, the highest score will be used for both primary and secondary analyses.

- Disease progression during or following treatment with at least one platinum-containing regimen (e.g., GC, MVAC, CarboGem, etc.) for inoperable, locally advanced or metastatic UBC or disease recurrence

A regimen is defined as patients receiving at least two cycles of a platinum-containing regimen.

Patients who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment with a platinum-containing adjuvant/neoadjuvant regimen will be considered as second-line patients.

Patients may have received no more than two prior regimens of treatment (including the required platinum-based regimen) for their advanced UBC. Patients must have demonstrated disease progression during or following all prior regimen(s).

Patients who have received one cycle of a platinum-containing regimen but discontinued because of a Grade 4 hematologic toxicity or a Grade 3/4 non-hematologic toxicity may also be eligible.

Patients with disease progression following chemoradiotherapy must demonstrate progression outside the prior radiotherapy port.

- ECOG performance status of 0 or 1
- Life expectancy \geq 12 weeks
- Measurable disease, as defined by RECIST v1.1
 - Previously irradiated lesions should not be counted as target lesions.
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment:

Appendix 1 Protocol Synopsis (cont.)

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

WBC counts $> 2500/\mu\text{L}$

Lymphocyte count $\geq 500/\mu\text{L}$

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

Hemoglobin ≥ 9.0 g/dL

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

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

Patients with documented liver metastases: AST and/or ALT $\leq 5 \times \text{ULN}$

Patients with documented liver or bone metastases: alkaline phosphatase $\leq 5 \times \text{ULN}$

Serum bilirubin $\leq 1.0 \times \text{ULN}$

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

INR and aPTT $\leq 1.5 \times \text{ULN}$

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

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

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 90 days after the last dose of atezolizumab, 3 months after the last dose of vinflunine and 6 months from the last dose of paclitaxel or docetaxel.

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

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

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

- 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 3 months after the last dose of vinflunine and 6 months from the last dose of paclitaxel or docetaxel. Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 28 days after the last dose of vinflunine, paclitaxel, or docetaxel.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence

Appendix 1

Protocol Synopsis (cont.)

(e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

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

Cancer-Specific 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 trial with therapeutic intent within 28 days prior to enrollment
- Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) 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, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)
- No history of intracranial or spinal cord hemorrhage
- No ongoing requirement for dexamethasone 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 with 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 requiring 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 > 12 mg/dL
 - Corrected serum calcium $> \text{ULN}$ (if serum albumin < 4.0 g/dL)

Atezolizumab—F. Hoffmann-La Roche Ltd
28/Statistical Analysis Plan GO29294

Clinical Study Report: RO5541267 - F. Hoffmann-La Roche Ltd
Protocol GO29294 Report Number 1074426

Appendix 1

Protocol Synopsis (cont.)

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.

Patients who are receiving denosumab prior to enrollment must be willing and eligible to discontinue its use and replace it with a bisphosphonate instead while on study.

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

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

Patients with low risk prostate cancer (defined as Stage T1/T2a, Gleason score \leq 6, and PSA \leq 10 ng/mL) who are treatment-naive and undergoing active surveillance are eligible.

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

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

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

General Medical Exclusions

- Pregnant and lactating
- Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina
- Patients with a known left ventricular ejection fraction (LVEF) $<$ 40% will be excluded.

Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF $<$ 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.
- Severe infections within 4 weeks prior to randomization including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received therapeutic oral or intravenous (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) 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
- Inability to understand the local language(s) for which the EORTC QLQ-C30 and EQ-5D (3L) questionnaires are available

Exclusion Criteria Related to Paclitaxel

- Prior treatment with paclitaxel for assignment of paclitaxel in the chemotherapy control arm prior to randomization

Atezolizumab—F. Hoffmann-La Roche Ltd
29/Statistical Analysis Plan GO29294

Clinical Study Report: RO5541267 - F. Hoffmann-La Roche Ltd
Protocol GO29294 Report Number 1074426

Appendix 1 Protocol Synopsis (cont.)

- History of severe hypersensitivity to paclitaxel or to other drugs formulated with polyoxyethylated castor oil

Exclusion Criteria Related to Docetaxel

- Prior treatment with docetaxel for assignment of docetaxel in the chemotherapy control arm prior to randomization
- History of severe hypersensitivity to docetaxel or to other drugs formulated with polysorbate 80
- Grade ≥ 2 peripheral neuropathy as defined by NCI CTCAE v4.0 criteria
- Inability to discontinue use of strong cytochrome P450 (CYP)3A4 inhibitors including but not limited to ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, or voriconazole

Exclusion Criteria Related to Vinflunine

- Prior treatment with vinflunine for assignment of vinflunine in the chemotherapy control arm prior to randomization
- History of severe hypersensitivity to vinflunine or other vinca alkaloids

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, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study.

Patients with controlled Type 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.
- Serum albumin < 2.5 g/dL
- Positive test for HIV

Atezolizumab—F. Hoffmann-La Roche Ltd
30/Statistical Analysis Plan GO29294

Clinical Study Report: RO5541267 - F. Hoffmann-La Roche Ltd
Protocol GO29294 Report Number 1074426

Appendix 1 Protocol Synopsis (cont.)

- Patients with active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C
 - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.
 - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Active tuberculosis (TB)
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study
 - Influenza vaccination should be given during influenza season only (approximately October through March in the Northern Hemisphere and approximately April through September in the Southern Hemisphere). Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist[®]) 28 days prior to randomization, during treatment or within 90 days following the last dose of atezolizumab (for patients randomized to atezolizumab).
- Prior treatment with CD137 agonists, anti-programmed death-1 (PD-1), or anti-PD-L1 therapeutic antibody or pathway-targeting agents
 - Patients who have had prior anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) may be enrolled, provided the following requirements are met:
 - Minimum of 12 weeks from the first dose of anti-CTLA-4 and >6 weeks from the last dose
 - No history of severe immune-related adverse effects from anti-CTLA-4 (NCI CTCAE Grade 3 and 4)
- Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin [IL]-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to randomization
- 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 randomization or anticipated requirement for systemic immunosuppressive medications during the trial
 - Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.
 - 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 the study is defined as the date when all patients have one of the following:

- Experienced an OS event
- Been lost to follow-up
- Withdrawn consent

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

Outcome Measures

Efficacy Outcome Measures

Primary Efficacy Outcome Measure

Atezolizumab—F. Hoffmann-La Roche Ltd
31/Statistical Analysis Plan GO29294

Clinical Study Report: RO5541267 - F. Hoffmann-La Roche Ltd
Protocol GO29294 Report Number 1074426

Appendix 1 Protocol Synopsis (cont.)

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

- OS, defined as the time between the date of randomization and death due to any cause

Secondary Efficacy Outcome Measures

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

- ORR, defined as the proportion of patients with an objective response (either a complete response [CR] or partial response [PR]) as determined by the investigator with use of RECIST v1.1
- PFS, defined as the time between the date of randomization and the date of first documented disease progression as determined by the investigator with use of RECIST v1.1 or death due to any cause, whichever occurs first
- DOR, defined as the time between the date of first documented response and the date of first documented disease progression as determined by the investigator with use of RECIST v1.1 or death due to any cause, whichever occurs first

Safety Outcome Measures

The safety outcome measures for this study are as follows:

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

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Maximum observed serum atezolizumab concentration (C_{max}) after infusion on Day 1 of Cycle 1
- Minimum observed serum atezolizumab concentration (C_{min}) prior to infusion on Day 1 of Cycles 1, 2, 3, 4, 8, and 16, at treatment discontinuation, and at 120 days (± 30 days) after the last dose of atezolizumab

Patient-Reported Outcome Measure

The PRO outcome measure for this study is as follows:

- UBC cancer symptoms, patient functioning, and HRQoL as measured by the EORTC QLQ-C30

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- PFS, ORR, and DOR with use of modified RECIST for patients randomized to atezolizumab
- DCR, defined as the rate of patients with complete or partial response as best response or stable disease maintained for ≥ 18 weeks per RECIST v1.1
- Status of tumor immune-related or disease type-related exploratory biomarkers in archival and/or freshly obtained tumor tissues and association with disease status and/or response to atezolizumab
- Status of exploratory biomarkers in plasma, whole blood, or serum (including but not limited to cytokines such as interleukin 6 [IL-6]) collected before or during treatment with atezolizumab or at progression and association with disease status and/or response to atezolizumab
- Utility scores of the EQ-5D (3L) for use in economic models

Atezolizumab—F. Hoffmann-La Roche Ltd
32/Statistical Analysis Plan GO29294

Clinical Study Report: RO5541267 - F. Hoffmann-La Roche Ltd
Protocol GO29294 Report Number 1074426

Appendix 1

Protocol Synopsis (cont.)

- Items from the EORTC QLQ-C30 that are not included in the main PRO outcome measure

Investigational Medicinal Products

Test Product

Atezolizumab is administered at a dose of 1200 mg by IV infusion on Day 1 of each 21-day cycle.

Comparators

Vinflunine is administered at a dose of 320 mg/m² by IV infusion on Day 1 of each 21-day cycle.

Paclitaxel is administered at a dose of 175 mg/m² over 3 hours by continuous IV infusion on Day 1 of each 21-day cycle.

Docetaxel is administered at a dose of 75 mg/m² on Day 1 of each 21-day cycle.

Statistical Methods

Primary Analysis

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

The primary analysis will occur when approximately 152, 403, and 652 deaths have been observed in the following populations: patients with an IHC score of IC2/3, patients with an IHC score of IC1/2/3, and ITT populations respectively, whichever occurs later.

Comparisons with respect to OS between the treatment and control arms will be tested using a hierarchical fixed-sequence procedure based on a stratified log-rank test at two-sided level of 5% significance within the following populations: patients with an IHC score of IC2/3, patients with an IHC score of IC1/2/3, and in the ITT population.

Determination of Sample Size

This study will enroll approximately 931 patients, including a minimum of 230 patients with a PD-L1 IHC score of IC2/3 and a minimum of 537 patients with a PD-L1 IHC score of IC1/2/3.

The number of events required to demonstrate efficacy of the atezolizumab experimental arm over the chemotherapy arm (i.e., vinflunine, paclitaxel, or docetaxel) with regard to OS are *estimated* based on the following assumptions:

- Two-sided significance level of 5%
- 94% for the primary analysis of OS in the population of patients with an IHC score of IC2/3 with an HR of 0.57, corresponding to an improvement in median OS from 7.5 months to 13.2 months
- 98% power for the primary analysis of OS in the population of patients with an IHC score of IC1/2/3 with an HR of 0.68, corresponding to an improvement in median OS from 7.5 months to 11 months
- 97% power for the primary analysis of OS in the ITT population with an HR of 0.74, corresponding to an improvement in median OS from 7.5 months to 10.1 months
- 1:1 randomization ratio
- Dropout rate of 5% per year over 24 months

Interim Analyses

No interim efficacy analyses are planned for this study.

An iDMC will be set up to evaluate safety results approximately every 6 months after FPI. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an external

Atezolizumab—F. Hoffmann-La Roche Ltd
33/Statistical Analysis Plan GO29294

Clinical Study Report: RO5541267 - F. Hoffmann-La Roche Ltd
Protocol GO29294 Report Number 1074426

Appendix 1 Protocol Synopsis (cont.)

iDCC. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.

Appendix 2 Schedule of Assessments

Assessment Window (Days)	Screening ^a	All Cycles	Treatment Discontinuation ^b	Follow-Up
	Days -28 to -1	Day 1 (±3 Days for Cycles ≥2)	≤30 Days after Last Dose	
Signed Informed Consent Form(s) ^a	x			
Review of eligibility criteria	x			
Medical, surgical, and cancer histories, including demographic information ^c	x			
HIV, HBV, HCV, EBV serology ^d	x			
TB test ^e	x			
Concomitant medications ^f	x	x	x	
Tumor assessment ^g	x	Every 9 weeks ±3 business days for 54 weeks and every 12 weeks ±6 business days thereafter until disease progression, death, or loss of follow-up		
Patient-reported outcomes ^h		x	x	x
Complete physical examination ⁱ	x		x	
Limited physical examination ⁱ		x ^j		x
ECOG performance status	x	x ^j	x	
Vital signs ^k	x	x	x	
12-lead ECG ^l	x	x ^l	x ^l	
Weight	x	x	x	
Height	x			
Hematology ^m	x	x ^j	x	

Appendix 2 Schedule of Assessments (cont.)

Assessment Window (Days)	Screening ^a	All Cycles	Treatment Discontinuation ^b	Follow-Up
	Days –28 to –1	Day 1 (±3 Days for Cycles ≥2)	≤30 Days after Last Dose	
Serum chemistry ⁿ	x	x ^j	x	
Coagulation panel (aPTT, INR) ⁿ	x		x	
Vitamin D assay	x			
C-reactive protein testing	x	x ^o		
Urinalysis ^p	x	x ^q	x	
Serum pregnancy test ^r	x			
TSH, free T3, free T4	x	x ^s	x	
Auto-antibody testing (atezolizumab patients only) ^t		x		
Serum sample for ATA assessment (atezolizumab patients only) ^u		x	x	
Serum sample for PK sampling (atezolizumab patients only) ^u		x	x	
Blood samples for pharmacodynamics biomarkers ^v		x	x	
Optional whole blood sample for RCR DNA ^w	x			
Adverse events ^x		x	x	x
Study drug infusion ^y		x		
Archival/screening FFPE tumor tissue specimen or 15 unstained slides ^z	x			

Appendix 2 Schedule of Assessments (cont.)

Assessment Window (Days)	Screening ^a	All Cycles	Treatment Discontinuation ^b	Follow-Up
	Days –28 to –1	Day 1 (±3 Days for Cycles ≥2)	≤30 Days after Last Dose	
Fresh biopsy (optional RCR)	x ^{aa}		Per investigator discretion, biopsy(ies) to be performed preferably at the time of radiographic progression (atezolizumab-treated patients only) ^z	
Survival and anti-cancer therapy follow-up ^{bb}				x

anti-HBc=antibody against hepatitis B core antigen; ATA=anti-therapeutic antibody; EBV=Epstein-Barr virus; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D (3L)=EuroQoL 5 Dimensions; FFPE=formalin fixed paraffin embedded; HBV=hepatitis B virus; HCV=hepatitis C virus; MUGA=multiple-gated acquisition; PD-L1=programmed death-ligand 1; PK=pharmacokinetic; PRO=patient-reported outcome; QLQ-C30=Quality-of-life Questionnaire Core 30; RCR=Roche Clinical Repository; RECIST=Response Evaluation Criteria in Solid Tumors; 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.
- ^b Patients will be asked to return to the clinic not more than 30 days after the last treatment for a treatment discontinuation visit.
- ^c 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.
- ^d 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 trial. Hepatitis B surface antigen, 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 prior to Cycle 1, Day 1. EBV serology tests will be performed centrally on the samples collected during screening only in patients who experience an acute inflammatory event such as systemic inflammatory response syndrome while receiving study treatment.

Appendix 2 Schedule of Assessments (cont.)

- ^e All patients will have a tuberculin (PPD) skin test or IGRA done locally prior to the inclusion into the study, and patients with active TB will be excluded from the clinical trial.
- ^f 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 the date of informed consent should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.
- ^g 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. For patients randomized to vinflunine or taxane, assessments will continue until disease progression per RECIST v1.1 (see Appendix 4), regardless of whether treatment has been discontinued. Patients randomized to atezolizumab will undergo assessments until disease progression or until treatment discontinuation (for patients who continue to receive atezolizumab following disease progression). Tumor assessments should continue regardless of whether patients start new anti-cancer therapy in the absence of disease progression unless they withdraw consent. 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. Patients assigned to atezolizumab who continue treatment beyond radiographic disease progression (see Section 4.6.1.1) will be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 9 weeks. If the scan frequency is every 12 weeks, the follow-up scan must be performed at 9 weeks (\pm 2 weeks) as an unscheduled tumor assessment, or earlier if clinically indicated. Investigators may perform additional scans or more frequent assessments if clinically indicated.
- ^h The PRO questionnaires (EORTC QLQ-C30, and EQ-5D [3L]) will be completed by the patients at the investigational site. All PRO questionnaires are required to be administered prior to administration of study treatment and/or prior to any other study assessment(s) to ensure that the validity of the instrument is not compromised and to ensure that data quality meets regulatory requirements. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site, and the hard copy originals of the questionnaires must be maintained as part of the patient's medical record when relevant at the site for source data verification. In addition, the EQ-5D only will be collected at 6, 12, and 24 weeks after disease progression per RECIST 1.1 through telephone interview by trained site staff and in compliance with best practices and recommendations by EuroQoL. Study personnel will record patient responses on a paper copy of the EQ-5D (3L) during the telephone interview as record of source documentation.
- ⁱ Complete and limited physical examinations are defined in Section 4.5.2.2.
- ^j ECOG performance status, limited physical examination, local laboratory assessments, and C-reactive protein assessment may be obtained \leq 96 hours before Day 1 of each cycle (including Cycle 1).

Appendix 2 Schedule of Assessments (cont.)

- ^k Vital signs include heart rate, respiratory rate, blood pressures, and temperature. At all infusions of study drug (atezolizumab, vinflunine, paclitaxel, or docetaxel), the patient's vital signs should be determined up to 60 minutes before and 30 (\pm 10) minutes after the infusion. For the atezolizumab arm, vital signs will also be collected during the first infusion (every 15 [\pm 5] minutes).
- ^l ECG recordings will be obtained during screening and when clinically indicated. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.
- ^m Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. See Section 4.1.1 for a list of laboratory results obtained within 14 days prior to the first study treatment.
- ⁿ Serum chemistry includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin. See Section 4.1.1 for a list of laboratory results obtained within 14 days prior to the first study treatment.
- ^o On Day 1 of Cycle 4 and every four cycles thereafter until Cycle 16.
- ^p Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood).
- ^q On Day 1 of Cycle 3 and every two cycles thereafter.
- ^r Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Day 1. Starting from Cycle 3, either serum or urine pregnancy test (positive urine test results will be confirmed with a serum pregnancy test) must be performed every two cycles during the study treatment, and as clinically indicated thereafter.
- ^s On Day 1 of Cycle 5 and every four cycles thereafter.
- ^t For patients assigned to atezolizumab only. Baseline sample to be collected on Cycle 1, Day 1 prior to the first dose of study treatment. For patients who show evidence of immune-mediated toxicity, additional samples will be collected, and all samples will be analyzed centrally. Includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.
- ^u For patients assigned to atezolizumab only. See Appendix 2 for details of the ATA and PK collection schedule. Blood samples should be processed to obtain serum. A post-treatment ATA and PK sample should be collected 120 (\pm 30) days after the last dose of atezolizumab unless the patient withdraws consent or the study closes.
- ^v See Appendix 2 for details of the pharmacodynamic sampling schedule.
- ^w Whole blood for DNA isolation will be collected from patients who have consented to optional RCR sampling at baseline. If, however, the RCR genetic blood sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study.

Appendix 2 Schedule of Assessments (cont.)

- ^x 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 adverse events will be reported until 90 days after the last dose of study treatment, whichever occurs first. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.
- ^y Patients should receive their first dose of study drug the day of randomization if possible. If this is not possible, the first dose should occur no later than 3 days after randomization. For atezolizumab, the will be delivered over 60 (\pm 15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (\pm 10) minutes. Atezolizumab treatment may be continued as long as the patient continues to experience clinical benefit in the opinion of the investigator until unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status. For vinflunine, paclitaxel, and docetaxel, study drug will be administered according to the local prescribing information, including premedication for paclitaxel (see Section 4.3.2) and docetaxel. Vinflunine, paclitaxel, and docetaxel treatment will continue until disease progression per standard RECIST v1.1 or unacceptable toxicity.
- ^z 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 of the Informed Consent Form, retrieval and submission of archival tumor sample can occur outside the 28-day screening period.
- ^{aa} For patients who have consented to collection of optional biopsies on the Optional Collection of Samples for RCR Informed Consent Form, optional tumor biopsy samples may be collected by core needle or excisional/punch biopsy per investigator discretion. Preferably, growing lesions should be selected, and samples collected at the time of radiographic progression. Optional biopsy tissue will be stored in the RCR. Not applicable for a site that has not been granted approval for RCR sampling.
- ^{bb} Starting from treatment discontinuation visit, survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by Roche. 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 study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.