

Official Title: A Phase III, Double-Blind, Multicenter, Randomized Study of Atezolizumab (Anti-PD-L1 Antibody) Versus Placebo as Adjuvant Therapy in Patients with High-Risk Muscle-Invasive Bladder Cancer who are ctDNA Positive Following Cystectomy

NCT Number: NCT04660344

Document Date: Protocol Amendment Version 10: 10-Nov-2025

PROTOCOL

PROTOCOL TITLE: A PHASE III, DOUBLE-BLIND, MULTICENTER, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) VERSUS PLACEBO AS ADJUVANT THERAPY IN PATIENTS WITH HIGH-RISK MUSCLE-INVASIVE BLADDER CANCER WHO ARE CTDNA POSITIVE FOLLOWING CYSTECTOMY

PROTOCOL NUMBER: BO42843

STUDY NAME: IMvigor011

VERSION NUMBER: 10

TEST COMPOUND: Atezolizumab (RO5541267)

STUDY PHASE: Phase III

REGULATORY AGENCY IDENTIFIER NUMBERS: IND Number: 120,827
EudraCT Number: 2020-004418-36
EU CT Number: 2022-502705-15-00
CIV ID: CIV-22-12-041650
PS ID: PS-22-12-041650
NCT Number: NCT04660344

SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS: F. Hoffmann-La Roche Ltd
Grenzacherstrasse 124
4058 Basel, Switzerland

APPROVAL: See electronic signature and date stamp on the final page of this document.

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 The information contained in this document, especially any unpublished data, is the property of F. Hoffmann-La Roche Ltd (or under its control) and therefore is provided to you in confidence as an investigator, potential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 HISTORY

Protocol		Associated Country-Specific Protocols		
Version	Date Final	Country	Version	Date Final
10	See electronic date stamp on the final page of this document.	—	—	—
9	12 February 2025	China	9	18 March 2025
8	22 March 2024	China	8	28 March 2024
7	16 February 2024	China	7	22 February 2024
6	15 March 2023	China	6	19 April 2023
5	22 July 2022	China	5	29 August 2022
4	6 January 2022	China	4	1 February 2022
3	8 March 2021	China	3	4 August 2021
2	5 November 2020	China	2	2 February 2021
1	30 October 2020	—	—	—

PROTOCOL AMENDMENT, VERSION 10: RATIONALE

Protocol BO42843 has been amended to align the adverse event management guidelines with the updates in the Atezolizumab Investigator's Brochure, Version 22. In addition, because the clinical cut-off date for the primary analysis has been reached and most of the analyses per the Statistical Analysis Plan (SAP) are complete, certain changes have been implemented to alleviate the burden on patients and sites as outlined below.

- As a result of the study meeting its primary endpoint of disease-free survival (DFS) and key secondary endpoint of overall survival (OS) at the primary analysis, the following changes have been introduced:
 - Tumor biopsy samples collected to provide histological confirmation of disease recurrence will no longer be sent to central labs and are to be performed if considered clinically feasible (Sections 3.1.1, 3.4.6, 4.5.5, and 4.5.6; Appendices 2 [Footnote 'u'] and 5).
 - The independent Data Monitoring Committee (iDMC) support for safety review activities has been terminated. Safety will be monitored at regular intervals by the Sponsor's study team (Sections 3.1.2, 5.7, 6.12.2, and 9.5).
 - The end of the study definition has been revised to the date at which the last data point required for statistical analysis (i.e., survival) is received from the last patient, which is now expected to occur approximately 18 months after the last patient is randomized. Consequently, the total length of the study is now estimated to be approximately 6 years (Section 3.2).
 - Assessments for patient-reported outcomes (PROs) are no longer required from Protocol Version 10 onwards (Sections 3.4.7, 4.5.8, and 4.6.1; Appendix 2 [PRO row and Footnote 'f']).
 - Information on unblinding has been updated to clarify that the Sponsor and its agents have been unblinded to treatment assignment and investigators may also be unblinded upon request to guide treatment decisions at the investigator's discretion, or in case of medical emergencies (Sections 4.2.1 and 4.2.2).
 - Disease recurrence in the Treatment Phase will no longer be evaluated by an Independent Review Facility (IRF), but only by the investigator (Section 4.5.5).
 - Collection of urine and blood samples for exploratory biomarker analyses has been considerably reduced and is now only required during the Treatment and Treatment Follow-Up Phases at the time of disease recurrence (Section 4.5.5; Appendices 2 and 5).
 - All patients, regardless of arm, are no longer required to perform one follow-up post-recurrence assessment after investigator assessment of radiographic disease recurrence per the Apolo criteria, because these data are no longer required as no further IRF analyses are planned (Section 4.5.5 and Appendix 2 [Footnote 'v']).

- New Research Biosample Repository (RBR) samples will not be collected but previously collected samples may still be analyzed (Sections 4.5.9.1 and 4.5.9.3).
- Collections for pharmacokinetic (PK) and anti-drug antibody (ADA) analyses are no longer required from Protocol Version 10 onwards since sufficient clinical pharmacology and immunogenicity data have been collected from the primary analysis (Appendices 2 and 4).
- Language has been added to indicate that patients who previously were discontinued from the Surveillance Phase as a result of experiencing investigator-assessed disease recurrence may be contacted to request consent for survival follow-up (Sections 3.1, 3.1.1, 4.5.5, and 4.6.5; Appendix 1 [Footnotes 'c' and 'd']). Accordingly, patients in the Surveillance Phase who experience disease recurrence are no longer to be discontinued from the study (Section 4.6.2 and Appendix 1 [Footnotes 'c' and 'r']).
- Collection of demographic data, including information on race and ethnicity, is of importance to the future interpretation of results from the clinical trial. A rationale has been provided in Section 3.4.8.
- Language had been added to indicate that for Cycle 2 and for subsequent cycles, atezolizumab may be infused over a longer period of time at the investigator's discretion (Section 4.3.2 [Table 1] and Appendix 2 [Footnote 'aa']).
- It has been clarified that information on survival follow-up (Surveillance and Treatment Phases) and new anti-cancer therapy (Surveillance Phase only) will be collected from time of disease recurrence (Sections 4.6.1; Appendix 1 [Footnote 'v'] and Appendix 2 [Footnote 'bb']).
- Language has been updated to indicate that patients may choose to withdraw consent for specific protocol-mandated assessments without fully withdrawing from the study (Section 4.6.2 and Appendix 2 [new Footnote 'a']).
- A definition of "lost to follow-up" had been added along with a list of actions to be taken if a patient fails to return to the clinic for a required study visit (new Section 4.6.6).
- The risk "uveitis" has been added to the list of identified risk for atezolizumab and removed from the list of adverse events of special interest for atezolizumab (Sections 5.1.1 and 5.2.3).
- An In-Vitro Diagnostics Regulation (IVDR)–aligned definition for "Definition of Serious Device Adverse Event" has been added (new Section 5.8.2).
- The number of participating sites has been updated to 205 (Section 9.5).
- It has been clarified that concomitant medications only need to be reported during surveillance follow-up if they are related to an unresolved adverse event that occurred during surveillance (Appendix 1 [Footnote 's']).
- It has been clarified that adverse events will be recorded until 30 days after the last surveillance follow-up visit at Year 3, which corresponds to the beginning of Year 4 (Appendix 1 [Footnote 'u']).

- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 22 (Appendix 12).

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

TABLE OF CONTENTS

PROTOCOL AMENDMENT ACCEPTANCE FORM	14
PROTOCOL SYNOPSIS	15
1. BACKGROUND	21
1.1 Background on Muscle-Invasive Bladder Cancer	21
1.1.1 Current Therapies and Unmet Medical Need in Patients with Muscle-Invasive Bladder Cancer	22
1.1.2 Neoadjuvant Chemotherapy	22
1.1.3 Adjuvant Therapy	23
1.1.4 Cisplatin-Ineligible Patients	24
1.2 Background on Atezolizumab	25
1.2.1 Clinical Activity of Adjuvant Atezolizumab in MIUC Patients Who Were ctDNA Positive Following Cystectomy	26
1.3 Study Rationale and Benefit-Risk Assessment	26
2. OBJECTIVES AND ENDPOINTS	28
2.1 Efficacy Objectives	29
2.1.1 Primary Efficacy Objective	29
2.1.2 Secondary Efficacy Objective	29
2.1.3 Exploratory Efficacy Objective	29
2.2 Safety Objective	30
2.3 Pharmacokinetic Objective	30
2.4 Immunogenicity Objectives	30
2.5 Biomarker Objective	30
2.6 Exploratory Patient-Reported Outcome Objective	31
2.7 Health Status Utility Objective	31
3. STUDY DESIGN	31
3.1 Description of the Study	31
3.1.1 Overview of Study Design	34
3.1.2 Independent Data Monitoring Committee	37
3.1.3 Patient Input into Study Design	38
3.2 End of Study and Length of Study	38
3.3 Duration of Participation	38

3.4	Rationale for Study Design	39
3.4.1	Rationale for Atezolizumab Dose and Schedule	39
3.4.2	Rationale for Patient Population	39
3.4.2.1	Circulating Tumor DNA as a Biomarker for Patient Selection in Muscle-Invasive Urothelial Carcinoma	40
3.4.2.2	Circulating Tumor DNA Can Potentially Predict Response to Immunotherapy	41
3.4.3	Rationale for Control Group	42
3.4.4	Rationale for Disease-Free Survival as Primary Endpoint	42
3.4.5	Rationale for Collection of Mandatory Resected Tumor, Blood, and Urine Specimens for ctDNA and Biomarker Analyses	43
3.4.6	Rationale for the Collection of Recurrence Biopsies	44
3.4.7	Rationale for Clinical Outcome Assessments	45
3.4.8	<i>Rationale for Collection of Information on Race and Ethnicity</i>	45
4.	MATERIALS AND METHODS	46
4.1	Patients	46
4.1.1	Inclusion Criteria	46
4.1.1.1	Inclusion Criteria for the Surveillance Phase	46
4.1.1.2	Additional Inclusion Criteria for the Treatment Phase	48
4.1.2	Exclusion Criteria	50
4.1.2.1	General Medical Exclusion Criteria for the Surveillance Phase	50
4.1.2.2	Cancer-Specific Exclusion Criteria for the Surveillance Phase	51
4.1.2.3	Additional Exclusion Criteria for the Treatment Phase	52
4.1.2.4	Additional Medication-Related Exclusion Criteria for the Treatment Phase	53
4.2	Method of Treatment Assignment and Blinding	54
4.2.1	Treatment Assignment	54
4.2.2	Blinding	55
4.3	Study Treatment	55
4.3.1	Study Treatment Formulation and Packaging	55
4.3.2	Study Treatment Dosage, Administration, and Compliance	56

4.3.3	Investigational Medicinal Product Handling and Accountability.....	57
4.3.4	Continued Access to Atezolizumab	58
4.4	Concomitant Therapy	58
4.4.1	Permitted Therapy	58
4.4.2	Cautionary Therapy for Atezolizumab-Treated Patients	59
4.4.2.1	Corticosteroids, Immunosuppressive Medications, and TNF Inhibitors	59
4.4.2.2	Herbal Therapies	59
4.4.3	Prohibited Therapy	60
4.5	Study Assessments	60
4.5.1	Informed Consent Forms and Screening Log	60
4.5.2	Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data.....	61
4.5.3	Physical Examinations.....	61
4.5.4	Vital Signs.....	61
4.5.5	Surveillance for Urothelial Carcinoma Recurrence	62
4.5.6	Laboratory, Biomarker, and Other Biological Samples	64
4.5.7	Electrocardiograms.....	70
4.5.8	Clinical Outcome Assessments	70
4.5.8.1	Data Collection Methods for Clinical Outcome Assessments	71
4.5.8.2	Description of Clinical Outcome Assessment Instruments.....	72
4.5.9	Optional Samples for Research Biosample Repository	72
4.5.9.1	Overview of the Research Biosample Repository.....	72
4.5.9.2	Approval by the Institutional Review Board or Ethics Committee	73
4.5.9.3	Sample Collection.....	73
4.5.9.4	Confidentiality	74
4.5.9.5	Consent to Participate in the Research Biosample Repository.....	74
4.5.9.6	Withdrawal from the Research Biosample Repository.....	75
4.5.9.7	Monitoring and Oversight.....	75
4.6	Treatment, Patient, Study, and Site Discontinuation.....	76
4.6.1	Study Treatment Discontinuation.....	76

4.6.2	Patient Discontinuation from the Study	76
4.6.3	Study Discontinuation	77
4.6.4	Site Discontinuation	77
4.6.5	Surveillance Phase Discontinuation and Follow-Up	78
4.6.6	<i>Lost to Follow-up</i>	78
5.	ASSESSMENT OF SAFETY	79
5.1	Safety Plan	79
5.1.1	Risks Associated with Atezolizumab	79
5.2	Safety Parameters and Definitions	80
5.2.1	Adverse Events	80
5.2.2	Serious Adverse Events (Immediately Reportable to the Sponsor)	80
5.2.3	Adverse Events of Special Interest (Immediately Reportable to the Sponsor)	81
5.3	Methods and Timing for Capturing and Assessing Safety Parameters	82
5.3.1	Adverse Event Reporting Period	82
5.3.2	Eliciting Adverse Event Information	83
5.3.3	Assessment of Severity of Adverse Events	83
5.3.4	Assessment of Causality of Adverse Events	84
5.3.5	Procedures for Recording Adverse Events	85
5.3.5.1	Infusion-Related Reactions and Cytokine Release Syndrome	85
5.3.5.2	Diagnosis versus Signs and Symptoms	86
5.3.5.3	Adverse Events That Are Secondary to Other Events	86
5.3.5.4	Persistent or Recurrent Adverse Events	86
5.3.5.5	Abnormal Laboratory Values	87
5.3.5.6	Abnormal Vital Sign Values	87
5.3.5.7	Abnormal Liver Function Tests	88
5.3.5.8	Deaths	88
5.3.5.9	Preexisting Medical Conditions	89
5.3.5.10	Recurrence of Urothelial Carcinoma	89
5.3.5.11	Hospitalization or Prolonged Hospitalization	89
5.3.5.12	Cases of Accidental Overdose or Medication Error	90

5.3.5.13	Patient-Reported Outcome Data.....	91
5.4	Reporting Requirements from Investigator to Sponsor	91
5.4.1	Medical Monitors and Emergency Medical Contacts	92
5.4.2	Reporting Requirements for Serious Adverse Events, Medical Device Adverse Events, and Adverse Events of Special Interest.....	92
5.4.2.1	Events That Occur prior to Study Treatment Initiation	92
5.4.2.2	Events That Occur after Study Treatment Initiation	93
5.4.3	Reporting Requirements for Pregnancies.....	93
5.4.3.1	Pregnancies in Female Patients	93
5.4.3.2	Abortions.....	94
5.4.3.3	Congenital Anomalies/Birth Defects	94
5.5	Follow-Up of Patients after Adverse Events.....	94
5.5.1	Investigator Follow-Up	94
5.5.2	Sponsor Follow-Up	94
5.6	Adverse Events That Occur after the Adverse Event Reporting Period.....	95
5.7	Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees.....	95
5.8	Medical Device Adverse Events	96
5.8.1	Definition of IVD Medical Device Adverse Event	96
5.8.2	<i>Definition of Serious Device Adverse Event</i>	96
5.8.3	Definition of Device Deficiency	97
5.8.4	Assessment of Causality of Medical Device Adverse Events.....	97
5.8.5	Reporting Medical Device Adverse Events.....	98
6.	STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN.....	98
6.1	Patient Populations.....	98
6.1.1	Enrolled Population.....	98
6.1.2	Efficacy Analysis Population.....	99
6.1.3	ctDNA-Negative Population	99
6.1.4	Safety Evaluable Population.....	99
6.2	Determination of Sample Size	99
6.2.1	Type I Error Control	99

6.2.2	Investigator-Assessed Disease-Free Survival	100
6.2.3	Overall Survival.....	100
6.3	Summaries of Conduct of Study	101
6.4	Summaries of Demographic and Baseline Characteristics	101
6.5	Efficacy Analyses.....	101
6.5.1	Primary Efficacy Endpoint.....	102
6.5.2	Secondary Efficacy Endpoints	102
6.5.2.1	Overall Survival.....	102
6.5.2.2	Independent Review Facility-Assessed Disease-Free Survival.....	103
6.5.2.3	Disease-Specific Survival	103
6.5.2.4	Distant Metastasis-Free Survival	103
6.5.2.5	Time to Confirmed Deterioration of Function and Quality of Life.....	103
6.5.2.6	ctDNA Clearance	104
6.5.3	Exploratory Efficacy Endpoints	105
6.5.3.1	Analyses at Selected Timepoints.....	105
6.5.3.2	Subgroup Analyses.....	105
6.5.3.3	Descriptive EORTC QLQ-C30 Summaries	105
6.5.3.4	Efficacy of ctDNA-Negative Population.....	106
6.6	Safety Analyses	106
6.7	Pharmacokinetic Analyses.....	106
6.8	Immunogenicity Analyses	107
6.9	Biomarker Analyses.....	107
6.10	Exploratory Patient-Reported Outcome Analyses.....	107
6.11	Health Status Utility Analyses	107
6.12	Interim Analyses	108
6.12.1	Disease-Free Survival	108
6.12.2	Overall Survival.....	108
7.	DATA COLLECTION AND MANAGEMENT	109
7.1	Data Quality Assurance	109
7.2	Electronic Case Report Forms.....	109
7.3	Source Data Documentation.....	110

7.4	Use of Computerized Systems	110
7.5	Retention of Records	110
8.	ETHICAL CONSIDERATIONS	111
8.1	Compliance with Laws and Regulations	111
8.2	Informed Consent	111
8.3	Institutional Review Board or Ethics Committee	112
8.4	Confidentiality	113
8.5	Financial Disclosure	114
9.	STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION	114
9.1	Study Documentation	114
9.2	Protocol Deviations	114
9.3	Management of Study Quality	114
9.4	Site Inspections	115
9.5	Administrative Structure	115
9.6	Dissemination of Data and Protection of Trade Secrets	115
9.7	Protocol Amendments	116
10.	REFERENCES	117

LIST OF TABLES

Table 1	Administration of First and Subsequent Atezolizumab/Placebo Infusions	57
Table 2	Timing for Vital Sign Measurements for First and Subsequent Infusions	62
Table 3	Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE	84
Table 4	Causal Attribution Guidance	85

LIST OF FIGURES

Figure 1	Study Schema	35
Figure 2	Surveillance Phase Imaging and Blood Collection Schedule	69
Figure 3	Type I Error Control and Analysis Hierarchy	100

LIST OF APPENDICES

Appendix 1	Schedule of Activities: Prescreening and Surveillance Phases	125
Appendix 2	Schedule of Activities: Treatment Phase	132
Appendix 3	Surveillance Screening Assessment Timeline	138
Appendix 4	Schedule of Pharmacokinetic and Immunogenicity Samples in Arms A and B	139
Appendix 5	Schedule of Biomarker Samples	140
Appendix 6	Guidelines for the Assessment of Muscle-Invasive Bladder Cancer at Screening and Disease Recurrence	142
Appendix 7	EORTC QLQ-C30	146
Appendix 8	European Organisation for Research and Treatment of Cancer Item Library 46 (EORTC IL46).....	148
Appendix 9	EQ-5D-5L.....	149
Appendix 10	Preexisting Autoimmune Diseases and Immune Deficiencies .	152
Appendix 11	Anaphylaxis Precautions.....	153
Appendix 12	Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab	154
Appendix 13	Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)	171

PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE: A PHASE III, DOUBLE-BLIND, MULTICENTER,
RANDOMIZED STUDY OF ATEZOLIZUMAB
(ANTI-PD-L1 ANTIBODY) VERSUS PLACEBO AS
ADJUVANT THERAPY IN PATIENTS WITH HIGH-RISK
MUSCLE-INVASIVE BLADDER CANCER WHO ARE
CTDNA POSITIVE FOLLOWING CYSTECTOMY

PROTOCOL NUMBER: BO42843

STUDY NAME IMvigor011

VERSION NUMBER: 10

TEST COMPOUND: Atezolizumab (RO5541267)

SPONSOR NAME: 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 the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

PROTOCOL TITLE: A PHASE III, DOUBLE-BLIND, MULTICENTER, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) VERSUS PLACEBO AS ADJUVANT THERAPY IN PATIENTS WITH HIGH-RISK MUSCLE-INVASIVE BLADDER CANCER WHO ARE CTDNA POSITIVE FOLLOWING CYSTECTOMY

REGULATORY IND Number: 120,827
AGENCY IDENTIFIER EudraCT Number: 2020-004418-36
NUMBERS: EU CT Number: 2022-502705-15-00
CIV ID: CIV-22-12-041650
PS ID: PS-22-12-041650
NCT Number: NCT04660344

STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of adjuvant treatment with atezolizumab compared with placebo in patients with muscle-invasive bladder cancer (MIBC) who are circulating tumor DNA (ctDNA) positive, as determined by the investigational Signatera™ (Natera, Inc.) assay (RD0827369), and are at high risk for recurrence following cystectomy. Because of the high risk of relapse with surgery alone, neoadjuvant and adjuvant treatments have been utilized in conjunction with radical cystectomy for MIBC. However, there is an urgent need for effective regimens for patients who decline or are ineligible for neoadjuvant chemotherapy or adjuvant chemotherapy.

OBJECTIVES AND ENDPOINTS

Primary Objective	Corresponding Endpoint
<u>Efficacy Objective:</u> To evaluate the efficacy of atezolizumab compared with placebo	- Investigator-assessed DFS, defined as the time from randomization to the first occurrence of a DFS event, defined as any of the following: - Local (pelvic) recurrence of UC (including soft tissue and regional lymph nodes) - Urinary tract recurrence of UC (including all pathological stages and grades) - Distant metastasis of UC - Death from any cause

Secondary Objectives	Corresponding Endpoints
<u>Efficacy Objective:</u> To evaluate the efficacy of atezolizumab compared with placebo	• OS, defined as the time from randomization to death from any cause • IRF-assessed DFS • Investigator-assessed disease-specific survival, defined as the time from randomization to death from UC per investigator assessment of cause of death • Investigator-assessed distant metastasis-free survival, defined as the time from randomization to the diagnosis of distant (i.e., non-locoregional) metastases or death from any cause • Time to confirmed deterioration of function and HRQoL, defined as the time from randomization to the date of a patient's first score decrease of ≥ 10 points from baseline on the EORTC QLQ-C30 physical function scale, role function scale, and the GHS/QoL scale (separately), held for at least two consecutive time points or followed by death • ctDNA clearance, defined as the proportion of patients who are ctDNA positive at baseline and ctDNA negative at Cycle 3, Day 1 or Cycle 5, Day 1
<u>Safety Objective:</u> To evaluate the safety of atezolizumab compared with placebo	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
<u>PK Objective:</u> To characterize the PK profile of atezolizumab	• Serum concentration of atezolizumab at specified timepoints
<u>Immunogenicity Objective:</u> To evaluate the immune response to atezolizumab	• Prevalence of ADAs to atezolizumab at baseline (baseline prevalence) and incidence of ADAs to atezolizumab after initiation of study treatment (post-baseline incidence)

ADA=anti-drug antibodies; ctDNA=circulating tumor DNA; DFS=disease-free survival; EORTC=European Organisation for Research and Treatment of Cancer; HRQoL=health-related quality of life; IRF=Independent Review Facility; NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; OS=overall survival; PK=pharmacokinetic; QLQ-C30=Quality of Life Questionnaire-Core 30; QoL=quality of life; UC=urothelial carcinoma.

OVERALL DESIGN AND STUDY POPULATION

This Phase III, double-blind, randomized, parallel-group, placebo-controlled study will evaluate the efficacy, safety, and pharmacokinetics of atezolizumab compared with placebo in patients with high-risk MIBC who are ctDNA positive following cystectomy.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase III	Population Type:	Adult patients
Control Method:	Placebo	Population Diagnosis or Condition:	Muscle-invasive bladder cancer
Interventional Model:	Parallel group	Population Age:	≥ 18 years
Test Compound:	Atezolizumab	Site Distribution:	Multi-site and multi-region
Active Comparator:	Not Applicable	Study Intervention Assignment Method:	Randomization and stratification
Number of Arms:	2	Number of Participants to Be Enrolled:	Up to 800

STUDY TREATMENT

Atezolizumab/placebo will be administered by IV infusion at a fixed dose of 1680 mg on Day 1 of each 28-day (± 3 days) cycle for 12 cycles or 1 year, whichever occurs first.

DURATION OF PARTICIPATION

For patients enrolled in the study who become ctDNA positive within 12 months of cystectomy, treatment will continue for 1 year or until disease recurrence, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor, whichever comes first. Subsequently, patients will receive follow-up tumor assessments for up to 5 years, with survival follow-up continuing until death, withdrawal of consent, or loss to follow-up. The anticipated maximum duration of participation for these patients is approximately 7 years, not including survival follow-up.

For patients enrolled in the study who remain ctDNA negative through 12 months after cystectomy, patients will receive follow-up tumor assessments for up to 2 years, with survival follow-up continuing for an additional 2 years. The anticipated maximum duration of participation for these patients is approximately 5 years.

COMMITTEES

Independent Committees: Independent Data Monitoring Committee

Other Committees: Not applicable

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ALK	anaplastic large-cell lymphoma kinase
ASCO	American Society of Clinical Oncology
CDF	cumulative distribution function
CDx	Companion Diagnostic
CIV ID	Clinical Investigation Identification Number
COVID-19	coronavirus disease 2019
CRO	contract research organization
CRS	cytokine release syndrome
CSR	Clinical Study Report
CT	computed tomography (scan)
ctDNA	circulating tumor DNA
DFS	disease-free survival
DMFS	distant metastasis-free survival
DSS	disease-specific survival
EAU	European Association of Urology
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
Fc	fragment crystallizable
FDA	(U.S.) Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GFR	glomerular filtration rate
GHS	global health status
HBcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio

Abbreviation	Definition
HRQoL	health-related quality of life
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IFN	Interferon
IHC	immunohistochemistry
IL	Interleukin
IL46	EORTC Item Library 46
IMP	investigational medicinal product
IRB	Institutional Review Board
IRF	Independent Review Facility
IRR	infusion-related reaction
ITT	intent-to-treat (population)
IVP	intravenous pyelogram
IxRS	interactive voice or web-based response system
LFT	liver function test
MAS	macrophage activation syndrome
MIBC	muscle-invasive bladder cancer
MIUC	muscle-invasive urothelial carcinoma
MN	mobile nursing
mPCR	multiplex Polymerase Chain Reaction
MRI	magnetic resonance imaging
NAC	neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
OS	overall survival
pCR	pathologic complete response
PFS	progression-free survival
PK	pharmacokinetic
PRO	patient-reported outcome
PSA	prostate-specific antigen
PS ID	Performance Study Identification Number
Q3W	every 3 weeks
Q4W	every 4 weeks
QoL	quality of life

Abbreviation	Definition
RBR	Research Biosample Repository
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SITC	Society for Immunotherapy of Cancer
T3	triiodothyronine
TCC	transitional cell carcinoma
TMB	tumor mutational burden
TNM	tumor, nodes, and metastases
TNF	tumor necrosis factor
TURBT	transurethral resection of bladder tumor
UC	urothelial carcinoma
ULN	upper limit of normal
UTUC	urinary tract urothelial carcinoma
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON MUSCLE-INVASIVE BLADDER CANCER

Urothelial carcinoma (UC) is the most common cancer of the urinary system worldwide. The majority of cases originate in the bladder (Leow et al. 2017). Urothelial carcinoma can be diagnosed as non-muscle invasive, muscle-invasive, or metastatic disease, with 1 in 3 new cases diagnosed as muscle-invasive disease (cT2–T4aNxM0) (Kaufman et al. 2009). Use of the term "muscle-invasive urothelial carcinoma" (MIUC) collectively refers to muscle-invasive bladder cancer (MIBC) and muscle-invasive urinary tract urothelial cancer (UTUC). However, the majority of relevant background and reported research focus on patients with MIBC.

MIBC is a global concern. In 2018, there were an estimated 549,393 new cases of bladder cancer and 199,922 deaths worldwide (Ferlay et al. 2018). In Europe, it was estimated that there were 197,110 new cases of bladder cancer and 64,970 deaths, including 164,450 new cases and 52,930 deaths in the 28 member states of the European Union (Ferlay et al. 2018). In the United States, in 2020, it is estimated that there will be 81,400 new cases of bladder cancer and 17,980 deaths (American Cancer Society 2020). Patients diagnosed with UC in the United States have a median age of 73, the highest age at diagnosis of all tumor types (SEER).

For MIBC, radical cystectomy with bilateral pelvic lymphadenectomy is the backbone of management. The surgery involves resection of the bladder, adjacent organs, and regional lymph nodes. There are also sex-based differences in the surgical approach: for men, the surgery includes removal of the prostate and seminal vesicles; and for women, the surgery includes removal of the uterus, cervix, ovaries, and anterior vagina. Urinary diversion is required after removal of the bladder. The perioperative mortality rate is approximately 2%–3% when cystectomy is performed at centers of excellence (Stein et al. 2001; Madersbacher et al. 2003).

In spite of this surgery, MIBC recurs in many patients, and they present with pain or constitutional symptoms such as fatigue, weight loss, anorexia, and failure to thrive. Approximately half of the patients with MIBC will develop a local and/or metastatic recurrence of their disease within 2 years of cystectomy and will eventually die from their disease (Raghavan et al. 1990; Stein et al. 2001; Stenzl et al. 2009). For those with high-risk features (pT3–T4a or pN+) who have not received neoadjuvant chemotherapy (NAC), the overall 5-year survival ranges from 10%–40% (Stein et al. 2001). The MIBC prognostic factors that have been associated with a higher risk for recurrence after surgery include the following: T-stage, nodal status, age at cystectomy, histology type, lymphovascular invasion, time from diagnosis to cystectomy, and male sex (Lotan et al. 2005; International Bladder Cancer Nomogram Consortium et al. 2006). Despite numerous attempted clinical trials, no adjuvant therapies have shown improved survival in MIBC (Sternberg et al. 2014).

1.1.1 Current Therapies and Unmet Medical Need in Patients with Muscle-Invasive Bladder Cancer

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

1.1.2 Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy has provided a modest survival benefit of 5% in MIBC (Advanced Bladder Cancer Meta-Analysis Collaboration 2003). The disadvantage of NAC is that it potentially delays definitive surgical management with radical cystectomy. Despite treatment with NAC, 60% of patients still have muscle-invasive disease at time of cystectomy (Rosenblatt et al. 2012). Researchers are actively investigating biomarkers, such as molecular subtypes, in an attempt to predict responders and non-responders to NAC (McConkey and Choi 2018). In addition, certain low-risk (e.g., cT2N0) patients may be over-treated with NAC because it is difficult to identify low-risk patients reliably before cystectomy (Meeks et al. 2012). An additional challenge has been under-utilization of NAC. It has been reported that less than 20% of patients who undergo radical cystectomy have received NAC prior to surgery (David et al. 2007; Miles et al. 2010; Porter et al. 2011; Raj et al. 2011); however, this number appears to be improving (Duplisea et al. 2019; Hussain et al. 2020).

A meta-analysis of data from 11 randomized trials has demonstrated that MIBC is most sensitive to cisplatin-based NAC (Advanced Bladder Cancer Meta-Analysis Collaboration 2003). European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend cisplatin-based NAC prior to cystectomy for patients with MIBC as a category 1 recommendation (EAU 2020; NCCN 2019). Patients with MIBC who achieve a pathologic complete response (pCR; pT0N0M0 stage) or who are down-staged to non-muscle-invasive disease after NAC demonstrate longer overall survival (OS) than those patients who fail to achieve pCR or are not down-staged (Grossman et al. 2003; Petrelli et al. 2014). For patients with residual muscle-invasive disease (pT2–4a) or lymph node-positive disease (pN+) at cystectomy, the median survival is only 3.7 and 2.4 years, respectively (Sonpavde et al. 2010).

1.1.3 Adjuvant Therapy

Many patients with MIBC choose to undergo definitive surgery (i.e., radical cystectomy) first and defer NAC. Patients at high risk for recurrence based on pathologic staging are recommended to consider adjuvant chemotherapy given its potential to eradicate micrometastatic disease. Both the EAU (2019) and NCCN (2019) guidelines suggest adjuvant cisplatin-based chemotherapy be considered for patients with pT3–T4 or pN+ at surgery as a category 2A recommendation if no neoadjuvant therapy was received (Nadal et al. 2018). However, unlike the benefits that have been shown with NAC, results from prospective studies of cisplatin-based adjuvant chemotherapy in patients with MIBC after a radical cystectomy are mixed. Two clinical trials have shown a survival benefit (Skinner et al. 1991; Stöckle et al. 1992); however, these trials enrolled less than 100 patients and the small datasets impact the interpretability of the results. A meta-analysis conducted in 2005 (Vale 2005) with data from 491 individual patients obtained from six adjuvant chemotherapy trials was inconclusive because of its small number and heterogeneity among the trials included. Meeks et al. 2012 performed a systematic review, which found no evidence that adjuvant chemotherapy improved survival outcomes, even in the highest-risk patients with pathologic extravesical and/or node-positive disease.

Four recent trials (by the Spanish Oncology Genitourinary Group [Paz-Ares et al. 2010], U.S. Intergroup [Stadler et al. 2011], Italian Multicenter [Cognetti et al. 2012], and the European Organisation for Research and Treatment of Cancer [EORTC] [Stenberg et al. 2015]), which were not included in the above mentioned meta-analysis, failed to meet their original accrual goals and were prematurely terminated. As one of the largest randomized trials ever reported for adjuvant chemotherapy in patients with MIBC, the EORTC trial was closed after recruitment of 284 of the planned 660 patients. In that study, 284 patients with pT3–pT4 or N+ M0 MIBC were randomized to receive either immediate versus deferred cisplatin-based combination chemotherapy after cystectomy. Immediate treatment significantly prolonged progression-free survival (PFS) compared with deferred treatment (hazard ratio [HR]: 0.54; 95% CI: 0.4 to 0.73; $p < 0.0001$). However, no significant improvement in OS was noted with immediate treatment when compared with deferred treatment (HR: 0.78; 95% CI: 0.56 to 1.08; $p = 0.13$). Thus, the benefit and utility of cisplatin-based adjuvant chemotherapy remains highly controversial.

The 2019 NCCN guidelines also recommend that adjuvant radiotherapy be considered for patients with pT3–T4 or pN+ at cystectomy who have not received neoadjuvant therapy. While there are no conclusive data demonstrating improvement in OS, there is an interest in using adjuvant radiation to improve outcomes and further prospective studies are needed to confirm benefit (Lewis et al. 2018).

The IMvigor010 trial (Study WO29636), the first trial evaluating adjuvant checkpoint inhibitor (atezolizumab) versus observation in patients with high-risk MIUC, did not meet its primary endpoint of disease-free survival (DFS). This study enrolled 809 patients with high-risk pathologic features at cystectomy and stratified for known prognostic factors in MIUC (tumor stage, nodal status, receipt of NAC, number of lymph nodes resected, and PD-L1 status) (Hussain et al. 2020).

Most recently, the CheckMate274 study, which evaluated adjuvant nivolumab versus placebo in patients with high-risk MIUC, met its primary endpoint of DFS in the intent-to-treat (ITT) population. This study enrolled 709 patients in a 1:1 ratio in which patients were stratified by PD-L1 status, pathological nodal status, and use of prior neoadjuvant cisplatin-based combination chemotherapy (Bajorin et al. 2021).

The median DFS was 20.8 months (95% CI: 16.5 to 27.6 months) in the nivolumab group and 10.8 months (95% CI: 8.3 to 13.9 months) in the placebo group in the ITT population (HR for disease recurrence or death: 0.70; 98.22% CI: 0.55 to 0.90; $p < 0.001$).

To date, no adjuvant therapies have shown improved survival in UC. Once MIUC becomes metastatic, 5-year OS is a dismal 5% (American Cancer Society 2020); therefore, adjuvant treatment of muscle-invasive disease is a potentially important opportunity to avoid metastasis and achieve cure.

1.1.4 Cisplatin-Ineligible Patients

Only approximately 50% of patients are eligible for cisplatin-based chemotherapy. For those patients with high-risk features (pT3–T4 or pN +) who have not received NAC, the overall 5-year survival ranges from 10% to 40% (Stein et al. 2001). Factors rendering patients ineligible for cisplatin therapy include an Eastern Cooperative Oncology Group (ECOG) Performance Status of 2, impaired renal function, hearing loss, and neuropathy (Dash et al. 2006). There is no evidence that non-cisplatin-based regimens (e.g., carboplatin-based chemotherapy) are as effective as cisplatin-based chemotherapy. On the basis of current clinical guidelines (EAU 2020; NCCN 2019), there is no standard neoadjuvant or adjuvant chemotherapy regimen for patients who are ineligible for cisplatin-based therapy. Patients who are cisplatin-ineligible or who refuse cisplatin-based therapy represent a population of high unmet need, particularly those patients with high-risk pathologic staging at time of cystectomy (pT3–4a or pN +) because there was no alternative treatment available to them. On 19 August 2021, the Food and Drug Administration (FDA) approved nivolumab for the adjuvant treatment of patients with UC who are at high risk of recurrence after undergoing radical resection. On 1 April 2022, the European Commission approved nivolumab as adjuvant treatment for patients with radically resected, high-risk MIUC with tumor cell PD-L1 expression $\geq 1\%$.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells.

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (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 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and in patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma, non-small cell lung cancer, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, melanoma, and alveolar soft part sarcoma.

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

1.2.1 Clinical Activity of Adjuvant Atezolizumab in MIUC Patients Who Were ctDNA Positive Following Cystectomy

The IMvigor010 trial (Study WO29636), the first trial to evaluate an adjuvant checkpoint inhibitor (atezolizumab) versus observation in patients with high-risk MIUC, did not meet its primary endpoint of DFS (Hussain et al. 2020). However, in a prospectively defined retrospective analysis, patients with MIUC who had circulating tumor DNA (ctDNA)-positive status following cystectomy showed poor prognosis consistent with previous literature (Christensen et al. 2019). Moreover, ctDNA-positive status post-cystectomy also suggested a benefit from atezolizumab monotherapy in both DFS and in interim OS. Such a benefit was not observed in previously established prognostic subgroups, such as high tumor stage, nodal status, and lack of prior platinum-based NAC treatment. The IMvigor010 ctDNA-positive subgroup analysis was the first adjuvant immunotherapy study to show that a sub-population may benefit from adjuvant checkpoint inhibitor therapy in MIUC, with a notable decrease in risk of recurrence or death (stratified HR: 0.57, 95% CI: 0.41 to 0.79), thus identifying patients most at risk for recurrence while simultaneously identifying patients (e.g., those who were ctDNA negative) who are potentially at risk for over-treatment and can be spared from receiving adjuvant treatment (Powles et al. 2020).

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).

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard of care therapies. Objective responses have been observed across a broad range of malignancies, including non-small cell lung cancer (NSCLC), UC, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results)

Given the evidence of the clinical activity of atezolizumab in advanced and metastatic UC (Rosenberg 2016, Balar et al. 2017) and suggested benefit observed in IMvigor010 patients with MIUC who are ctDNA positive, treatment with atezolizumab offers the potential for clinical benefit in patients with high-risk MIBC who are ctDNA positive following cystectomy. Because atezolizumab has been generally well tolerated to date and adverse events have been manageable with treatment and supportive care, it is anticipated that adjuvant treatment with atezolizumab will have a manageable safety profile and an acceptable benefit-risk assessment for the conduct of the study.

Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness endocrinopathies, hepatitis or transaminitis, pneumonitis colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment or interruption of atezolizumab treatment.

In the IMvigor010 trial, the safety analysis for all patients treated with atezolizumab (n=390) showed that the treatment was well tolerated with no new safety signals and that treatment-related adverse events that did arise were expected, manageable by investigators with protocol guidelines, and generally reversible (Hussain et al. 2020).

COVID-19 Benefit–Risk Assessment

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

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

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

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

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

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

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

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

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of atezolizumab compared with placebo in patients with high-risk MIBC who are ctDNA positive, as determined by the investigational Signatera™ (Natera, Inc.) assay (RD0827369), following cystectomy. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab compared with placebo on the basis of the following endpoint:

- Investigator-assessed DFS, defined as the time from randomization to the first occurrence of a DFS event, defined as any of the following:
 - Local (pelvic) recurrence of UC (including soft tissue and regional lymph nodes)
 - Urinary tract recurrence of UC (including all pathological stages and grades)
 - Distant metastasis of UC
 - Death from any cause

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of atezolizumab compared with placebo on the basis of the following endpoints:

- OS, defined as the time from randomization to death from any cause
- Independent Review Facility (IRF)-assessed DFS
- Investigator-assessed disease-specific survival (DSS), defined as the time from randomization to death from UC per investigator assessment of cause of death
- Investigator-assessed distant metastasis-free survival (DMFS), defined as the time from randomization to the diagnosis of distant (i.e., non-locoregional) metastases or death from any cause
- Time to confirmed deterioration of function and health-related quality of life (HRQoL), defined as the time from randomization to the date of a patient's first score decrease of ≥ 10 points from baseline on the EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) physical function scale, role function scale, and the global health status (GHS)/QoL scale (separately), held for at least two consecutive time points or followed by death
- ctDNA clearance, defined as the proportion of patients who are ctDNA positive at baseline and ctDNA negative at Cycle 3, Day 1 or Cycle 5, Day 1

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of atezolizumab compared with placebo on the basis of the following endpoints:

- Cumulative distribution function (CDF) curves of score change from baseline to Cycle 7 for the EORTC QLQ-C30 Physical Function, Role Function, GHS/QoL scales
- Descriptive score and score change from baseline summaries for each EORTC QLQ-C30 scale
- OS and investigator-assessed DFS in the enrolled population that remains ctDNA negative

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of atezolizumab compared with placebo on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

The exploratory safety objective for this study is to evaluate the safety of atezolizumab compared with placebo from the patient's perspective on the basis of the following endpoint:

- Overall patient-reported adverse event burden over time, as assessed by the patient global impression of cancer treatment side effects burden item from the EORTC Item Library 46 (IL46)

2.3 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is to characterize the PK profile of atezolizumab on the basis of the following endpoint:

- Serum concentration of atezolizumab at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab on the basis of the following endpoints:

- Prevalence of anti-drug antibody (ADAs) to atezolizumab at baseline (baseline prevalence) and incidence of ADAs to Atezolizumab after initiation of study treatment (postbaseline incidence)

The exploratory immunogenicity objective for this study is to evaluate patient demographics, PK, efficacy, and safety endpoints by atezolizumab ADA status.

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to atezolizumab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of atezolizumab activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between biomarkers in blood, urine, and tumor tissue (listed in Section 4.5.6) and efficacy, safety, PK, or other biomarker endpoints
- Status of tumor immune-related or disease type-related exploratory biomarkers in archival and/or freshly obtained tumor tissues and association with disease recurrence
- Status of exploratory biomarkers in plasma, blood, or urine collected before or during treatment with atezolizumab or at recurrence and association with disease recurrence

2.6 EXPLORATORY PATIENT-REPORTED OUTCOME OBJECTIVE

The exploratory patient-reported outcome (PRO) objective for this study is to characterize patient-reported symptoms, function, and QoL for patients in the Surveillance Phase.

2.7 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status objective for this study is to evaluate the health status for patients treated with atezolizumab compared with placebo on the basis of the following endpoint:

- Utilities and visual analog scale score based on the EuroQoL EQ-5D-5L.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a global Phase III, randomized, placebo-controlled, double-blind study designed to evaluate the efficacy and safety of adjuvant treatment with atezolizumab compared with placebo in patients with MIBC who are ctDNA positive, as determined by the investigational Signatera™ (Natera, Inc.) assay, and are at high risk for recurrence following cystectomy.

Patients aged ≥ 18 years with ECOG Performance Status ≤ 2 who have histologically confirmed MIUC (also termed transitional cell carcinoma [TCC]) of the bladder are eligible.

All patients must have undergone radical cystectomy with lymph node dissection.

Patients who have received prior platinum-based NAC are eligible but must have tumor staging of ypT2–4aN0 or ypT0–4aN+ and M0 at pathological examination of the cystectomy specimen.

Patients who have not received prior platinum-based NAC must have tumor staging of pT2–4aN0 or pT0–4aN+ and M0 at pathological examination of the cystectomy specimen. These patients are eligible for the study regardless of whether they are candidates for cisplatin-based adjuvant chemotherapy. The reason why cisplatin-based adjuvant chemotherapy is not being offered should be recorded on the electronic Case Report Form (eCRF). These include:

- Ineligible ("unfit") for cisplatin, as defined by any one of the following criteria:
 - Impaired renal function (glomerular filtration rate [GFR] <60 mL/min); GFR should be assessed by direct measurement (i.e., creatinine clearance or ethyldiaminetetra-acetate) or, if not available, by calculation from serum/plasma creatinine (Cockcroft-Gault formula)
 - A hearing loss (measured by audiometry) of 25 dB at two contiguous frequencies
 - Grade 2 or greater peripheral neuropathy (i.e., sensory alteration or paresthesia including tingling)
 - ECOG Performance Status of 2
- Patient refusal
- Investigator decision

Tumor specimens from surgical resection (i.e., radical cystectomy or lymph node dissection) from patients who have provided informed consent will be collected for Whole Exome Sequencing (WES) and PD-L1 testing. Tumor tissue specimen is strongly encouraged to be submitted as soon as possible, and optimally within 18 weeks of cystectomy in order to obtain results within the time window required for eligibility into surveillance. Tumor tissue specimen will be evaluated for PD-L1 expression by immunohistochemistry (IHC) by a central pathology laboratory prior to enrollment of the patient in the study. Tumor specimens will also undergo WES. Matched blood samples will be collected for control and only somatic variants will be analyzed as part of the WES assay. The first blood collection for plasma ctDNA testing can be collected at the same time as the matched blood sample and submission of tumor tissue specimen, provided that the matched blood sample and tissue is submitted at least 6 weeks post cystectomy. If feasible, tumor tissue specimen and matched blood sample can be submitted as soon as the patient consents to the screening phase, as the 6-week post-cystectomy requirement is only applicable for the collection of plasma ctDNA blood sample. Patients' tumor specimens will be sequenced against matched blood to create a panel of multiplex PCR (mPCR) assays for the top 16 clonal mutations unique to each patient's tumor tissue. Only patients whose tumors have sufficient amounts of viable tumor, evaluable for WES (ctDNA assay designability) and for PD-L1 expression, will be eligible. The WES–evaluable (ctDNA assay designability) result is based on (a) sequencing of the whole exome of the tumor and matched blood and (b) successful primer design (mPCR assay) for each patient. All patients with a WES evaluable (ctDNA assay designability) report, who have consented to participate in the Surveillance Phase

and have no residual disease, will be considered eligible for enrollment in the Surveillance Phase of the study provided that all the eligibility assessments have been completed within 24 weeks of cystectomy. The date the patient has moved to surveillance in the interactive voice or web-based response system (IxRS [IxRS transaction date]) will be used as date of enrollment into the Surveillance Phase, after meeting all inclusion/exclusion criteria for the Surveillance Phase. The date of the first blood collection for plasma ctDNA testing will be used as an anchor point to calculate the date of blood collection of subsequent visits in the Surveillance Phase.

Patients may be enrolled in the Surveillance Phase a minimum of 6 weeks but not more than 24 weeks from the date of cystectomy.

Patients can undergo their first blood collection for plasma ctDNA testing at the same time as the matched blood sample, provided that they have consented to participate in the Surveillance Phase. Blood collection will then occur every 6 weeks (± 5 days) from the date of the first blood collection for plasma ctDNA testing until Week 36 or until 36 weeks from the date of cystectomy have passed, whichever occurs first. After the latest blood collection prior to 36 weeks from date of cystectomy has been reached, blood collection should follow the surveillance imaging schedule going forward. Surveillance imaging for the Surveillance Phase will be performed every 12 weeks from the date of the first blood collection for plasma ctDNA testing until Week 48 or until 12 months from the date of cystectomy have passed, whichever occurs first. Based on this testing frequency, a patient's last scheduled ctDNA test will occur anywhere between 42 and 52 weeks from cystectomy. Patients whose last scheduled ctDNA test occurs more than 4 weeks prior to surveillance completion may have an optional unscheduled ctDNA test performed before the 12 months are complete. *Patients who were previously discontinued from the Surveillance Phase as a result of experiencing investigator-assessed disease recurrence may be contacted to request consent for survival follow-up.*

Patients' blood samples collected for the Surveillance Phase will be evaluated for the presence of up to 16 mutations identified from the primary tumor and matched blood. Plasma samples evaluated to have 2 or more mutations out of the 16 mutations identified will be considered ctDNA positive. Patients will enter the Treatment Phase of the study and be randomized to treatment at the first plasma sample that is ctDNA positive provided that they have fully recovered from cystectomy, provided that there is no evidence of disease recurrence on imaging within 28 days of randomization as per investigator and IRF assessment, and provided that they have consented to participate in the Treatment Phase. Only patients who are ctDNA positive will enter the Treatment Phase. Patients who are ctDNA negative will continue to undergo surveillance until they are either ctDNA positive, ctDNA negative at 12 months from the date of their cystectomy, or have investigator-assessed radiographic recurrence.

Patients entering the Treatment Phase will be randomized to one of the following arms in a 2:1 ratio:

- Arm A (experimental arm): atezolizumab 1680 mg IV infusion every 4 weeks (Q4W) on Day 1 of each 28-day cycle
- Arm B (control arm): placebo IV infusion Q4W on Day 1 of each 28-day cycle

Randomization should occur within 14 days of a patients' plasma sample being confirmed as ctDNA positive. Study drug administration must begin within 4 calendar days of randomization.

Randomization will be stratified by the following factors:

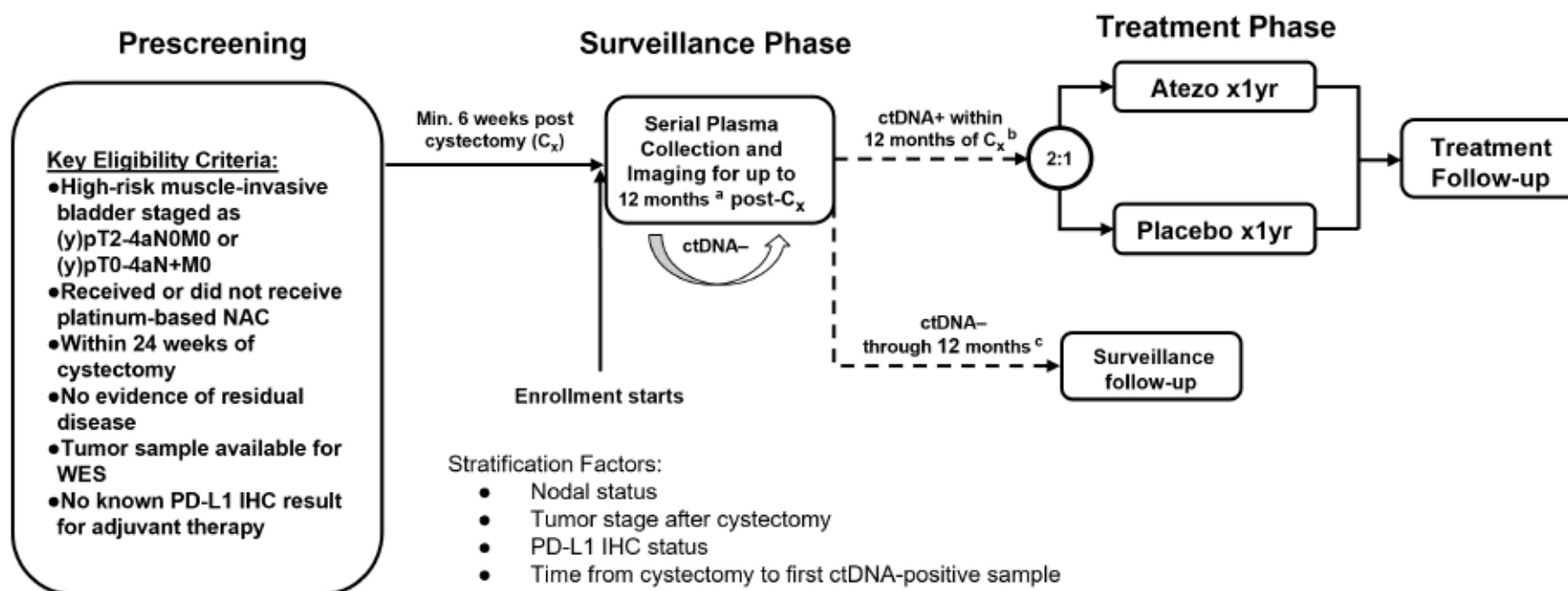
- Nodal status (positive vs. negative)
- Tumor stage after cystectomy ($\leq$ (y)pT2 vs. (y)pT3/pT4)
- PD-L1 IHC status (IHC score of IC0/1 vs. IC2/3)
 - PD-L1 expression (IC2/3, corresponding to the presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering $\geq$ 5% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peritumoral stroma) will be assessed by a central laboratory using the VENTANA PD-L1 (SP142) Assay.
- Time from cystectomy to first ctDNA-positive sample ($\leq$ 20 weeks vs. >20 weeks)

3.1.1 Overview of Study Design

Patients who do not meet the criteria for participation in this study (screen failure) cannot be re-screened. The investigator will record reasons for screen failure in IxRS (see Section 4.5.1).

Figure 1 presents an overview of the study design. The schedule of activities for prescreening and Surveillance Phase and Treatment Phase are provided in Appendix 1 and Appendix 2, respectively.

Figure 1 Study Schema



atezo = atezolizumab; ctDNA = circulating tumor DNA; ctDNA+ = ctDNA positive; ctDNA- = ctDNA negative; Cx = cystectomy; IHC = immunohistochemistry; Min. = minimum; NAC = neoadjuvant chemotherapy; SOC = standard of care; WES = whole exome sequencing; yr = year.

^a 1 month = 1 calendar month; thus 12 months would be equal to 1 calendar year.

^b Patients will enter the Treatment Phase of the study and be randomized to treatment at the first plasma sample that is ctDNA positive provided that they have fully recovered from cystectomy and that there is no evidence of disease recurrence on imaging as confirmed by investigator and IRF within 28 days of randomization.

^c Patients who remain ctDNA negative at 12 months from the date of cystectomy will not be randomized to treatment and will enter follow-up.

After screening and 6 weeks (minimum) post-cystectomy, all enrolled patients will enter the Surveillance Phase for imaging and ctDNA testing. Disease-free patients who are ctDNA-positive will be randomized to receive 12 cycles or up to 1 year (whichever occurs first) of treatment with either atezolizumab (fixed dose of 1680 mg) or matching placebo. Treatment will be administered by IV infusion on Day 1 of each 28-day cycle.

Atezolizumab/placebo will be discontinued in the event of disease recurrence, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor.

All patients entered in the Treatment Phase will undergo scheduled assessments for tumor recurrence at baseline and every 9 weeks (± 7 days) in the first year following randomization. Upon completion of the treatment/placebo phase, patients will enter treatment follow-up. Disease status assessments for tumor recurrence will be performed every 9 weeks (± 7 days) for Year 2; every 12 weeks (± 10 days) for Year 3; every 24 weeks (± 10 days) for Years 4–5; and at Year 6 (approximately 48 weeks after the last assessment in Year 5).

In the absence of an investigator-assessed DFS event (defined as any of the following: local [pelvic] recurrence of UC; urinary tract recurrence of UC; distant metastasis of UC; or death from any cause), monitoring of tumor recurrence during treatment follow-up should continue regardless of whether patients start new anti-cancer therapy, until withdrawal of consent, loss to follow-up, or study termination by the Sponsor, whichever occurs first. Monitoring for tumor recurrence will include physical examination, laboratory evaluation, and imaging studies of the chest, abdomen, upper urinary tracts, and pelvis. Disease recurrence in the Treatment Phase will be as determined by investigators based on radiographic evidence and independently assessed by IRF. A confirmatory tumor biopsy is *requested* if clinically feasible at the time of disease recurrence. Cases for which biopsy results definitively rule out recurrence of UC will not be considered as disease recurrence for this study.

Safety assessments will include the incidence, nature, and severity of adverse events, with severity graded per NCI CTCAE v5.0, changes in vital signs, and laboratory abnormalities. Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of ADAs to atezolizumab. A sample of archived tumor tissues, as well as urine, blood, serum and plasma samples, will be collected for future exploratory biomarker assessments.

Patients enrolled in the Surveillance Phase who remain ctDNA negative at 12 months from the date of cystectomy will not be randomized to treatment and will enter a 4-year surveillance follow-up period. During this time, disease status assessments for tumor recurrence will be performed every 6 months (± 10 days) for the first 2 years, or until death, investigator-assessed unequivocal radiographic evidence of disease recurrence, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. Thereafter, survival information will be collected by telephone or office visit

every 6 months (± 2 months) for an additional 2 years to complete the 4-year surveillance follow-up period, or until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. After the 4-year follow-up period, patients will be encouraged to continue disease recurrence monitoring outside the study as per their local standard of care. *Patients who were previously discontinued from the Surveillance Phase as a result of experiencing investigator-assessed disease recurrence may be contacted to request consent for survival follow-up.*

The Efficacy Analysis population is defined as patients with a ctDNA-positive sample obtained following cystectomy who are randomized to the Treatment Phase. It is projected that up to 800 patients with MIBC will be enrolled in the Surveillance Phase in order to identify approximately 178 events in approximately 240 ctDNA-positive patients at the time of DFS primary analysis (see Sections 4.2.1 and 6.2 for additional details).

The sample size of up to 800 patients for the surveillance population is based on the assumption that approximately 30%–46% of patients will either be ctDNA-positive at the time of enrollment or will become ctDNA positive following cystectomy.

Randomization to the Treatment Phase will end after the projected number of DFS events is expected to be reached. After this timepoint, patients who are still enrolled in the Surveillance Phase will not be randomized but may continue with ctDNA testing for the remainder of the 12-month surveillance period and may receive treatment outside the study per the investigator's discretion.

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

A schedule of activities for the Surveillance Phase is provided in [Appendix 1](#). A schedule of assessments for the Treatment Phase is provided in [Appendix 2](#).

3.1.2 Independent Data Monitoring Committee

An iDMC will evaluate safety data during the study. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC roles and responsibilities.

Unblinded safety data will be reviewed on a periodic basis as described in the iDMC Charter. All summaries and analyses for the iDMC review will be prepared by an independent Data Coordinating Center (iDCC).

After reviewing the data, the iDMC will provide a recommendation to the Sponsor as described in the iDMC Charter. Final decisions will rest with the Sponsor.

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

As of the date of the primary analysis, the iDMC support for safety review activities has been terminated after study unblinding. Safety will continue to be reviewed at regular intervals by the Sponsor's study team.

3.1.3 Patient Input into Study Design

Representatives from different organizations within the patient community were interviewed and asked to provide feedback on recruitment mitigation strategies. This feedback was taken into consideration when developing the protocol. Patient advocates also contributed to creating multimedia content as part of the informed consent process to enhance patient understanding of the complexities of the study.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date at which the last data point required for statistical analysis (i.e., survival) or safety follow-up is received from the last patient. The end of the study is expected to occur approximately *18 months* after the last patient is randomized.

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

Study recruitment *was completed in 48 months*. Last patient last visit *is* expected to occur approximately *18 months* after last patient *was* randomized. Therefore, the total length of the study is approximately *6 years*.

3.3 DURATION OF PARTICIPATION

For patients enrolled in the study who become ctDNA positive within 12 months of cystectomy, treatment will continue for 1 year or until disease recurrence, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor, whichever comes first (see [Appendix 6](#)). Subsequently, patients will receive follow-up tumor assessments for up to 5 years, with survival follow-up continuing until death, withdrawal of consent, or loss to follow-up. The anticipated maximum duration of participation for these patients is approximately 7 years, not including survival follow-up.

For patients enrolled in the study who remain ctDNA negative through 12 months after cystectomy, patients will receive follow-up tumor assessments for up to 2 years, with survival follow-up continuing for an additional 2 years. The anticipated maximum duration of participation for these patients is approximately 5 years.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 1680 mg Q4W (1680 mg on Day 1 of each 28-day cycle), which is an approved dosage for atezolizumab, as outlined in the prescribing information. The average concentration following the 1680 mg Q4W dosage is expected to be equivalent to that of 1200 mg every 3 weeks (Q3W). Anti-tumor activity has been observed across doses ranging from 1 mg/kg–20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached, and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight-based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical PK, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

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

3.4.2 Rationale for Patient Population

The majority of urothelial tumors arise in the bladder, with TCC (also called UC) being the most common histologic subtype. Transitional cell carcinoma accounts for 90% of all MIBC cases in the industrialized world (Chalasani et al. 2009). For patients undergoing radical cystectomy alone, recurrence-free survival and OS in male and female patients is reported as 66%–68% and 58%–66% at 5 years and 60%–73% and 43%–49% at 10 years, respectively (Stein et al. 2001; Hautmann et al. 2012; Madersbacher et al. 2003). In node-positive patients, 10-year DSS and OS rates decrease to 27.7% and 20.9%, respectively (Gschwend et al. 2002).

European Society for Medical Oncology (ESMO), EAU, and NCCN clinical practice guidelines recommend cisplatin-based NAC prior to cystectomy for MIBC patients based on a meta-analysis that showed a 5% net benefit in 5-year OS (Advanced Bladder Cancer Meta-analysis Collaboration 2003). Patients with pT0 or <pT2N0 disease at cystectomy following NAC were associated with better median survival (13.6 and 12.5 years, respectively). However, median survival (3.7 and 2.4 years, respectively) was very poor for patients with residual muscle-invasive disease (ypT2–4a) or lymph node-positive disease (ypN+) following NAC (Sonpavde et al. 2010). Study BO42483 includes MIBC patients with pathological staging of ypT2–4aN0M0 or ypT0–4aN+M0 at cystectomy following platinum-based NAC in this trial because this segment of the MIBC patient population has a high unmet medical need.

It has been reported that less than 20% of patients who undergo radical cystectomy have received NAC prior to surgery (David et al. 2007; Miles et al. 2010; Porter et al. 2011; Raj et al. 2011); however, this number appears to be improving

(Duplissea et al. 2019; Hussain et al. 2020). Both the EAU (2019) and NCCN (2019) guidelines suggest adjuvant cisplatin-based chemotherapy be considered for patients with pT3–T4 or pN+ at surgery as a category 2A recommendation if no NAC was received (Nadal et al. 2018). However, unlike the benefits that have been shown with neoadjuvant chemotherapy, results from prospective studies of cisplatin-based adjuvant chemotherapy in patients with MIBC after a radical cystectomy are mixed. Moreover, only approximately 50% of patients are eligible for cisplatin-based adjuvant chemotherapy, and factors rendering patients ineligible for cisplatin therapy include ECOG performance status of 2, impaired renal function, hearing loss, and neuropathy (Dash et al. 2006). With radical cystectomy alone, patients with extravesical (pT3–T4a) or lymph node-positive (pN+) disease are at high risk for relapse (40%–67%) and associated with poor 5-year OS (25%–30%) (Gschwend et al. 2002; Shariat et al. 2006). Thus, this population of MIBC patients (with pT3–4a or pN+ disease who did not receive prior platinum-based NAC and have declined or are ineligible for cisplatin-based adjuvant chemotherapy) represents another area of high unmet medical need and are included in this trial.

Finally, for patients with pT2N0 staging at radical cystectomy who were not treated with preoperative chemotherapy, the 5-year DSS rate is reported as 73.5% (Hautmann et al. 2012). Since nearly one-fifth of pT2N0 patients have regional lymph node metastasis within 5 years of resection, this makes them an ideal subgroup for treatment selection guided by ctDNA relapse (Tilki et al. 2010).

3.4.2.1 Circulating Tumor DNA as a Biomarker for Patient Selection in Muscle-Invasive Urothelial Carcinoma

The use of ctDNA as a biomarker for early detection of metastatic relapse is an emerging field in multiple solid tumor types, including colorectal carcinoma, lung cancer, and early breast cancer (Mok et al. 2015; Tie et al. 2016; Garcia-Murillas et al. 2019). ctDNA differs from host cell-free DNA through characteristic somatic genomic alterations (Ptashkin et al. 2019). Circulating tumor DNA shed from cancer cells into the peripheral blood can be collected non-invasively and tested for the presence of tumor-specific mutations. Changes in ctDNA levels over time can potentially be used to detect disease recurrence (Moding et al. 2018).

Several characteristics of UC make it a strong candidate for prognostication of disease recurrence utilizing ctDNA testing. Urothelial carcinoma carries a high somatic mutation rate, meaning that very small numbers of genes or targeted regions can be highly informative to predict disease characteristics (Todenhöfer et al. 2018). Furthermore, metastatic recurrence in UC has been observed to have a clonal origin, not differing significantly in mutational analysis from the original tumor (Thomsen et al. 2017). In several analyses of paired tumors in UC, few subclones were identified, bolstering the prognostic potential of longitudinal ctDNA testing after definitive therapy (Nordentoft et al. 2014; Lamy et al. 2016). In 2019, Christensen and colleagues used the ctDNA assay to show that in 68 patients with MIBC receiving

NAC and cystectomy, the presence of ctDNA at longitudinal timepoints was associated with disease progression and metastatic disease (Christensen et al. 2019). In particular, patients that were ctDNA positive at any timepoint post-cystectomy had an overall recurrence rate of 76% versus 0% for patients that maintained ctDNA negativity post-cystectomy (median follow-up 21 months). These data present a biomarker-selected subpopulation of patients with MIBC who have a high unmet need for urgent treatment options.

The IMvigor010 (Study WO29636) ctDNA subgroup analysis corroborated the findings of Christensen et al. (2019) that ctDNA status after cystectomy is a prognostic biomarker for disease recurrence in UC. In this analysis, the Sponsor evaluated patients in the IMvigor010 observation arm who did not receive any adjuvant treatment. Patients who were ctDNA positive after cystectomy were markedly more likely to have a DFS event (stratified HR: 6.27; 95% CI: 4.39 to 9.09) as well as an OS event (stratified HR: 8.08; 95% CI: 4.83 to 13.51).

3.4.2.2 Circulating Tumor DNA Can Potentially Predict Response to Immunotherapy

Checkpoint inhibitors, particularly PD-1 and PD-L1, have shown clinical efficacy across multiple tumor types, particularly in those with a high number of somatic mutations, such as melanoma and UC. Somatic alterations detectable in ctDNA, such as those present in mismatch repair deficiency or tumor mutational burden (TMB), may facilitate selection of patients likely to benefit from immunotherapy (Snyder et al. 2019). In a retrospective analysis of the POPLAR study (Study GO28753) of atezolizumab versus chemotherapy in second-line NSCLC, for example, increased blood TMB was associated with improved PFS and OS with atezolizumab relative to chemotherapy (Gandara et al. 2018).

The subgroup analysis of ctDNA-positive patients in the IMvigor010 (Study WO29636) suggested a treatment benefit of atezolizumab compared with observation in DFS (stratified HR: 0.57; 95% CI: 0.41 to 0.79; median: 5.9 vs. 4.4 months). The OS interim analysis also suggested treatment benefit of atezolizumab (stratified HR: 0.58; 95% CI: 0.39 to 0.85). Median follow-up for patients in the ctDNA-positive subgroup was 16.9 months (range: 0.6–48.6 months) (Powles et al. 2020).

For patients who were positive for ctDNA and who were treated with atezolizumab, non-relapse was associated with immune response signatures and basal-squamous gene features. These data suggest that adjuvant atezolizumab may be associated with improved outcomes compared with observation in patients who are positive for ctDNA and who are at a high risk of relapse (Powles et al. 2021).

Evaluating ctDNA testing prospectively in a clinical trial investigating immunotherapy could potentially offer a much-needed treatment option for patients with MIBC at high risk for relapse and death.

3.4.3 Rationale for Control Group

There is no clear consensus on standard of care after cystectomy for patients with MIBC.

In the Checkmate 274 trial, patients with MIBC (n=709) were assigned to receive adjuvant nivolumab or placebo for 1 year. The study met its primary endpoint of DFS in the ITT population (HR: 0.70; 95% CI: 0.54 to 0.89; median follow-up of 20.9 months). DFS was also improved in the subset of patients who were PD-L1 positive (HR: 0.53; 95% CI: 0.34 to 0.84). OS (a secondary endpoint) has not yet been presented. Nivolumab has been approved as an adjuvant treatment for patients with UC for the ITT population (Opdivo® U.S. Package Insert) and in patients with UC with PD-L1 $\geq 1\%$ (Opdivo® EMA Summary of Product Characteristics).

In the IMvigor010 trial, patients with MIBC (n=809) were assigned to receive adjuvant atezolizumab or observation for 1 year. Atezolizumab did not improve DFS (HR: 0.89; 95% CI: 0.74 to 1.08) or OS (HR: 0.85; 95% CI: 0.66 to 1.09). There was no enrichment for outcome in patients who were PD-L1 positive (Bellmunt et al. 2021).

Due to conflicting results across trials involving immunotherapy, clinical guidelines offer differing recommendations. NCCN and EAU guidelines have weak recommendations for nivolumab in the adjuvant setting (EAU 2022; NCCN 2022), whereas ESMO suggests an OS advantage is needed before it can be recommended as standard therapy (Powles et al. 2022).

Furthermore, while cisplatin-based adjuvant regimens are used, NCCN, EAU, and American Society of Clinical Oncology (ASCO) guidelines have varying levels of recommendation for use. In light of the concurrent approval of nivolumab as an adjuvant treatment, the decision regarding which patients to consider recruiting into the trial will be left to the investigator's discretion.

The Sponsor has chosen a double-blinded study design with placebo as control rather than an open-label study design with observation as the control primarily given the advantages of double-blinded control studies in reducing potential bias in the assessment of disease recurrence or progression, PROs, and safety. Additional advantages include reduced chances of dropout (attrition) and improved study retention for follow-up in the control arm, as well as the potential to minimize the risk of off-label use of currently approved therapies in the metastatic setting. The choice of a placebo arm will allow maintenance of effective scientific integrity and rigor.

3.4.4 Rationale for Disease-Free Survival as Primary Endpoint

Improvement in DFS represents clinically meaningful benefit to patients with MIBC. Up to 65% of patients with MIBC who relapsed after cystectomy had symptoms associated with disease recurrence (Volkmer et al. 2009). An improvement in DFS would delay symptoms associated with recurrence and the initiation of toxic therapy and

therefore reflects direct benefit to patients. Relative to OS as an endpoint, DFS is not confounded by subsequent therapies and allows for an earlier primary analysis in which to offer potentially beneficial treatment to this population with high unmet need.

Disease recurrence can be objectively determined by the investigators given the well-defined recurrence criteria in the FDA-NCI public workshop on eligibility and radiologic assessment in adjuvant clinical trials in bladder cancer (Apolo et al. 2019). The IMvigor011 study is double blinded, therefore, mitigating potential bias in disease assessment by the investigator.

3.4.5 Rationale for Collection of Mandatory Resected Tumor, Blood, and Urine Specimens for ctDNA and Biomarker Analyses

Collection of blood and tumor tissue specimens is required for this study to prospectively test for the presence of ctDNA after surgery, to screen for eligibility into the surveillance and Treatment Phases, and for continued ctDNA clearance analysis or for continued ctDNA surveillance during the study. If a site has not been granted approval for sample collection for WES, it will not be possible for the site to participate in the study given the requirement for analysis of ctDNA status. Both blood and tumor tissue samples are required to enable ctDNA screening at a central laboratory using a next-generation sequencing (NGS) assay. Tumor mutation calls are identified from sequencing of blood and resected tumor tissue to identify low-frequency variant calls from the plasma in order to confirm ctDNA status at later analysis timepoints.

In this study, surgical resection specimens from patients will also be prospectively tested for PD-L1 expression by a central laboratory during the screening period and PD-L1 status (IHC score of IC0/1 vs. IC2/3) will be used as one of the stratification factors. Published results suggest that the expression of PD-L1 in tumors correlates with response to anti-PD-1 and anti-PD-L1 therapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). In addition to the assessment of PD-L1 status, other exploratory markers, such as potential predictive and prognostic markers related to the clinical benefit of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may also be analyzed.

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

Additional exploratory analyses may be performed on WES data to understand the mechanism of response or resistance to atezolizumab. The WES analysis performed during the screening process will be used to identify variants that may be predictive of

response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants.

Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole genome sequencing (WGS) and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

Changes in different blood and urine biomarkers may provide evidence for biologic activity of atezolizumab in humans and may allow for the development of a blood and urine-based biomarkers to help predict which patients may benefit from atezolizumab. Blood and urine samples will be collected at baseline and during the study to evaluate changes in surrogate biomarkers. In addition, potential correlations of these pharmacodynamic markers with the dose, safety, and anti-tumor activity of atezolizumab will be explored.

Refer to Section 4.5.6 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

3.4.6 Rationale for the Collection of Recurrence Biopsies

Randomized ctDNA positive patients in both treatment arms *are requested to* undergo biopsy sample collection to confirm disease recurrence, unless not clinically feasible. Leftover biopsy samples from confirmed disease recurrence will be used for evaluation of potential biomarkers for disease progression using characterized assays for analysis of proteins, RNA, and DNA. These evaluations of the tumor sample will help in

understanding the potential mechanisms of resistance and recurrence in patients treated with atezolizumab compared with treatment with placebo. This exploratory biomarker evaluation will not be used for any treatment-related decisions.

3.4.7 Rationale for Clinical Outcome Assessments

Patient experience data will be collected in this study to inform the benefit-risk profile of atezolizumab. It is important that DFS and other efficacy benefits can be achieved without impairing patients' functioning and QoL. There is also limited information about treatment impacts on patients' lives in this adjuvant MIBC setting. As such, the patient's perspective on treatment burden and impact is needed to achieve a comprehensive evaluation of clinical benefit and to inform treatment decision-making.

PRO data will also be collected during the Surveillance Phase to characterize changes in symptom, function, and QoL outcomes following cystectomy between 6 weeks post-enrollment and end of the Surveillance Phase. These data may help to elucidate whether PROs differ between ctDNA-positive and ctDNA-negative patients, and the extent to which ctDNA-positive patients' symptoms, function, and QoL have changed between the surveillance and the treatment/placebo phases.

Three PRO instruments will be administered in this study: EORTC QLQ-C30, a standalone item from the EORTC IL46, and EQ-5D-5L. The EORTC QLQ-C30 (Aaronson et al. 1993; Fitzsimmons et al. 1999) is a widely used, validated, cancer-specific instrument that assesses symptoms associated with cancer and/or its treatment (e.g., fatigue), functioning (physical, role, emotional, cognitive, and social), and GHS/QoL. The EORTC IL46 includes a single summary measure of overall adverse event burden from the patient's perspective. The EQ-5D-5L (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) is a generic health status questionnaire that will primarily be used to evaluate changes in quality of life over the course of the disease and inform the health economic model.

As of BO42843 Protocol Version 10, PRO assessments will no longer be performed.

3.4.8 Rationale for Collection of Information on Race and Ethnicity

Data pertaining to participant race and ethnicity represents a component of the broad demographic profile of the study population. Collection of demographic data, including information on race and ethnicity, is of importance to the future interpretation of results from the clinical trial, including identification of potential differences in efficacy, safety, and pharmacokinetics among participants. Collection of race and ethnicity data may enable investigation of potential relationships between biomarkers and race or ethnicity, including determination of whether race or ethnicity could be a prognostic factor. Collection of these data may also contribute to a better understanding of the distribution of MIBC according to race or ethnicity.

4. MATERIALS AND METHODS

4.1 PATIENTS

It is projected that approximately up to 800 patients with MIBC will be enrolled in this study.

4.1.1 Inclusion Criteria

4.1.1.1 Inclusion Criteria for the Surveillance Phase

Patients must meet the following criteria for enrollment into the Surveillance Phase of the study:

- Signed Informed Consent Form
- Age $\geq$ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- Histologically confirmed MIUC (also termed TCC) of the bladder

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

- Tumor, nodes, and metastases (TNM) classification (based on the American Joint Committee on Cancer [AJCC] Cancer Staging Manual 8th ed; Amin et al. 2016) at pathological examination of surgical resection specimen as follows:
 - Patients who received, or did not receive, platinum-based NAC with tumor stage of (y)pT2–4aN0M0 or (y)pT0–4aN+ M0

Patients who have received at least three cycles of a platinum-containing regimen will be considered as having received prior NAC.

Patients who have not received platinum-based NAC must be ineligible ("unfit") for cisplatin-based adjuvant chemotherapy, have refused it, or will not receive it based on the treating physician's decision.

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

- Impaired renal function (glomerular filtration rate [GFR] $<$ 60 mL/min); GFR should be assessed by direct measurement (i.e., creatinine clearance or ethyldiaminetetra-acetate) or, if not available, by calculation from serum/plasma creatinine (Cockcroft-Gault formula)
 - A hearing loss (measured by audiometry) of 25 dB at two contiguous frequencies
 - Grade 2 or greater peripheral neuropathy (i.e., sensory alteration or paresthesia including tingling)
 - ECOG Performance Status of 2
- Surgical resection of MIUC of the bladder

Radical cystectomy may be performed by the open, laparoscopic, or robotic approach. Cystectomy must include bilateral lymph node dissection, the extent of which will be at the discretion of the treating surgeon but optimally

should extend at a minimum from the mid common iliac artery proximally to Cooper's ligament distally, laterally to the genitofemoral nerve, and inferiorly to the obturator nerve. The method of urinary diversion for patients undergoing cystectomy will be at the discretion of the surgeon and choice of the patient.

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

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

- Full recovery from cystectomy and enrollment within 24 weeks following cystectomy
A minimum of 6 weeks must have elapsed from surgery.
- Availability of a surgical tumor specimen that is suitable (e.g., adequate quality and quantity) for use in determining PDL1 expression, WES evaluable (ctDNA assay designability) report, and for exploratory biomarker research assessed by central laboratory testing

A representative formalin-fixed, paraffin-embedded (FFPE) tumor block must be submitted along with an associated pathology report; two FFPE tumor blocks are recommended, if available.

If an intact FFPE tumor block cannot be provided, then submittal of at least 20 slides containing unstained, freshly cut serial sections derived from an FFPE tumor block prepared and shipped as outlined in the laboratory manual is allowed. A copy of the de-identified biospecimen associated pathology report must be submitted together with the specimen. Patients with fewer than 16 slides may still be eligible for the study after consulting the Medical Monitor. Refer to Section 4.5.6 for additional information on tumor specimens collected at screening.

Tumor tissue should be of good quality based on total and viable tumor content and must contain a muscle invasive component (i.e., T2 or greater) of the tumor as verified by local pathology review. Fine needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. Tumor tissue from surgical resection is preferred (see Section 4.5.6 for details).

If resected tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy (e.g., transurethral resection of bladder tumor [TURBT]) can be submitted for the determination of ctDNA status and PD-L1 expression, but will need to meet the requirement for tissue as stated above for resected tumor.

In addition, diagnostic core-needle biopsy tumor tissue samples may be submitted for determination of PD-L1 expression, only. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.

- Submission of a post-surgery matched blood sample for the identification of somatic mutations in tumor tissue.
- Submission of blood sample for plasma ctDNA testing, collected at least 6 weeks post-surgery.
- Availability of a WES-evaluable (ctDNA assay designability) report that is based on tumor tissue specimen and matched blood.
- Tumor PD-L1 expression per IHC that is evaluable by central testing of a representative tumor tissue specimen.
- Absence of residual disease and absence of metastasis, as confirmed by a negative baseline computed tomography (CT) or magnetic resonance imaging (MRI) scan of the pelvis, abdomen, and chest no more than 28 days prior to enrollment.

Imaging of the upper urinary tracts is required and may include one or more of the following: intravenous pyelogram (IVP), CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy or MRI urogram. However, separate imaging of the upper urinary tracts via one of these modalities is not required if the upper tracts are covered in the imaging of the abdomen and pelvis. Imaging must be completed no more than 28 days prior to enrollment into surveillance.

Other examinations should be performed as clinically indicated.

4.1.1.2 Additional Inclusion Criteria for the Treatment Phase

Patients enrolled in the Surveillance Phase must meet the following criteria for randomization into the Treatment Phase of the study:

- Blood for plasma ctDNA sample evaluated to be ctDNA positive, defined as the presence of two or more mutations out of the 16 mutations identified based on patient's WES evaluable (ctDNA assay designability) report
- Absence of residual disease and absence of metastasis, as confirmed by a negative baseline CT or MRI scan of the pelvis, abdomen, and chest no more than 28 days prior to randomization, as assessed by the investigator

Confirmation of disease-free status will be assessed by an independent central radiologic review of imaging data.

Imaging of the upper urinary tracts is required and may include one or more of the following: IVP, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy or MRI urogram. However, separate imaging of the upper urinary tracts via one of these modalities is not required if the upper tracts are covered in the imaging of the abdomen and pelvis. Imaging must be completed no more than 28 days prior to randomization.

Other examinations should be performed as clinically indicated.

- ECOG Performance Status of ≤ 2
- Life expectancy ≥ 12 weeks

- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
 - ANC $\geq 1.5 \times 10^9/L$ ($1500/\mu L$) without granulocyte colony-stimulating factor support
 - WBC counts $> 2500/\mu L$
 - Lymphocyte count $\geq 0.3 \times 10^9/L$ ($300/\mu L$)
 - Platelet count $\geq 100 \times 10^9/L$ ($100,000/\mu L$) without transfusion
 - Hemoglobin ≥ 90 g/L (9 g/dL)

Patients may be transfused or receive erythropoietic treatment to meet this criterion.
 - AST, ALT, and ALP $\leq 2.5 \times$ upper limit of normal (ULN)
 - Total bilirubin $\leq 1.5 \times$ ULN with the following exception:

Patients with known Gilbert disease: total bilirubin $\leq 3 \times$ ULN
 - For patients not receiving therapeutic anticoagulation: INR and aPTT $\leq 1.5 \times$ ULN or INR $< 1.7 \times$ ULN
 - For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
 - Creatinine clearance ≥ 20 mL/min (calculated using the Cockcroft-Gault formula)
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception and agreement to refrain from donating eggs, as defined below:

Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 5 months after the final dose of atezolizumab. Women must refrain from donating eggs during this same period.

A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, 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 adequate methods of contraception.

If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

4.1.2.1 General Medical Exclusion Criteria for the Surveillance Phase

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

- Known PD-L1 IHC result for adjuvant therapy
The decision for the adjuvant therapy should not be based on the PD-L1 IHC result.
- Pregnancy or breastfeeding
- Positive test for HIV, with the following exception:
Patients with a positive HIV test at screening are eligible provided they are stable on antiretroviral therapy, have a CD4 count $\geq 200/\mu\text{L}$, and have an undetectable viral load.
- Patients with active hepatitis B virus (HBV; chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C
Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody and the absence of HBsAg) are eligible. A negative HBV DNA test must be obtained in these patients prior to enrollment.
Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Active tuberculosis confirmed by a test performed within 3 months prior to treatment initiation
Investigators may perform tuberculosis test within 3 months prior to enrollment into surveillance. Depending on the length of time patients undergo monitoring in surveillance, it may be necessary to repeat testing within 3 months of treatment initiation to avoid the inclusion of any patient with active disease.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, granulomatosis with polyangiitis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis
Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.

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

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

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

- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within the previous 3 months, unstable arrhythmias, or unstable angina

Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction <50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

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

4.1.2.2 Cancer-Specific Exclusion Criteria for the Surveillance Phase

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

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

Hormone-replacement therapy or oral contraceptives are allowed.

- Adjuvant chemotherapy or radiation therapy for UC following cystectomy

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

- Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days or 5 half-lives of the drug, whichever is longer, prior to enrollment

- Malignancies other than UC within 5 years prior to study enrollment

Patients with high risk UTUC (defined as tumor stage (y)pT2–4a or (y)pN+) within 5 years prior to Cycle 1 Day 1 will be ineligible.

Patients with localized low-risk prostate cancer (defined as Stage $\leq$ T2c, Gleason score $\leq$ 7, and prostate-specific antigen [PSA] at prostate cancer diagnosis $\leq$ 20 ng/mL [if measured]) treated with curative intent and without PSA recurrence are eligible.

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

4.1.2.3 Additional Exclusion Criteria for the Treatment Phase

Patients who meet any of the following additional criteria will be excluded from entry in the Treatment Phase:

- Any approved anti-cancer therapy, including chemotherapy, or hormonal therapy within 3 weeks prior to randomization to the Treatment Phase
Hormone-replacement therapy or oral contraceptives are allowed.
- Adjuvant chemotherapy or radiation therapy for UC following cystectomy
Patients who have received primary chemoradiation for bladder preservation before cystectomy are eligible and will be treated as the same as patients who have received prior NAC.
- Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days or 5 half-lives of the drug, whichever is longer, prior to randomization to the Treatment Phase
- Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1 are ineligible.
- Receipt of therapeutic oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1
Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.
- Major surgical procedure other than for diagnosis within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study

- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
 Influenza vaccination should be given during influenza season only (approximately October through May in the Northern Hemisphere and approximately April through September in the Southern Hemisphere). Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to randomization, during treatment or within 5 months following the final dose of atezolizumab (for patients randomized to atezolizumab).
- Serum albumin < 2.5 g/dL
- Positive test for HIV, with the following exception:
 Patients with a positive HIV test at screening are eligible provided they are stable on antiretroviral therapy, have a CD4 count $\geq 200/\mu\text{L}$, and have an undetectable viral load.
- Patients with active hepatitis B virus (HBV; chronic or acute; defined as having a positive HBsAg test at screening) or hepatitis C
 Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody and the absence of HBsAg) are eligible. A negative HBV DNA test must be obtained in these patients prior to enrollment.
 Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Active tuberculosis confirmed by a test performed within 3 months prior to treatment initiation

4.1.2.4 Additional Medication-Related Exclusion Criteria for the Treatment Phase

Patients in the Surveillance Phase who meet any of the following additional medication-related criteria will be excluded from entry in the Treatment Phase:

- Prior treatment with CD137 agonists or immune checkpoint-blockade therapies, including anti-CD40, anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, IFNs, IL-2) within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to Cycle 1, Day 1

- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to Cycle 1, Day 1, or anticipated requirement for systemic immunosuppressive medications during the trial

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

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

- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of study treatment

Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blind study. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number. Blinded treatment assignment will be provided by the interactive voice or web-based response system (IxRS) for patients eligible to be randomized in the Treatment Phase of the study.

Approximately 240 patients who are or become ctDNA positive following cystectomy will be randomized to treatment and will constitute the Efficacy Analysis population.

Patients will be randomized to one of the following arms:

- Arm A (experimental arm): atezolizumab 1680 mg IV infusion Q4W on Day 1 of each 28-day cycle
- Arm B (control arm): placebo IV infusion Q4W on Day 1 of each 28-day cycle

Randomization will occur in a 2:1 ratio through the use of a stratified permuted-block randomization method. Randomization will be stratified by the following factors:

- Nodal status (positive vs. negative)
- Tumor stage after cystectomy ($\leq$ (y)pT2 vs. (y)pT3/pT4)
- PD-L1 IHC status (IHC score of IC0/1 vs. IC2/3)
- Time from cystectomy to first ctDNA-positive sample (≤ 20 weeks vs. > 20 weeks)

Patients who remain ctDNA negative through 12 months after cystectomy will not be randomized to treatment and will enter surveillance follow-up.

Randomization to the Treatment Phase will end after the projected number of DFS events is expected to be reached. After this timepoint, patients who are still enrolled in the Surveillance Phase will not be randomized but may continue with ctDNA testing for the remainder of the 12-month surveillance period and may receive treatment outside the study at the investigator's discretion.

As a result of the study meeting its primary endpoint of DFS and key secondary endpoint of OS at the primary analysis, the Sponsor and its agents have been unblinded to treatment assignment and investigators may also be unblinded as described in Section 4.2.2. Patients randomized to the comparator arm might discontinue placebo and may receive treatment outside the study at the investigator's discretion.

4.2.2 Blinding

Originally, study site personnel and patients *were* blinded to treatment assignment during the study. The Sponsor and its agents *were* also blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial.

As a result of the study meeting its primary endpoint of DFS and key secondary endpoint of OS at the primary analysis, the Sponsor and its agents were unblinded to treatment assignment. In addition, study site personnel may be unblinded per investigator's request, in case this information is useful in guiding further treatment decisions at the investigator's discretion and in dialogue with their patient, or in case of medical emergencies to determine the suitability of subsequent medical care for the patient. The investigator will be able to break the treatment code by contacting the IxRS or the study team.

Once the study is completed, the investigator may tell the patient which treatment they received, either if the patient asks or at the investigator's discretion.

4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is atezolizumab. [Appendix 13](#) identifies all investigational, auxiliary, and non-investigational medicinal products for this study.

4.3.1 Study Treatment Formulation and Packaging

The atezolizumab Drug Product will be supplied by the Sponsor as a sterile liquid in a single-use, 14-mL glass vial. The vial contains approximately 14 mL (840 mg) of atezolizumab solution.

For information on the atezolizumab formulation, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

The placebo will be identical in appearance to atezolizumab and will comprise the same excipients but without atezolizumab Drug Product. It should be handled, stored, and used in the same manner as atezolizumab. Placebo will be supplied by the Sponsor.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

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

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 12.

Atezolizumab/placebo will be administered by IV infusion at a fixed dose of 1680 mg on Day 1 of each 28-day (± 3 days) cycle for 12 cycles or 1 year, whichever occurs first. This dose level is equivalent to an average body weight-based dose of approximately 20 mg/kg.

Administration of atezolizumab/placebo will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 11. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Atezolizumab/Placebo Infusions

First Infusion	Subsequent Infusions
- No premedication is permitted prior to the atezolizumab/placebo infusion. - Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. - Atezolizumab/placebo should be infused over 60 ($\pm$ 15) minutes. - If clinically indicated, vital signs should be measured every 15 ($\pm$ 5) minutes during the infusion and at 30 ($\pm$ 10) minutes after the infusion. - Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	- If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, anti-pyretic medications, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. - Vital signs should be measured within 60 minutes prior to the infusion. - Atezolizumab/placebo should be infused over 30 ($\pm$ 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 ($\pm$ 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. ^a - If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 ($\pm$ 10) minutes after the infusion.

^a For Cycle 2 and subsequent cycles, atezolizumab may be infused over a longer period of time at the investigator's discretion.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in [Appendix 12](#).

No dose modification for atezolizumab is allowed.

4.3.3 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated)

area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

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

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied 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 accountability log.

Refer to the pharmacy manual and/or the Atezolizumab Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Atezolizumab

Currently, the Sponsor does not have any plans to provide Roche IMP (atezolizumab) or any other study treatments to patients who have completed the study. The Sponsor may evaluate whether to continue providing atezolizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

https://assets.roche.com/ff/176343/x/1b18e080e0/2025-revision-roche_global_policy_on_continued_access_to_investigational_interventions.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the treatment/placebo discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of < 1% per year (see Section 4.1.1)
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)

- Vaccinations (such as influenza, COVID-19)
Live, attenuated vaccines are not permitted (see Section 4.4.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

Premedication with antihistamines, anti-pyretic medications, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H₂-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 -adrenergic agonists; see Appendix 11).

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.2.1 Corticosteroids, Immunosuppressive Medications, and TNF Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 12 for details).

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.3) may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority-approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease recurrence is documented and the patient has discontinued study treatment.
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the final dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, IFNs and IL-2) are prohibited within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the prescreening and Surveillance Phases is provided in [Appendix 1](#) and a timeline of assessments is provided in [Appendix 3](#) and the schedule of activities to be performed during the Treatment Phase until discontinuation from the study is provided in [Appendix 2](#). All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study.

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.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations).

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

Prior to signing the main Informed Consent Forms (Surveillance and Treatment Phase Informed Consent Forms) for the study, patients must consent to the collection of tumor tissue (archival or newly obtained via fresh tumor specimens) for determination of PD-L1 expression, WES-evaluable (ctDNA assay designability) result, and baseline imaging to determine eligibility in the Surveillance Phase by signing Prescreening Informed Consent Form. The timing of Informed Consent Form signature is at the discretion of the site, but preferred to have the Prescreening and Surveillance Informed Consent Forms signed at

the same time at the patient's and/or site staff convenience. The baseline blood sample for ctDNA testing may be collected during the Prescreening phase after the Surveillance Informed Consent Form is signed, prior to confirmation of eligibility into the Surveillance Phase.

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

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

4.5.3 Physical Examinations

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

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Vital signs should be measured within 60 minutes prior to each atezolizumab or placebo infusion and, if clinically indicated, during or after the infusion. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see [Appendix 2](#)).

Table 2 Timing for Vital Sign Measurements for First and Subsequent Infusions

Drug	Timing for Vital Sign Measurements	
	First Infusion	Subsequent Infusions
Atezolizumab or Placebo	• Within 60 minutes prior to the infusion • Record patient's vital signs during or after the infusion if clinically indicated.	• Within 60 minutes prior to the infusion • Record patient's vital signs during or after the infusion if clinically indicated

4.5.5 Surveillance for Urothelial Carcinoma Recurrence

The date the patient has moved to Surveillance Phase in IxRS (date of IxRS transaction) will be used as the date of enrollment into the Surveillance Phase after meeting all the inclusion and exclusion criteria. The date of the first blood collection for plasma ctDNA testing will be used as an anchor point to calculate the date of blood collection of subsequent visits in the Surveillance Phase.

During the surveillance visits, patients will undergo blood collection for plasma ctDNA testing and surveillance imaging for tumor recurrence. Blood collection will occur every 6 weeks (± 5 days) from the date of the first blood collection for plasma ctDNA testing until Week 36 or until 36 weeks from the date of cystectomy have passed, whichever occurs first. After the latest blood collection prior to 36 weeks from cystectomy has been reached, blood collection should follow the surveillance imaging schedule going forward. Surveillance imaging will be performed every 12 weeks from the Week 0 date, which is the first blood collection for plasma ctDNA testing, until Week 48 or until 12 months from the date of cystectomy have passed, whichever occurs first. Based on this testing frequency, a patient's last scheduled ctDNA test will occur anywhere between 42 and 52 weeks from cystectomy. Patients whose last scheduled ctDNA test occurs more than 4 weeks prior to surveillance completion may have an optional unscheduled ctDNA test performed before the 12 months are complete.

Tumor recurrence in the Surveillance Phase will be assessed by investigators. *Patients who were previously discontinued from the Surveillance Phase as a result of experiencing investigator-assessed disease recurrence may be contacted to request consent for survival follow-up.* See [Figure 2](#) in Section 4.5.6 for the sample collection and imaging schema.

Patients' blood samples collected during the surveillance run-in phase will be evaluated for the presence of mutations identified on their personalized tumor tissue-based assay. Plasma samples evaluated to have a presence of two or more mutations out of 16 mutations identified based on patient's WES evaluable (ctDNA assay designability) report will be considered ctDNA positive.

All patients entered in the Treatment Phase will undergo scheduled assessments for tumor recurrence at baseline and every 9 weeks in the first year following randomization. Upon completion of the treatment/placebo period, patients will enter treatment follow-up. Disease status assessments for tumor recurrence will be performed every 9 weeks (± 7 days) for Year 2; every 12 weeks (± 10 days) for Year 3; every 24 weeks (± 10 days) for Years 4–5; and at Year 6 (approximately 48 weeks after the last assessment in Year 5) until occurrence of a DFS event, death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first, regardless of length of treatment/placebo. Tumor recurrence in the Treatment Phase will be determined by investigators and by an IRF.

Plasma samples will be collected during the Treatment Phase at every scheduled imaging assessment for tumor recurrence to evaluate ctDNA clearance. *As of BO42843 Protocol Version 10, only the blood for plasma ctDNA sample collection at disease recurrence is required.*

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

All eligible patients will undergo a contrast-enhanced CT or MRI of the chest, abdomen, and pelvis at screening for surveillance and/or Treatment Phases. Eligibility into the Treatment Phase will be confirmed by an IRF review of imaging data, pathology reports if available, as well as any historical scans that may support the interpretation of benign radiographic objects. In patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance), MRIs of the abdomen and pelvis with a non-contrast CT scan of the chest may be used.

For patients with renal impairment or contrast allergy, upper tract medical imaging is still required. For patients with renal impairment, CT urography with a reduced contrast agent or a non-contrasted MRI is recommended. For patients with a contrast allergy, non-contrasted MRI urogram or ureteroscopy is recommended.

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

Imaging studies should use the same imaging modality that was used at screening and be performed at the timepoints specified in [Appendix 2](#), regardless of drug delays or interruptions.

If recurrent disease or occurrence of a new primary tumor is suspected on clinical grounds, imaging assessment must be performed expeditiously, even if not mandated in the schedule of activities. Determination of disease recurrence should be based on presence of unequivocal disease.

All patients in the Treatment Phase who present with findings for disease recurrence *are requested to* undergo a confirmatory biopsy for histopathologic confirmation, *if deemed clinically feasible*. For patients in the Surveillance Phase who present with findings suspicious for disease recurrence, biopsy may be performed to confirm or rule out disease recurrence at the discretion of the investigator.

Disease recurrence in the Treatment Phase will be determined by the investigator and by an IRF based on radiographic evidence. Cases for which biopsy results definitively rule out recurrence of UC will not be considered as disease recurrence for this study. Equivocal scans should only be used as date of recurrence if followed by biopsy confirming recurrence. Biopsy dates and results will be shared with the IRF to support the independent assessment of recurrence.

As of BO42843 Protocol Version 10, disease recurrence in the Treatment Phase will only be determined by the investigator.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), serum troponin (at baseline, if considered standard of care/required per local clinical practice, and as clinically indicated during the study), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH
- Coagulation: INR and aPTT

- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- HIV serology: HIV-1/2 antibody
Patients with a positive HIV result are eligible provided their CD4 count $\geq 200/\mu\text{L}$ and they have an undetectable viral load.
- HBV serology: HBsAg, hepatitis B surface antibody (HBsAb), and total hepatitis B core antibody (HBcAb) for all patients; HBV DNA for patients with negative HBsAg and HBsAb tests and a positive total HBcAb test
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA
- Tuberculosis test as per local practices
- Pregnancy test
All women of childbearing potential will have a serum pregnancy test at screening for the Treatment Phase. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Post-surgery matched blood sample for WES used as a normal control to identify somatic mutations in tumor tissue for subsequent ctDNA assay
- Post-surgery blood samples for plasma ctDNA preparation at multiple timepoints for ctDNA surveillance and exploratory research on biomarkers (including biomarker assay development)
- Post-surgery blood samples for PBMC preparation at multiple timepoints for exploratory research on biomarkers (including biomarker assay development)
- Urine samples at multiple timepoints for exploratory research on biomarkers (including biomarker assay development)
- Serum sample for auto-antibody testing; baseline sample to be collected on Cycle 1, Day 1 prior to the first dose of study drug. For patients who show evidence of immune-mediated toxicity, additional samples may be collected, and all samples will be analyzed centrally.
 - Anti-nuclear antibody

- Anti-double-stranded DNA
- Circulating anti-neutrophil cytoplasmic antibody
- Perinuclear anti-neutrophil cytoplasmic antibody
- Serum samples for atezolizumab PK analysis through use of a validated assay
 - C-reactive protein testing will be performed using the residual baseline PK samples.
- Serum samples for assessment of ADAs to atezolizumab through use of a validated assay
- Resected tumor tissue sample obtained at surgery for use in determining WES evaluable (ctDNA assay designability) and PD-L1 expression to meet inclusion criteria into the Surveillance Phase of the study and for exploratory biomarker analysis. Analysis of ctDNA status will be performed using the investigational Signatera™ (Natera, Inc.) assay. Analysis of PD-L1 status will be performed using the VENTANA PDL1 (SP142) Assay.

Tumor tissue specimen is strongly encouraged to be submitted as soon as possible and optimally within 18 weeks of cystectomy in order to obtain results within the time window required for eligibility into Surveillance Phase.

At least one representative FFPE tumor block is to be submitted along with an associated de-identified pathology report (two FFPE tumor blocks are recommended, if available).

If an intact FFPE tumor block cannot be provided, then submittal of at least 20 slides containing unstained, freshly cut serial sections derived from an FFPE tumor block prepared and shipped as outlined in the laboratory manual is allowed. Patients with fewer than 16 slides may still be eligible for the study after consultation with the Medical Monitor. A copy of the de-identified biospecimen-associated pathology report must be submitted together with the specimen.

Tumor tissue should be of good quality based on total and viable tumor content as described in the laboratory manual. Tumor tissue from surgical resection is preferred.

If resected tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy (e.g., TURBT) can be submitted for the determination of ctDNA status and PD-L1 expression, but will need to meet the requirement for tissue as stated above for resected tumor. Diagnostic core-needle biopsy tumor tissue samples may be submitted for determination of PD-L1 expression, only. Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. If submitting core-needle biopsy specimens, at least 3 cores should be submitted for evaluation. Samples collected via fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural

effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

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

- Tumor tissue sample obtained at time of disease recurrence, if deemed clinically feasible, for exploratory research on biomarkers and biomarker assay development

For samples collected at the time of disease recurrence: Biopsies at the time of progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

As of BO42843 Protocol Version 10, tumor biopsy samples collected to confirm disease recurrence will no longer be sent to central labs.

Exploratory biomarker research may include, but will not be limited to, analysis of ctDNA, genes or gene signatures associated with tumor immunobiology, PD-L1, lymphocyte subpopulations, T-cell receptor repertoire, or cytokines associated with T-cell activation. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of NGS of a comprehensive panel of genes. The DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. The NGS methods may include WGS or WES of tissue and blood samples.

Screening blood and tumor tissue samples, including those collected from patients who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

The NGS may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator may obtain an NGS report through Foundation Medicine's web portal. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results will not be available for samples that do not meet criteria for testing.

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.9), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report (CSR), with the following exceptions:

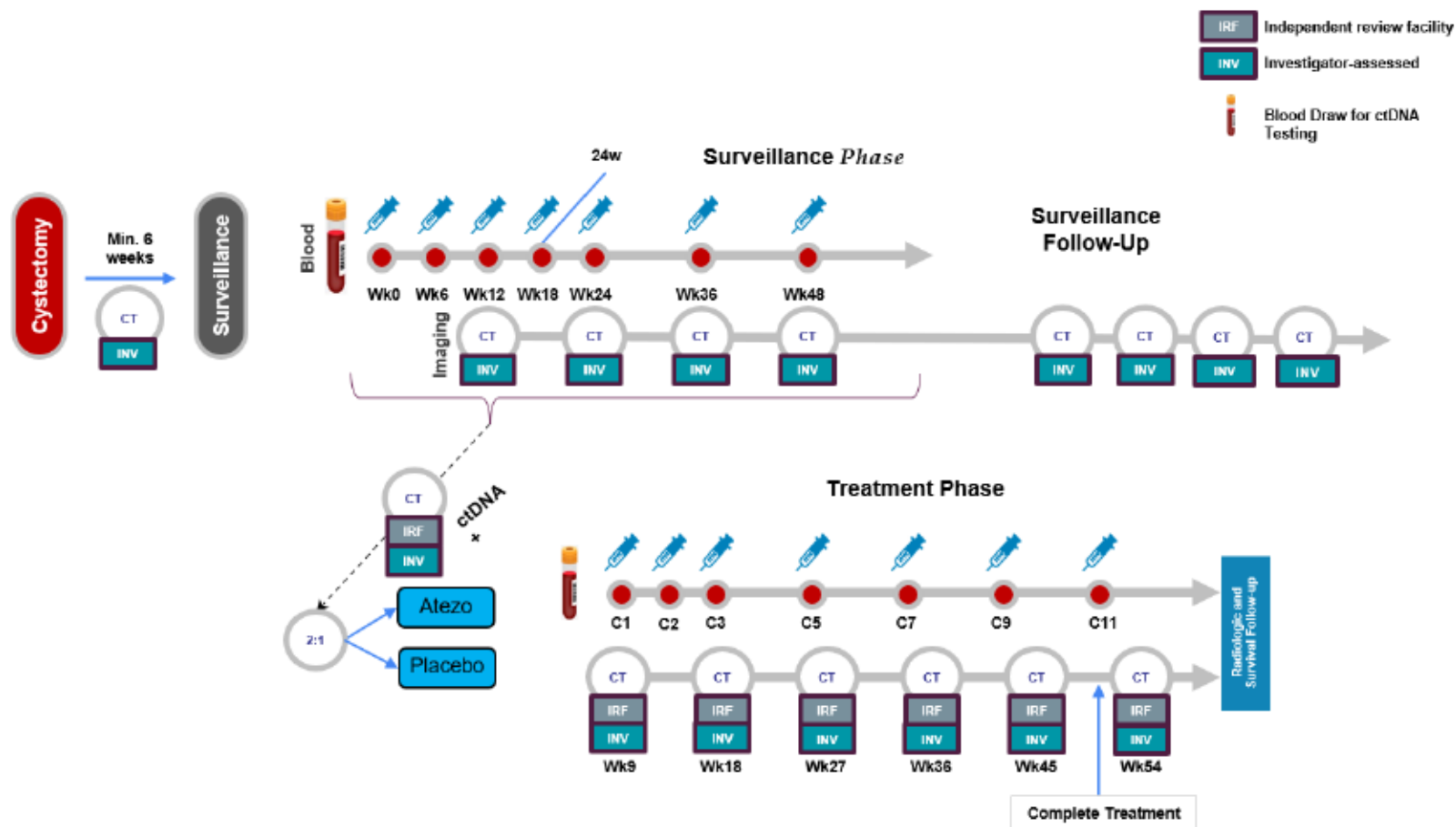
- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final CSR has been completed.
- Blood, plasma, urine, and tumor tissue samples collected for biomarker research and for biomarker assay development will be destroyed no later than 5 years after the final CSR has been completed, with the exception of tissue and blood samples that undergo WGS or WES, which will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

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

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. Outcomes from ctDNA analyses conducted to inform potential eligibility for the study will be provided to study investigators. If allowed by local laws, the investigator may share the results with the patient, unless the patient chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Figure 2 Surveillance Phase Imaging and Blood Collection Schedule



C=cycle; CT=computed tomography; ctDNA=circulating tumor DNA; INV=investigator-assessed; IRF=independent review facility; min=minimum; Wk=week.

4.5.7 Electrocardiograms

A 12-lead ECG is required at screening for the Treatment Phase and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible.

The 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.

4.5.8 Clinical Outcome Assessments

PRO instruments will be completed to more fully characterize the clinical profile of atezolizumab. In addition, PRO instruments will enable the capture of each patient's direct experience with atezolizumab.

PRO data will be collected through use of the following instruments: EORTC QLQ-C30, EORTC IL46, and EQ-5D-5L.

During the Surveillance Phase, patients will complete the EORTC QLQ-C30 and EQ-5D-5L questionnaires at the clinic or over the telephone at the same schedule as for blood collection for ctDNA testing.

Patients will complete the EORTC QLQ-C30, EORTC IL46, and EQ-5D-5L questionnaires at the clinic or over the telephone on Day 1 of each odd-numbered cycle visit during the treatment/placebo period (i.e., Cycles 1, 3, 5, 7, 9, and 11) until disease recurrence, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor (see Section 3.1.1 for details), and at the treatment/placebo discontinuation visit. Upon completion of the treatment/placebo period, patients will complete PRO questionnaires at the same schedule as the surveillance schedule for tumor recurrence (every 9 weeks for Year 2; every 12 weeks for Year 3; every 24 weeks for Years 4–5; and at Year 6, approximately 48 weeks after the last assessment in Year 5) at the clinic or via telephone until death, unequivocal radiographic evidence of disease recurrence, loss to follow-up, end of Year 6, withdrawal of consent, or study termination by the Sponsor. During survival follow-up, PRO instruments will be administered at the clinic or via telephone approximately every 3 months until death, loss to follow-up, or study termination by Roche.

As of BO42843 Protocol Version 10, PRO instruments will no longer be administered.

4.5.8.1 Data Collection Methods for Clinical Outcome Assessments

The PRO instruments will be self-administered or interviewer-administered (as appropriate) at the clinic or over the telephone at specified timepoints during the study (see schedule of activities in [Appendix 2](#)). At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

In scenarios where laboratory assessments (e.g., blood draws) are done at a different location than the one providing treatment or when they are done on a different day than study treatment administration, laboratory assessments can be completed before the completion of PROs as long as results have not been discussed with patients.

The PRO instruments, translated into the local language as appropriate, may be completed on pre-printed paper booklets provided by the Sponsor. If the patient is unable to complete the questionnaire on her or his own, interviewer assessment is allowed but may only be conducted by a member of the clinic staff. Telephone administration is also permitted.

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 15 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.
- Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

4.5.8.2 Description of Clinical Outcome Assessment Instruments

EORTC QLQ-C30

The EORTC QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) (see [Appendix 7](#)). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), GHS and QoL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the GHS and QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent."

The EORTC QLQ-C30 module takes approximately 10 minutes to complete.

EORTC IL46

The EORTC IL46 global impression of cancer treatment side effects burden item asks patients to rate how much they are bothered by treatment side effects (see [Appendix 8](#)). A similarly worded item has been shown to be a valid and useful summary measure of overall adverse event burden from the patient's perspective to complement clinician-rated adverse event reporting (Pearman et al. 2018). The item is rated on a 4-point scale that ranges from "not at all" to "very much" and has a recall period of one week. The EORTC IL46 item takes approximately 1 minute to complete.

EQ-5D-5L

The EQ-5D-5L is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (see [Appendix 9](#)). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

4.5.9 Optional Samples for Research Biosample Repository

4.5.9.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides).

The collection, storage, and analysis of RBR samples 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.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

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

As of BO42843 Protocol Version 10, RBR samples will no longer be collected. Previously collected samples may still be analyzed.

4.5.9.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.9) will not be applicable at that site.

4.5.9.3 Sample Collection

As of BO42843 Protocol Version 10, the collection of new RBR samples will be discontinued. All RBR samples that have already been collected will remain stored and utilized for research purposes, as permitted by the patients' original consent. The research may include, but will not be limited to, research on biomarkers related to atezolizumab, diseases, or drug safety:

- An optional blood sample collected *under previous versions of the protocol* at any time during the study
- Leftover blood, serum, plasma, PBMC, urine, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for

developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples *may* be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

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

4.5.9.4 Confidentiality

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

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

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

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

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

4.5.9.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be

required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

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

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

4.5.9.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

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

4.5.9.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (atezolizumab) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Disease recurrence (local recurrence, urinary tract recurrence, or distant metastasis of UC) documented by radiographic evidence

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

Every effort should be made to obtain information on patients who withdraw from the Treatment Phase of the study.

Patients who withdraw from the study will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit ≤ 30 days after the final dose of study treatment. Patients who discontinue study treatment for any reason other than disease recurrence will continue to undergo tumor response assessments as outlined in the schedule of activities (see [Appendix 2](#)).

Information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months *from time of disease recurrence* until death (unless the patient withdraws consent or the Sponsor terminates the study).

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent

- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF.

At any time during the study, patients may choose to withdraw consent for specific protocol-mandated assessments without fully withdrawing from the study. In this situation, the specific assessments that the patient agrees to participate in should be documented in the source documents. The study staff may use medical records to obtain information about health status and non-protocol anti-cancer therapies for patients who choose to partially withdraw consent unless the patient specifically withdraws consent for this activity.

If a patient requests to be *fully* withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced. If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the ICH guideline for Good Clinical Practice

- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

4.6.5 Surveillance Phase Discontinuation and Follow-Up

Patients in the Surveillance Phase who remain ctDNA negative at 12 months from the date of cystectomy and who will never be randomized or receive study treatment will enter a 4-year follow-up period. During this time, disease status assessments for tumor recurrence will be performed every 6 months (± 10 days) for the first 2 years, until death, investigator-assessed unequivocal radiographic evidence of disease recurrence, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. Thereafter, survival information will be collected by *medical records*, telephone or office visit every 6 months (± 2 months) for an additional 2 years to complete the 4-year surveillance follow-up period, until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first (see [Appendix 1](#)).

Patients who previously were discontinued from the Surveillance Phase as a result of experiencing investigator-assessed disease recurrence may be contacted to request consent for survival follow-up. For such patients who provide consent, survival status should be assessed as soon as feasible after consent is obtained. Thereafter, survival information will be collected by medical records, telephone or office visit every 6 months (± 2 months) to complete the 4-year surveillance follow-up period, until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. The date of disease recurrence should be used as the anchor point to calculate the 4-year window (see [Appendix 1](#)).

4.6.6 Lost to Follow-up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- *The site must attempt to contact the patient as soon as possible to reschedule the missed visit and counsel the patient on the importance of maintaining the assigned visit schedule. If the patient is unable or unwilling to comply with study visits, site personnel should assess reasons the patient is unable or unwilling to return to the clinic, and determine if there are ways to support patient participation.*
- *Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (whenever possible, three telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.*
- *Should the patient continue to be unreachable, the patient will be considered lost to follow-up and will be withdrawn from the study.*

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing patients who experience anticipated adverse events, including criteria for treatment interruption or discontinuation, are provided in [Appendix 12](#). See Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

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

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

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, severe cutaneous adverse reactions, *and uveitis*. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). See [Appendix 12](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Guidelines for managing patients who experience anticipated adverse events are provided in [Appendix 12](#).

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

Certain types of events require immediate reporting to the Sponsor, as outlined in Section [5.4](#).

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections [5.3.5.9](#) and [5.3.5.10](#) for more information)
- 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, Xray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
 - This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section [5.3.5.11](#))

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE v5.0; 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 are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, 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 study treatment is suspected.

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, CRS, HLH, and macrophage activation syndrome (MAS)
- Nephritis

- Ocular toxicities (e.g., retinitis, optic neuritis)
- Grade ≥ 2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

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 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4–5.6.

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

5.3.1 Adverse Event Reporting Period

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

For the prescreening, surveillance, and surveillance follow-up phases:

After informed consent has been obtained, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as blood sampling) and serious adverse events considered related to Signatera™ (Natera, Inc.) assay (including any device-related procedures) should be reported immediately (i.e., no more than 24 hours after the investigator becomes aware of the event). In addition, during this period, non-serious adverse events considered related to Signatera™ (Natera, Inc.) assay (including any device-related procedures and adverse events that may be a consequence of device deficiencies) should be reported within 5 days after the investigator becomes aware of the event (see Section 5.4.2 for instructions for reporting events). All other medical events occurring in patients during this period are considered preexisting medical conditions and should be recorded as described in Section 5.3.5.9.

For the Treatment Phase:

After informed consent has been obtained, but prior to the initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, blood sampling, discontinuation of medications) and serious adverse events considered related to Signatera™ (Natera, Inc.) assay (including

any device-related procedures) should be reported immediately (i.e., no more than 24 hours after the investigator becomes aware of the event). In addition, non-serious adverse events considered related to Signatera™ (Natera, Inc.) assay (including any device-related procedures and adverse events that may be a consequence of device deficiencies) should be reported within 5 days after the investigator becomes aware of the event (see Section 5.4.2 for instructions for reporting events). All other medical events occurring in patients during this period are considered preexisting medical conditions and should be recorded as described in Section 5.3.5.9.

After initiation of study treatment, all adverse events will be recorded until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. In addition, non-serious adverse events considered related to Signatera™ (Natera, Inc.) assay (including any device-related procedures and adverse events that may be a consequence of device deficiencies) will be reported within 5 days after the investigator becomes aware of the event.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

The investigator will be informed of any device deficiencies detected at the testing site that might have an impact on clinical study participants (e.g., a test result leading to inappropriate participant management decision). This will enable the investigator to assess and report any adverse events associated with the device deficiency (see Section 5.8.3).

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

Note: Based on the most recent version of NCI CTCAE v5.0, which can be found at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 4):

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

Table 4 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions and Cytokine Release Syndrome

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF.

Avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

There may be significant overlap in signs and symptoms of IRRs and CRS. In recognition of the challenges in clinically distinguishing between these two events, consolidated guidelines for medical management of IRRs and CRS are provided in [Appendix 12](#).

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment
- Note: For oncology trials, certain abnormal values may not qualify as adverse events.

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

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

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

5.3.5.6 Abnormal Vital Sign Values

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

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

- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

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

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

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3 \times \text{ULN}$) 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 (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is a secondary efficacy endpoint. Deaths must be recorded on the appropriate eCRF as described below (see also Section 5.6).

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

All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent monitoring committee will monitor the frequency of deaths from all causes.

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Recurrence of Urothelial Carcinoma

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

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

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

The patient has not experienced an adverse event.

- Hospitalization due solely to recurrence/progression of the underlying cancer

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

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

5.3.5.12 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For atezolizumab or matching placebo, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with atezolizumab or matching placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

5.4 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 treatment:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

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

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

5.4.1 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.

An Emergency Medical Call Center will be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

5.4.2 Reporting Requirements for Serious Adverse Events, Medical Device Adverse Events, and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Treatment Initiation

For the prescreening, surveillance, and Treatment Phases of the study, after informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention and serious adverse events considered related to Signatera™ (Natera, Inc.) assay (including any device-related procedures) should be reported immediately (i.e., no more than 24 hours after learning of the event) using the Screening Adverse Event eCRF or using the paper Clinical Trial Adverse Event/Special Situations Form if the EDC is not available.

In addition, during this period, non-serious adverse events considered related to Signatera™ (Natera, Inc.) assay (including any device-related procedures) should be reported within 5 days after the investigator becomes aware of the event using the Screening Adverse Event eCRF or the paper Investigational Medical Device Adverse Event and Device Deficiency Form if the EDC system is not available.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events, adverse events of special interest, and non-serious medical device adverse events that are considered related to Signatera™ (Natera, Inc.) assay (including any device-related procedures) will be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. For serious adverse events and adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF. For non-serious medical device adverse events that are considered related to Signatera™ (Natera, Inc.) assay (including any device-related procedures), investigators should record all case details within 5 days on the Adverse Event eCRF. Reports will be submitted via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of study treatment. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

5.4.3.2 Abortions

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

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

5.4.3.3 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment or Signatera™ (Natera, Inc.) assay (including any device-related procedures), the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form (study drug-related events) or Investigational Medical Device Adverse Event and Device Deficiency Form (medical device-related events) using the fax number or email address provided to investigators.

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

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

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information listed below:

Drug	Document
Atezolizumab	Atezolizumab Investigator's Brochure

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

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

An iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities. *As of the date of the primary analysis, the iDMC support for safety review activities has been terminated.*

5.8 MEDICAL DEVICE ADVERSE EVENTS

This study will comply with International Standard (ISO) 20916 on in vitro diagnostic medical devices—clinical performance studies using specimens from human subjects—good study practice and Regulation (EU) 2017/746 on in vitro diagnostic medical devices requirements for medical device adverse event collection and reporting for events associated with the use of Signatera™ (Natera, Inc.) assay (including any device-related procedures) (also see Sections 5.3.1, 5.3.2, and 5.4.2).

5.8.1 Definition of IVD Medical Device Adverse Event

Any untoward medical occurrence, inappropriate patient management decision, unintended disease or injury, or untoward clinical signs, including an abnormal laboratory finding, in subjects, users, or other persons, with any connection to study related activities, whether or not related to the IVD medical device under investigation. Adverse events can be caused by, for instance, insufficient or inadequate instructions for use, deployment, installation, operation, or any malfunction of the IVD medical device under investigation. This definition includes the malfunction or deterioration of a device which has not yet caused death or serious injury, but which could lead to death or serious injury. This definition is not intended to be used in determining whether an event is reportable to a regulatory authority. For users or other persons, this definition is restricted to events related (defined as possible, probable, or causal relationship) with the investigational IVD medical device or device-related procedures. False negative or false positive results are not considered an adverse event unless in an interventional study, inappropriate patient management decisions are made based on those false results.

5.8.2 Definition of Serious Device Adverse Event

This definition is applicable to Signatera™ (Natera, Inc.) assay.

A Serious Device Adverse Event is a device adverse event that led to any of the following:

- *Death*
- *Serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:*
 - *A life-threatening illness or injury, or*
 - *A permanent impairment of a body structure or a body function including chronic diseases, or*
 - *Inpatient or prolonged hospitalization, or*

- *Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function*
- *Fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment*

Planned hospitalization for a pre-existing condition, or a procedure required by the study, without serious deterioration in health, is not considered a serious adverse event.

5.8.3 Definition of Device Deficiency

A device deficiency is any inadequacy in the identity, quality, durability, reliability, usability, safety, or performance of an investigational medical device, including malfunction of the device, use error, or inadequate manufacturer-supplied instructions (including labelling) for use, deployment, installation, or operation of the device (See Section 5.3.2).

5.8.4 Assessment of Causality of Medical Device Adverse Events

The circumstances surrounding the event, an evaluation of any potential alternative causes, and any knowledge about the clinical study participant, user, or other person should be used to determine whether an adverse event is considered to be related to the use of Signatera™ (Natera, Inc.) (including any device-related procedures). The guidance provided below should be used to assess the causality of these adverse events.

Note: Events associated with a procedure that would have been performed in a clinical study participant with or without use of the device should be classified as not related.

Relationship	Criteria for Classification
Not related	The relationship of the event to the device or device-related procedures can be excluded when The event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device; the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; The serious adverse event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); The event does not depend on a false result given by the investigational device used for diagnosis, when applicable. In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

Relationship	Criteria for Classification
Possible	The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
Causal	The adverse event/serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when The event is a known side effect of the specimen collection procedures for the investigational IVD; The event has a temporal relationship with investigational device use/application or procedures; The serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known); Other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; Harm to the subject is due to error in use; The event depends on a false result given by the investigational device used for diagnosis, when applicable. In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

Note: Events associated with a procedure that would have been performed in a clinical study participant with or without use of the device should be classified as not related.

5.8.5 Reporting Medical Device Adverse Events

See Section 5.4 for details on reporting medical device adverse events in participants. User injury adverse events must be reported using the paper Investigational Medical Device Adverse Event and Device Deficiency Form.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 PATIENT POPULATIONS

6.1.1 Enrolled Population

The enrolled population is defined as patients who enter the surveillance run-in phase of the study, which includes all patients who are randomized to receive study treatment (see Section 6.1.2) as well as those who are not randomized, including the ctDNA-negative population (see Section 6.1.3).

6.1.2 Efficacy Analysis Population

The Efficacy Analysis population includes all patients randomized to receive study treatment regardless of the length of time between cystectomy and ctDNA-positive status, when approximately 178 DFS events are reached.

6.1.3 ctDNA-Negative Population

The ctDNA-negative population is defined as enrolled patients who were ctDNA negative at all timepoints tested. These patients will not be randomized to treatment. This population is considered to be an exploratory analysis population.

6.1.4 Safety Evaluable Population

The safety evaluable population is defined as all randomized patients who received at least one dose of study treatment (atezolizumab or placebo).

6.2 DETERMINATION OF SAMPLE SIZE

It is projected that up to 800 patients with MIBC will be enrolled in surveillance in order to identify 178 events in approximately 240 ctDNA-positive patients at the time of DFS primary analysis.

The sample size of up to 800 patients for the surveillance population is based on the assumption that approximately 30%–46% of patients will either be ctDNA-positive at the time of enrollment or will become ctDNA positive following cystectomy.

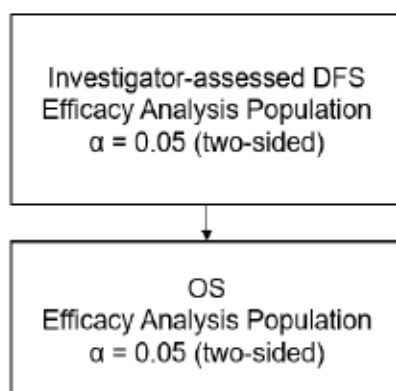
Randomization to the Treatment Phase will end after the projected number of DFS events is expected to be reached.

6.2.1 Type I Error Control

The type 1 error (α) for this study is 0.05 (two-sided). Type 1 error will be controlled for the primary endpoint of investigator-assessed DFS and the key secondary endpoint of OS. To control the type 1 error at $\alpha=0.05$ (two-sided) for the investigator-assessed DFS and OS endpoints, the treatment arms will be compared in a hierarchical fashion as follows (see also [Figure 3](#)):

- Step 1: Investigator-assessed DFS for the Efficacy Analysis population will be evaluated at $\alpha=0.05$ (two-sided).
- Step 2: If the investigator-assessed DFS analysis results are statistically significant, $\alpha=0.05$ will be passed to the analysis of OS (see [Section 6.12.2](#) for more details). If the investigator-assessed DFS results are not statistically significant, formal treatment comparison of OS will not be performed.

Figure 3 Type I Error Control and Analysis Hierarchy



DFS=disease-free survival; OS=overall survival.

6.2.2 Investigator-Assessed Disease-Free Survival

The analysis of the primary endpoint of investigator-assessed DFS in the Efficacy Analysis population will take place when approximately 178 DFS events have occurred (approximately 74% of the expected 240 patients). The estimated number of events required for the analysis is based on the following assumptions:

- Two-sided log-rank test at the 0.05 significance level
- 80% power
- 2:1 randomization ratio (atezolizumab to control)
- Median DFS for the control arm of 4.4 months and estimated median DFS in the atezolizumab arm of 6.9 months (corresponding to a HR of 0.64)
- 10% probability of drop-out by 24 months in each arm

The required number of investigator-assessed DFS events is projected to occur at Month 40 from the time the first patient is randomized. It is projected that an observed HR of 0.73 or lower will result in a statistically significant difference between treatment arms (i.e., the minimally detectable difference at the analysis; this corresponds to an improvement of 1.6 months in median DFS, from 4.4 months in the control arm to 6.0 months in the atezolizumab arm).

6.2.3 Overall Survival

The final analysis of the secondary endpoint of OS will take place when approximately 130 deaths have occurred on the basis of the following assumptions:

- Two-sided log-rank test at the 0.05 significance level
- 60% power
- 2:1 randomization ratio (atezolizumab to control)
- Median OS for the control arm of 15.4 months and estimated median OS in the atezolizumab arm of 23.3 months (corresponding to a HR of 0.66)

- 10% probability of drop-out by 24 months in each arm
- One interim analysis for OS (see Section 6.12.2)

On the basis of these assumptions, the required number of OS events is projected to occur at Month 49 from the time the first patient is randomized. It is projected that an observed HR of 0.688 or lower will result in a statistically significant difference between treatment arms (i.e., the minimally detectable difference at the analysis; this corresponds to an improvement of 7 months in median OS, from 15.4 months in the control arm to 22.4 months in the atezolizumab arm).

6.3 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol deviations including major deviations of inclusion/exclusion criteria, and reasons for discontinuation from the study will be summarized by treatment arm. Enrollment and major protocol deviations will be summarized for the ctDNA-negative and total enrolled populations.

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

6.4 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic variables such as age, sex, and race/ethnicity will be summarized by treatment arm. Demographic variables will be summarized for the ctDNA-negative and total enrolled populations.

Stratification factors (nodal status, tumor stage after cystectomy, PD-L1 IHC status, and time from cystectomy to first ctDNA-positive sample), baseline and disease characteristics (e.g., time since initial diagnosis, time since cystectomy, surgery-related information, type of urinary diversion, ECOG Performance Status, number of lymph nodes resected, and prior NAC) will be summarized by treatment arm and for the ctDNA-negative populations.

Continuous variables will be summarized using means, standard deviations, medians, and ranges. Categorical variables will be summarized by proportions. The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment (or prior to study enrollment for the ctDNA-negative population).

6.5 EFFICACY ANALYSES

Patients will be grouped according to the treatment assigned at randomization. See Section 6.1 for analysis population definitions.

6.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is investigator-assessed DFS, defined as the time from randomization to the first occurrence of a DFS event (see Section 2.1.1 for the definition of a DFS event). Data for patients without a DFS event will be censored at the last date the patient was assessed to be alive and recurrence free. Data for patients with no post-baseline disease assessment will be censored at the randomization date.

DFS will be compared between treatment arms using the stratified log-rank test. The null and alternative hypotheses can be phrased in terms of the survival functions $S_A(t)$ and $S_B(t)$ in Arm A (atezolizumab) and Arm B (placebo), respectively:

$$H_0: S_A(t) = S_B(t) \text{ versus } H_1: S_A(t) \neq S_B(t)$$

The HR, λ_A/λ_B , where λ_A and λ_B represent the hazard of a DFS event in Arm A and Arm B respectively, will be estimated using a stratified Cox regression model with the same stratification variables used for the stratified log-rank test, and the 95% CI will be provided. Results from an unstratified analysis will also be provided. $HR < 1$ indicates treatment benefit in favor of atezolizumab. The stratification factors will include nodal status, tumor stage after cystectomy and PD-L1 IHC status; however, stratification factors may be combined for analysis purposes if necessary to minimize small stratum cell sizes. Combination of stratification factors, if any, would be specified in the Statistical Analysis Plan (SAP) prior to analysis. The stratification factors will be obtained from the IxRS at the time of randomization. Kaplan-Meier methodology will be used to estimate median DFS for each treatment arm; Kaplan-Meier curves will be produced. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median DFS for each treatment arm.

The DFS rate at various timepoints (i.e., every 6 months after randomization) will be estimated by Kaplan-Meier methodology for each treatment arm, and the 95% CI will be calculated using Greenwood's formula. The 95% CI for the difference in rates between the two arms will be estimated using the normal approximation method.

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

Analyses at selected timepoints, described in Section 6.5.3.1

Subgroup analyses, described in Section 6.5.3.2

6.5.2 Secondary Efficacy Endpoints

6.5.2.1 Overall Survival

OS is defined as the time from randomization to death from any cause. Data for patients who have not died at the time of analysis will be censored at the date last known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization.

OS will be analyzed in a hierarchical fashion as described in Section 6.2.1. Methods for comparison of OS between treatment arms will be the same as the methods for treatment comparison for the primary efficacy endpoint of investigator-assessed DFS. A summary of OS by patient subgroups will be provided in the same fashion as for investigator-assessed DFS.

Two analyses of OS are planned (one interim analysis and one final analysis; see Section 6.12.2). The interim analysis of OS will occur at the time that the primary endpoint of DFS is analyzed in the Efficacy Analysis population. The type I error control for OS is described in Section 6.2.1.

6.5.2.2 Independent Review Facility-Assessed Disease-Free Survival

IRF-assessed DFS is defined as the time from randomization to the first occurrence of a DFS event. See Section 2.1.1 for the definition of a DFS event. IRF-assessed DFS will be analyzed in the Efficacy Analysis population. Methods of analysis will be the same as for investigator-assessed DFS (see Section 6.5.1).

6.5.2.3 Disease-Specific Survival

Investigator-assessed DSS is defined as the time from randomization to death from bladder cancer. Data for patients who have not died will be censored at the last date they were known to be alive. Data for patients who died from causes other than bladder cancer will be censored at the date of death. Methods for comparison of DSS between treatment arms will be the same as the methods for treatment comparison for the secondary efficacy endpoint of OS. For the purposes of evaluating DSS, for each patient death, the cause of death will be assessed as related or not related to bladder cancer by the investigator. DSS will be analyzed in the Efficacy Analysis population.

6.5.2.4 Distant Metastasis-Free Survival

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

6.5.2.5 Time to Confirmed Deterioration of Function and Quality of Life

Time to confirmed deterioration of physical and role function is defined as the time from randomization to the first documented confirmed deterioration. A confirmed deterioration is defined as a patient's first ≥ 10 -point score decrease from baseline on the EORTC QLQ C30 physical or role function scale (Osoba et al. 1998), that must be held for at

least two consecutive time points or followed by death attributable to cancer progression (not death from other causes, including adverse events) within 8 weeks from the last PRO assessment. Patients without a confirmed deterioration at the time of clinical data cutoff are censored at the last non missing PRO assessment date (regardless of whether there was deterioration at that time).

Time to confirmed deterioration of HRQoL is defined as the time from randomization to the first documented confirmed deterioration. A confirmed deterioration is defined as a patient's first ≥ 10 -point score decrease from baseline on the EORTC QLQ-C30 GHS/QoL scale, that must be held for at least two consecutive time points or followed by death attributable to cancer progression (not death from other causes, including adverse events) within 8 weeks from the last PRO assessment. Patients without a confirmed deterioration at the time of clinical data cutoff are censored at the last PRO assessment date (regardless of whether there was deterioration at that time).

Additional sensitivity analyses will be performed using time to confirmed deterioration alternative score deterioration thresholds (Cocks et al. 2012). Confirmed physical function deterioration is defined as an initial ≥ 5 -point score decrease from baseline on the PF scale that is held for at least two consecutive time points or followed by death within 8 weeks from the last PRO assessment. Confirmed role function deterioration is defined as an initial ≥ 7 -point score decrease from baseline on the RF scale that is held for at least two consecutive time points or followed by death within 8 weeks from the last PRO assessment. Confirmed QoL deterioration is defined as an initial ≥ 5 -point score decrease from baseline on the QoL/GHS scale that is held for at least two consecutive time points or followed by death within 8 weeks from the last PRO assessment.

Analysis methods for the time to confirmed deterioration endpoints will be the same as those performed for the primary efficacy endpoint. The PRO data will be analyzed in the Efficacy Analysis population.

6.5.2.6 ctDNA Clearance

ctDNA clearance, defined as the proportion of patients ctDNA positive at baseline and ctDNA negative at Cycle 3, Day 1 or Cycle 5, Day 1, will be analyzed in the Efficacy Analysis population. An estimate of the proportion of patients with ctDNA clearance and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. The CI for the difference in the proportion between the two arms will be determined using the normal approximation to the binomial distribution. The proportions will be compared between the two arms with the use of the stratified Cochran-Mantel-Haenszel test. The stratification factors of this analysis will be the same as those described in Section 6.5.1.

6.5.3 Exploratory Efficacy Endpoints

6.5.3.1 Analyses at Selected Timepoints

Analyses at selected timepoints will be performed. The rates of investigator-DFS and OS at various timepoints (i.e., every 6 months after randomization) will be estimated by the Kaplan-Meier methodology for each arm and the 95% CI will be calculated using Greenwood's formula. The 95% CIs for the difference in rates between the two arms will be estimated using the normal approximation method.

6.5.3.2 Subgroup Analyses

To assess the consistency of study results in subgroups defined by demographic and baseline characteristics and stratification factors, efficacy outcomes in patient subgroups will be examined.

Summaries of these endpoints, including unstratified HRs and Kaplan-Meier estimates of the median will be produced separately for each level of the categorical variables.

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

- Age at randomization (<65 years vs. ≥65 years)
- Race
- Sex
- Region
- PD-L1 IHC status (IHC score of IC0/1 vs. IC2/3) (IxRS)
- Number of lymph nodes resected
- Nodal status (positive, negative) (IxRS)
- Tumor stage after surgery (≤(y)pT2 vs. (y)pT3/pT4) (IxRS)
- Prior NAC
- ECOG Performance Status at baseline
- Time from cystectomy to first ctDNA-positive sample (≤20 weeks vs. >20 weeks) and (≤12 months vs. >12 months)

6.5.3.3 Descriptive EORTC QLQ-C30 Summaries

Compliance rates for the EORTC QLQ-C30 in the analysis populations will be calculated as the number of patients who completed the assessment divided by the number of patients expected to complete the assessment at each timepoint for each treatment arm. Reasons for missing assessments, if available, will be summarized using frequencies and percentages.

Descriptive analyses of each EORTC QLQ-C30 scale will include summary statistics (mean, standard deviation, median, interquartile range, minimum, maximum) of scores and score changes from baseline at each assessment timepoint by treatment arm.

Graphs of mean scores and/or score changes from baseline along with two-sided 95% CIs may be presented.

The CDF plots of mean score change from baseline to Cycle 7 by treatment arm will be presented for the EORTC QLQ-C30 physical function, role function, and GHS/QoL scales.

6.5.3.4 Efficacy of ctDNA-Negative Population

Exploratory analyses of investigator-assessed DFS and OS will be performed for descriptive purpose for the ctDNA-negative population. The statistical details for the analysis will be documented in the SAP.

6.6 SAFETY ANALYSES

Safety analyses will include all randomized patients who received at least one dose of study treatment (atezolizumab or placebo). Patients will be grouped by the study treatment received.

Exposure to study treatment and length of safety follow-up will be summarized by arm with descriptive statistics.

Verbatim descriptions of adverse events will be mapped to MedDRA terms. Treatment-emergent events (defined as events occurring on or after the first dose of atezolizumab or placebo) will be summarized by MedDRA term, appropriate MedDRA levels, and NCI CTCAE v5.0 grade. For each patient, the maximum severity reported will be used in the summaries. Adverse events will be summarized regardless of relationship to study drug as assessed by the investigator. All adverse events, adverse events leading to discontinuation of study treatment, adverse events leading to dose interruption, Grade 3–4 adverse events, adverse events leading to death, serious adverse events, and adverse events of special interest will be summarized. Deaths and cause of death will be summarized.

Changes in NCI CTCAE v5.0 grade for selected laboratory tests will be tabulated by arm. Changes in selected vital signs will be summarized. The ADA results will be summarized and listed by patient for atezolizumab-treated patients.

Patient-reported overall adverse event burden, as measured by the EORTC IL46 item, will be summarized descriptively at each assessment timepoint. The number and percentage of patients reporting each response option ("Not at all" to "Very much") to the item and the change from baseline by response option will be summarized at each assessment timepoint by treatment arm. The distribution of responses and/or change from baseline will be illustrated by stacked bar charts for each 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 (see [Appendix 2](#)). Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate. Exposure by ADA status will also be summarized.

Additional PK and pharmacodynamic analyses will be conducted as appropriate.

6.8 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by treatment group. When determining post-baseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The evaluation of PK, efficacy and safety endpoints by ADA status may be analyzed and reported via descriptive statistics.

6.9 BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with study drug response, including efficacy and/or adverse events. Planned analyses of biomarkers in this study will be described separately in a BAP. These results may be reported separately from the CSR.

6.10 EXPLORATORY PATIENT-REPORTED OUTCOME ANALYSES

Descriptive score summaries of symptoms, function, and QoL, as measured by the EORTC QLQC30, will be examined for patients in the Surveillance Phase as follows:

For patients who remain ctDNA negative at all timepoints tested

Before and after ctDNA-positivity for patients who are ctDNA positive

These results may be reported separately from the CSR.

6.11 HEALTH STATUS UTILITY ANALYSES

Health utility data from the EQ-5D-5L will be evaluated in pharmacoeconomic models. Results from health economic data analyses will be reported separately from the CSR.

6.12 INTERIM ANALYSES

6.12.1 Disease-Free Survival

No interim efficacy analyses of investigator-assessed DFS are planned in any analysis population.

6.12.2 Overall Survival

A total of two analyses of OS will be performed by the Sponsor (one interim analysis and one final analysis).

The boundaries for statistical significance at the interim and final OS analyses will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming use function (Lan and DeMets 1983). The projected p-value boundaries for statistical significance stated below are based on the number of projected events; the actual boundary p-values will be calculated at the time of analysis based on the actual number of events observed.

The final analysis of OS will be performed when approximately 130 deaths have occurred (see Section 6.2.3). If 130 deaths have occurred at the final analysis, statistical significance will be declared if $p \leq 0.0441$ (two-sided).

One interim analysis of OS will be performed at the time of the planned analysis of investigator-assessed DFS in the Efficacy Analysis population. Based on the OS assumptions in Section 6.2.3, it is projected that approximately 98 deaths will have occurred at the interim analysis of OS, which corresponds to approximately 75% of the 130 deaths required for the final analysis of OS. If 98 deaths have occurred at this analysis, statistical significance will be declared if $p \leq 0.0197$ (two-sided); an observed HR of 0.607 or lower will result in a statistically significant difference between treatment arms at this analysis.

However, if there are less than 91 deaths observed at the time of the DFS analysis, this OS interim analysis will be considered as descriptive with only an administrative alpha spend of 0.0001 and OS will be formally tested only at the final analysis.

An iDMC will be convened to evaluate safety results at periodic intervals until the analysis of the primary endpoint (see Section 3.1.2). *As of the date of the primary analysis, the iDMC support for safety review activities has been terminated.*

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

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

Imaging data will be transferred electronically from the site to the IRF in a pseudonymized non-proprietary DICOM®/video/other format.

Imaging data will be transferred electronically from the IRF to the Sponsor at the end of the trial for data retention in a pseudonymized, annotated and non-proprietary DICOM®/Video/ or other format.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, 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 and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, medication inventory records, and images must be retained by the Principal Investigator for 15 years after completion or discontinuation of

the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

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

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

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

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

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

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 (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

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

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

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

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

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

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted CSRs and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

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

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 205 sites globally will participate to enroll up to 800 patients and randomize approximately 240 patients. Screening and enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will monitor and evaluate patient safety throughout the study on the basis of analyses provided by an iDCC. Tumor response and progression will be evaluated by an IRF. *As of the date of the primary analysis, the iDMC support for safety review activities has been terminated.*

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted CSRs and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

<https://www.roche.com/innovation/process/clinical-trials/data-sharing/>

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

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

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

10. **REFERENCES**

- Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365–76.
- Abol-Enein H, El-Mekresh M, El-Baz M, et al. Neo-adjuvant chemotherapy in the treatment of invasive transitional bladder cancer: a controlled prospective randomised study. *Br J Urol* 1997;79(Suppl 4):174.
- Advanced Bladder Cancer Meta-Analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Lancet* 2003;361:1927–34.
- American Cancer Society. Bladder cancer [resource on the Internet].2020 [cited: 25 August 2020]. Available from: <http://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-key-statistics>.
- Amin MB, Edge SB, Greene FL, et al. *AJCC cancer staging manual*. 8th ed. New York: Springer, 2016.
- Balar AV, Galsky MD, Rosenberg JE et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet* 2017;389:67–76.
- Bajorin, DF, Witjes, JA, Gschwend, JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *New Engl J Med* 2021;384:2102–14.
- Bellmunt J, Hussain M, Gschwend JE, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. *Lancet* 2021;22:525–37.
- 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.
- Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015;373:1627–39.
- Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37:53–72.
- Butte MJ, Keir ME, Phamduy TB. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. *Immunity* 2007;27:111–22.

- Chalasani V, Chin JL, Izawa JI. Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. *Can Urol Assoc J* 2009;3(Suppl 4):S193–8.
- Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. *Clin Cancer Res* 2012;18:6580–7.
- Christensen E, Birkenkamp-Demtröder K, Sethi H, et al. Early detection of metastatic relapse and monitoring of therapeutic efficacy by ultra-deep sequencing of plasma cell-free DNA in patients with urothelial bladder carcinoma. *J Clin Oncol* 2019;37:1547–57.
- Cognetti F, Ruggeri EM, Felici A, et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. *Ann Oncol* 2012;23:695–700.
- Cocks K, King MT, Velikova G et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Eur J Cancer* 2012;48:1713–21.
- Dash A, Galsky MD, Vickers AJ, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. *Cancer* 2006;107:506–13.
- David KA, Milowsky MI, Ritchey J. Low incidence of perioperative chemotherapy for stage III bladder cancer 1998 to 2003: a report from the National Cancer Data Base. *J Urol* 2007;178:451–4.
- De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II results of EORTC study 30986. *J Clin Oncol* 2009;27:5634–9.
- Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. *MAbs* 2016;8:593–603.
- Duplissea JJ, Mason RJ, Reichard CA, et al. Trends and disparities in the use of neoadjuvant chemotherapy for muscle-invasive urothelial carcinoma. *Can Urol Assoc J* 2019;13:24–8.
- [EAU] European Association of Urology muscle-invasive and metastatic bladder cancer [MIBC] 2020 guidelines [resource on the Internet]. 2020 [cited: 25 August 2020]. Available from: <https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/>.

[EAU] European Association of Urology Muscle-invasive and metastatic bladder cancer [MIBC] 2020 guidelines [resource on the Internet]. 2022 [cited 23 January 2023]. Available from: <https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/>.

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.

Fehrenbacher L, Spira A. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016;387:1837–46.

Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer* 2018;103:356–87.

Ferlay J, Colombet M, Soerjomataram I, et al. Global and Regional Estimates of the Incidence and Mortality for 38 Cancers: GLOBOCAN 2018. *Ca Cancer J Clin* 2018;68:394–424.

Fitzsimmons D, Johnson CD, George S, et al. Development of a disease-specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. *Eur J Cancer* 1999;35:939–41.

Frebel H, Nindl V, Schuepbach RA, et al. Programmed death 1 protects from fatal circulatory failure during systemic virus infection of mice. *J Exp Med* 2012;209:2485–99.

Gandara DR, Paul SM, Kowanetz M, et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. *Nat Med*. 2018;24:1441–8.

Garcia-Murillas I, Chopra N, Comino-Méndez I, et al. Assessment of molecular relapse detection in early-stage breast cancer [published correction appears in *JAMA Oncol*. *JAMA Oncol* 2019;5:1473–8.

Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003;349:859–66.

Gschwend JE, Dahm P, Fair WR. Disease specific survival as endpoint of outcome for bladder cancer patients following radical cystectomy. *Eur Urol* 2002;41:440–8.

Hautmann RE, de Petroni RC, Pfeiffer C, et al. Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. *Eur Urol* 2012;61:1039–47.

Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol* 1971 44:793–7.

- Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016;387:1540–50.
- Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody atezolizumab in cancer patients. *Nature* 2014;515:563–7.
- Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727–36.
- 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.
- Hussain MHA, Powles T, Albers P, et al. IMvigor010: Primary analysis from a phase III randomized study of adjuvant atezolizumab (atezo) versus observation (obs) in high-risk muscle-invasive urothelial carcinoma (MIUC). *J Clin Oncol* 2020;38(Suppl 15):5000.
- International Bladder Cancer Nomogram Consortium, Bochner BH, Kattan MW, et al. Postoperative nomogram predicting risk of recurrence after radical cystectomy for bladder cancer. *J Clin Oncol* 2006;24:3967–72.
- Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013;22:1717–27.
- Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363:411–22.
- Kaufman DS, Shipley WU, Feldman AS. Bladder cancer. *Lancet* 2009;374:239–49.
- Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. *Annual Rev Immunol* 2008;26:677–704.
- Lamy P, Nordentoft I, Birkenkamp-Demtröder K, et al. paired exome analysis reveals clonal evolution and potential therapeutic targets in urothelial carcinoma. *Cancer Res* 2016;76:5894.
- Lan KKG and DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;70:659–63.
- Leow JJ, Chong KT, Chang SL, et al. Upper tract urothelial carcinoma: a different disease entity in terms of management. *ESMO Open* 2017;1:e000126.
- Lewis GD, Haque W, Verma V, et al. The role of adjuvant radiation therapy in locally advanced bladder cancer. *Bladder Cancer* 2018;26;4:205–13.
- Lotan Y, Gupta A, Shariat SF, et al. Lymphovascular invasion is independently associated with overall survival, cause-specific survival and local and distant recurrence in patients with negative lymph nodes at radical cystectomy. *J Clin Oncol* 2005;23:6533–9.

- Madersbacher S, Hochreiter F, Burkhard F, et al. Radical cystectomy for bladder cancer today—a homogeneous series without neoadjuvant therapy. *J Clin Oncol* 2003;21:690–6.
- McConkey DJ, Choi W. Molecular subtypes of bladder cancer. *Curr Oncol Rep* 2018;20:77.
- Meeks JJ, Bellmunt J, Bochner BH, et al. A systematic review of neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer. *Eur Urol* 2012;62:523–33.
- Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol* 2020;20:355–62.
- Miles BJ, Fairey AS, Eliasziw M, et al. Referral and treatment rates of neoadjuvant chemotherapy in muscle-invasive bladder cancer before and after publication of a clinical practice guideline. *Can Urol Assoc J* 2010;4:263–7.
- Moding EJ, Diehn M, Wakelee HA. Circulating tumor DNA testing in advanced non-small cell lung cancer. *Lung Cancer*. 2018;119:42–7.
- Mok T, Wu YL, Lee JS, et al. Detection and dynamic changes of EGFR mutations from circulating tumor DNA as a predictor of survival outcomes in NSCLC patients treated with first-line intercalated erlotinib and chemotherapy. *Clin Cancer Res* 2015;21:3196–203.
- Nadal R, Apolo AB. Overview of current and future adjuvant therapy for muscle-invasive urothelial carcinoma. *Curr Treat Options Oncol* 2018;28;19:36.
- [NCCN] National Comprehensive Cancer Network®. NCCN clinical practice guidelines in oncology (NCCN guidelines®). Bladder cancer, Version 1.2019 [resource on the Internet]. 2019 [cited: 27 November 2019]. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx.
- [NCCN] National Comprehensive Cancer Network. Recommendations of the NCCN COVID-19 Vaccination Advisory Committee [resource on the Internet]. 2021 [cited: 28 May 2021]. Available from: https://www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v2-0.pdf?sfvrsn=b483da2b_2
- [NCCN] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines®). Bladder cancer, Version 3.2022 [resource on the Internet]. 2022 [cited: 23 January 2023]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.
- Nordentoft I, Lamy P, Birkenkamp-Demtröder K, et al. Mutational context and diverse clonal development in early and late bladder cancer. *Cell Rep* 2014;7:1649–63.

Opdivo® (nivolumab) Summary of Product Characteristics, Bristol-Myers Squibb Pharma EEIG. 7 December 2022 [cited: 23 January 2023]. Available from: https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf.

Opdivo® (nivolumab) U.S. Package Insert, Bristol-Myers Squibb Co. March 2022. [cited: 23 January 2023]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125554s112lbl.pdf.

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.

Paz-Ares LG, Solsona E, Esteban E, et al. Randomized phase III trial comparing adjuvant paclitaxel/gemcitabine/cisplatin (PGC) to observation in patients with resected invasive bladder cancer: results of the Spanish Oncology Genitourinary Group (SOGUG) 99/01 study [abstract LBA4518]. *J Clin Oncol* 2010;28(Suppl 18):LBA4518.

Pearman TP, Beaumont JL, Mroczek D, et al. Validity and usefulness of a single-item measure of patient-reported bother from side effects of cancer therapy. *Cancer* 2018;124:991–7.

Petrelli F, Coinu A, Cabiddu M, et al. Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy: a meta-analysis. *Eur Urol* 2014;65:350–7.

Porter MP, Kerrigan MC, Donato BM, et al. Patterns of use of systemic chemotherapy for Medicare beneficiaries with urothelial bladder cancer. *Urol Oncol* 2011;29:252–8.

Powles T, Assaf ZJ, Davarpanah N, et al. Clinical outcomes in post-operative ctDNA-positive muscle-invasive urothelial carcinoma (MIUC) patients after atezolizumab adjuvant therapy [abstract]. *Ann Oncol* 2020 ;31(Suppl 7) :S1417–24.

Powles, T, Assaf ZJ, Davarpanah, N, et al. ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. *Nature* 2021;595:432–7.

Powles T, Bellmunt J, Comperat E, et al. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2022;33:244–58.

Ptashkin RN, Mandelker DL, Coombs CC, et al. Prevalence of clonal hematopoiesis mutations in tumor-only clinical genomic profiling of solid tumors [published correction appears in *JAMA Oncol* 2019; 5:122]. *JAMA Oncol* 2018;4:1589–93.

Raghavan D, Shipley WU, Garnick MB, et al. Biology and management of bladder cancer. *N Engl J Med* 1990;322:1129–38.

Raj GV, Karavadia S, Schlomer B. Contemporary use of perioperative cisplatin-based chemotherapy in patients with muscle-invasive bladder cancer. *Cancer* 2011;117:276–82.

- Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* 2016;387:1909–20.
- Rosenblatt R, Sherif A, Rintala E, et al. Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. *Eur Urol* 2012;61:1229–38.
- Shariat SF, Karakiewicz PI, Palapattu GS, et al. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. *J Urol* 2006;176:2414–22.
- [SITC] Society for Immunotherapy of Cancer. SITC statement on SARS-CoV-2 vaccination and cancer immunotherapy [press release on the Internet]. 23 December 2020 [cited: 28 May 2021]. Available from: <https://www.sitcancer.org/aboutsitc/press-releases/2020/sitc-statement-sars-cov-2-vaccination-cancer-immunotherapy>.
- Skinner D, Daniels J, Russell C, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. *J Urol* 1991;145:459–67.
- Snyder A, Morrissey MP, Hellmann MD. Use of circulating tumor DNA for cancer immunotherapy. *Clin Cancer Res* 2019;25:6909–15.
- 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.
- Stadler WM, Lerner SP, Groshen S, et al. Phase III study of molecularly targeted adjuvant therapy in locally advanced urothelial cancer of the bladder based on p53 status. *J Clin Oncol* 2011;29:3443–9.
- Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001;19:666–75.
- Stenzl A, Cowan NC, De Santis M, et al. The updated EAU guidelines on muscle-invasive and metastatic bladder cancer. *Eur Urol* 2009;55:815–25.
- Sternberg CN, Sylvester R. Thoughts on a systematic review and meta-analysis of adjuvant chemotherapy in muscle-invasive bladder cancer. *Eur Urol* 2014;66:55–6.
- Sternberg CN, Skoneczna I, Kerst JM, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. *Lancet Oncol* 2015;16:76–86.

- Stöckle M, Meyenburg W, Wellek S, et al. Advanced bladder cancer (stages pT3b, pT4a, pN1 and pN2): improved survival after radical cystectomy and 3 adjuvant cycles of chemotherapy. Results of a controlled prospective study. *J Urol* 1992;148:302–6.
- Szabados B, Kockx M, Assaf ZJ, et al. Final results of neoadjuvant atezolizumab in cisplatin-ineligible patients with muscle-invasive urothelial cancer of the bladder. *Eur Urol* 2022;82:212–22.
- Thomsen MBH, Nordentoft I, Lamy P, et al. Comprehensive multiregional analysis of molecular heterogeneity in bladder cancer. *Sci Rep* 2017;7:11702.
- Tie J, Wang Y, Tomasetti C, et al. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. *Sci Transl Med* 2016;8:346ra92.
- Tilki D, Reich O, Karakiewicz P, et al. Validation of the AJCC TNM substaging of pT2 bladder cancer: deep muscle invasion is associated with significantly worse outcome. *Eur Urol* 2010;58:112–7.
- Todenhöfer T, Struss WJ, Seiler R, et al. Liquid biopsy-analysis of circulating tumor DNA (ctDNA) in bladder cancer. *Bladder Cancer* 2018;4:19–29.
- 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.
- Vale CL. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data. Advanced Bladder Cancer (ABC) Meta-Analysis Collaboration. *Eur Urol* 2005;48:189–201.
- Volkmer BG, Kuefer R, Bartsch GC Jr, et al. Oncological followup after radical cystectomy for bladder cancer-is there any benefit? *J Urol* 2009;181:1587–93.
- 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.
- World Health Organization. Bladder fact sheet. GLOBOCAN 2018 [resource on the Internet]. 2019 [cited: 28 September 2020]. Available from: <https://gco.iarc.fr/today/data/factsheets/cancers/30-Bladder-fact-sheet.pdf>.
- Yang J, Riella LV, Chock S, et al. 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 Activities: Prescreening and Surveillance Phases

	Screening ^a	Surveillance Phase ^{b, c}	Surveillance Follow-Up ^d	
Study Procedures	Cystectomy date to Surveillance Enrollment date	Week 6 to Week 48 visits (Year 1)	Years 2–3	Years 4–5
Prescreening and Surveillance Informed Consents ^e	Prior to any study-related procedures			
Shipment of surgical tumor tissue sample for WES, PD-L1 analysis, and exploratory biomarkers ^{f, g}	As soon as possible following cystectomy. It is strongly recommended to ship samples no later than 18 weeks post cystectomy. ^h			
Post-surgery matched blood sample collections for WES ^g	As soon as possible following cystectomy. It is strongly recommended to ship samples no later than 18 weeks post cystectomy. ^h			

Appendix 1: Schedule of Activities: Prescreening and Surveillance Phases

	Screening ^a	Surveillance Phase ^{b, c}	Surveillance Follow-Up ^d	
Study Procedures	Cystectomy date to Surveillance Enrollment date	Week 6 to Week 48 visits (Year 1)	Years 2–3	Years 4–5
Blood collection for plasma for ctDNA testing ^{h, i, j}	Within 42 days prior to Surveillance enrollment date (minimum 6 weeks after cystectomy)	Blood collection will start on or before enrollment date into the Surveillance Phase and then occur every 6 weeks (± 5 days) from the date the first blood collection for ctDNA testing until 36 weeks from the date of the patient's cystectomy have passed. After the latest blood collection prior to 36 weeks from cystectomy has been reached, blood collection should follow the surveillance imaging schedule going forward. ⁱ		
Blood collection for plasma for exploratory biomarkers ^{h, i, j}	On or before Surveillance enrollment date, ideally at the same time as plasma collection for ctDNA testing	Blood collection will start on or before enrollment date into the Surveillance Phase and then occur every 6 weeks (± 5 days) from the date of first blood collection for ctDNA testing until 36 weeks from the date of the patient's cystectomy have passed. After the latest blood collection prior to 36 weeks from cystectomy has been reached, blood collection should follow the surveillance imaging schedule going forward.		
Medical, surgical, and cancer histories, including baseline conditions and demographic data ^k	Within 42 days prior to Surveillance enrollment date			
ECOG Performance Status	Within 42 days prior to Surveillance enrollment date			

Appendix 1: Schedule of Activities: Prescreening and Surveillance Phases

	Screening ^a	Surveillance Phase ^{b, c}	Surveillance Follow-Up ^d	
Study Procedures	Cystectomy date to Surveillance Enrollment date	Week 6 to Week 48 visits (Year 1)	Years 2–3	Years 4–5
Weight	Within 42 days prior to Surveillance enrollment date			
Height	Within 42 days prior to Surveillance enrollment date			
Complete physical examination ⁱ	Within 42 days prior to Surveillance enrollment date			
Patient-reported outcomes ^m		Surveillance assessments are to be conducted on the same schedule as ctDNA testing.		
HIV, HCV, HBV serology, tuberculosis test ⁿ	Within 3 months prior to Surveillance enrollment date			
Pregnancy test ^o	Within 42 days prior to Surveillance enrollment date			
Blood sample for RBR (optional) ^{p, q}		x		

Appendix 1: Schedule of Activities: Prescreening and Surveillance Phases

Study Procedures	Screening ^a	Surveillance Phase ^{b, c}	Surveillance Follow-Up ^d	
	Cystectomy date to Surveillance Enrollment date	Week 6 to Week 48 visits (Year 1)	Years 2–3	Years 4–5
Assessments for UC recurrence ^r	Within 28 days of Surveillance enrollment date	Surveillance imaging for the Surveillance Phase will be performed every 12 weeks (± 10 days) from the date of Week 0 until Week 48 or until 12 months from the date of cystectomy have passed, whichever occurs first.	Imaging will be performed every 6 months (± 10 days) for 2 years following final surveillance scan (4 scans) or until death, investigator assessed unequivocal radiographic evidence of disease recurrence, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.	
Concomitant medications ^s	x	x	x	
Adverse events ^t	x	x	x	x ^u
Survival follow-up ^v			x	x

ctDNA = circulating tumor DNA; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; HBV = hepatitis B virus; HCV = hepatitis C virus; IxRS = interactive voice or web-based response system; MRI = magnetic resonance imaging; QLQ-C30 = Quality of Life–Core 30 Questionnaire; RBR = Research Biosample Repository; UC = urothelial carcinoma; WES = whole exome sequencing.

^a Screening activities should be scheduled with the intent to minimize the time between cystectomy and surveillance enrollment because it is in the patient's best interest to begin disease monitoring as soon as possible. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 42 days prior to enrollment may be used; such tests do not need to be repeated for surveillance screening.

Appendix 1: Schedule of Activities: Prescreening and Surveillance Phases

- ^b The date of the first blood collection for plasma ctDNA to determine presence of ctDNA in the patients' blood will be collected during prescreening and/or surveillance screening and will mark the anchor point to calculate the date of blood collection for subsequent visit schedule in the Surveillance Phase. The date the patient has moved to surveillance in IxRS (IxRS transaction date) will mark the entrance into the Surveillance Phase and must be at least 6 weeks post-cystectomy and within 24 weeks from the date of cystectomy. Patients enrolled in the Surveillance Phase will undergo blood collection for plasma ctDNA testing and surveillance imaging for tumor recurrence. Surveillance visits are to be conducted every 6 weeks from the date of surveillance visit Week 0 until 36 weeks after cystectomy have elapsed and then every 12 weeks thereafter until 12 months from date of cystectomy. After the latest surveillance visit prior to 36 weeks from cystectomy has been reached, surveillance visits for blood collection should follow the surveillance imaging schedule going forward. Patients enrolled more than 24 weeks after surgery are not eligible for the study. Please refer to the plasma collection and UC recurrence assessment schedules for details on when surveillance visits should occur.
- ^c Patients with a ctDNA positive plasma sample will complete the Surveillance Phase and enter the Treatment Phase of the study provided that they have fully recovered from cystectomy and that there is no evidence of disease recurrence on imaging within 28 days of randomization. Refer to [Appendix 2](#) for the Treatment Phase schedule of activities. Patients who remain ctDNA negative until Week 48 or until 12 months from the date of cystectomy have passed, whichever occurs first, should proceed to the surveillance follow-up phase. *Patients who previously were discontinued from the Surveillance Phase as a result of experiencing investigator-assessed disease recurrence may be contacted to request consent for survival follow-up.*
- ^d Patients who remain ctDNA negative at 12 months from the date of cystectomy will not be enrolled in the Treatment Phase and will enter a 4-year surveillance follow-up period. During this time, follow-up assessments for tumor recurrence will be performed every 6 months (± 10 days) for the first 2 years (4 scans). After the final follow-up scan, survival information will be collected by telephone or site visit every 6 months (± 2 months) for an additional 2 years. *Patients who previously were discontinued from the Surveillance Phase as a result of experiencing investigator-assessed disease recurrence may be contacted to request consent for survival follow-up. For such patients who provide consent, survival status should be assessed as soon as feasible after consent is obtained. Thereafter, survival information will be collected by medical records, telephone or office visit every 6 months (± 2 months) to complete the 4-year surveillance follow-up period, until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. The date of disease recurrence should be used as the anchor point to calculate the 4-year window.*
- ^e Prescreening and Surveillance Informed Consent Forms must be completed and signed before any study-specific procedure is performed. The timing of Informed Consent Form signature is at the discretion of the site, but it is preferred to have the Prescreening and Surveillance Informed Consent Forms signed at the same time at the patient's and/or site staff convenience.
- ^f Tumor tissue from radical cystectomy 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 or unable to undergo WES [ctDNA assay designability]). Matched blood WES specimen should be submitted with tumor tissue from radical cystectomy.
- ^g Sample analysis may also include exploratory biomarker research including biomarker assay development.

Appendix 1: Schedule of Activities: Prescreening and Surveillance Phases

- ^h Retrieval and submission of tumor sample and matched blood sample should occur as soon as possible after signing the Prescreening Informed Consent Form to allow sufficient time for development of the WES assay (ctDNA assay designability) so that results can be received and patients enrolled within the protocol-defined eligibility window.
- ⁱ Patients enrolled in the surveillance run-in phase will continue plasma collection for ctDNA testing and exploratory biomarkers. The date of the first blood collection for plasma ctDNA to determine presence of ctDNA in the patients' blood will occur prior to enrollment into the Surveillance Phase and then occur every 6 weeks (± 5 days) from the date the first blood collection for ctDNA testing until 36 weeks from the date of the patient's cystectomy have passed. After the latest blood collection prior to 36 weeks from cystectomy has been reached, blood collection should follow the surveillance imaging schedule going forward. The date the patient has moved to Surveillance Phase (date of IxRS transaction) will be used as date of enrollment into surveillance, after meeting all inclusion/exclusion criteria for Surveillance Phase. The date of first blood collection for plasma ctDNA testing will be used as an anchor point to calculate the date of blood collection of subsequent visits in the Surveillance Phase. Patients will enter the Treatment Phase of the study at the first plasma sample that is ctDNA positive.
Based on the testing frequency, a patient's last scheduled ctDNA test will occur anywhere between 42 and 52 weeks from cystectomy. Patients whose last scheduled ctDNA test occurs more than 4 weeks prior to surveillance completion may have an optional unscheduled ctDNA test performed before the 12 months are complete.
- ^j Surveillance Informed Consent Form has to be signed prior to week 0 plasma ctDNA blood collection.
- ^k Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Inclusion and exclusion criteria as defined in Sections 4.1.1.1, 4.1.2.1, and 4.1.2.2 will be reviewed to confirm the eligibility of the patient for the Surveillance phase. Demographic information includes sex, age, and self-reported race or ethnicity.
- ^l Complete physical examination is defined in Section 4.5.3.
- ^m During the Surveillance Phase, patients will complete the EORTC QLQ-C30 and EQ-5D-5L questionnaires at the clinic or over the telephone at the same schedule as for blood collection for ctDNA testing.
- ⁿ See Section 4.5.6 for serology tests. HIV testing is required to verify patient's eligibility for the study. HIV testing should be performed in accordance with national and/or institutional guidelines. Patients with a positive HIV result are eligible provided they have a CD4 count $\geq 200/\mu\text{L}$ and an undetectable viral load. HBV DNA must be collected before enrollment in patients who have negative serology for hepatitis B surface antigen and positive serology for anti-HBc. Investigators may perform tuberculosis test within 3 months prior to enrollment to avoid the inclusion of any patient with active disease prior to treatment.
- ^o Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 42 days prior to enrollment.
- ^p Blood will be collected from patients who have consented to optional RBR sampling. However, if the RBR blood sample is not collected during the scheduled visit, it may be collected as soon as possible during the conduct of the clinical study.
- ^q Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

Appendix 1: Schedule of Activities: Prescreening and Surveillance Phases

- ^r Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of enrollment do not have to be repeated at screening. Screening assessments must include CT scans with IV and oral contrast (oral contrast can be omitted depending on local practice) or MRI of the chest, abdomen, and pelvis at screening for the Surveillance Phase. Surveillance for tumor recurrence must include physical examination and imaging studies of the chest, abdomen, upper urinary tracts, and pelvis. Other examinations such as laboratory or urine cytology should be performed as clinically indicated. Physical examination for the purposes of evaluating tumor recurrence may be performed as per the local standard of care evaluations for tumor surveillance and may differ from the complete and/or limited physical examinations performed at screening. Eligibility into the Surveillance Phase will be based on investigator review of imaging data, as well as any historical scans that may support the interpretation of benign radiographic objects. Baseline imaging for determining eligibility into the Surveillance Phase may begin after the patient has signed the Prescreening Informed Consent Form.
- ^s Concomitant medications include any prescription medications or over-the-counter medications. The medications related to those specific serious adverse events reportable during surveillance (Section 5.3.1) will be reported on the Concomitant Medication Form. Any known medical history will be reported at the screening visit of the Surveillance Phase and the related concomitant medications will be reported on the Concomitant Medication Form. *Concomitant medications only need to be reported during surveillance follow-up if they are related to an unresolved AE that occurred during surveillance.*
- ^t After informed consent has been obtained for the prescreening and Surveillance Phase but prior to the first study drug infusion in the Treatment Phase, only serious adverse events caused by a protocol-mandated intervention and serious adverse events considered related to Signatera™ (Natera, Inc.) assay (including any device-related procedures) should be reported immediately (i.e., no more than 24 hours after the investigator becomes aware of the event). In addition, non-serious adverse events considered related to Signatera™ (Natera, Inc.) assay (including any device-related procedures and adverse events that may be a consequence of device deficiencies) should be reported within 5 days after the investigator becomes aware of the event. Patients who experience a serious adverse event caused by a protocol-mandated intervention will be followed for safety until their last surveillance or surveillance follow-up visit. 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 caused by a protocol-mandated intervention until a final outcome can be reported.
- ^u Adverse events will be recorded until 30 days after the last surveillance follow-up visit at Year 3, *which corresponds to the beginning of Year 4.*
- ^v Survival follow-up information will be recorded via telephone calls, patient medical records, and/or clinic visits approximately every 6 months (± 2 months) *from the date of disease recurrence* for 2 years to complete 4 years of total follow up after the final surveillance assessment or until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. 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. 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

Schedule of Activities: Treatment Phase

	Arm A (Atezolizumab) and Arm B (Placebo) ^a			
	Screening ^b	Treatment Cycles (28-day cycles)	Treatment Follow-Up	
	Days – 28 to – 1	Day 1 (± 3 Days for Cycles ≥ 2)	Discontinuation ^c ≤ 30 Days after Final Dose	Follow-Up
Signed Informed Consent Form ^d	x			
Medical history, prior and on-going medications ^e	x			
Patient-reported outcomes ^f		<i>No longer collected from Protocol Version 10 onwards</i>		
Vital signs ^g	x	x	x	
Weight	x	x	x	
Complete physical examination ^h	x		x	
Limited physical examination ⁱ		x ^j		
ECOG Performance Status	x	x ^j	x	
12-Lead ECG ^k	x	As clinically indicated		
Hematology ^l	x ^m	x ^j	x	
Chemistry ⁿ	x ^m	x ^j	x	
Pregnancy test ^p	x ^m	x ^{j, p}	x	
Coagulation panel (aPTT, INR)	x ^m		x	
TSH, free T3 (or total T3), free T4 ^q	x	x ^j	x	
Auto-antibody testing ^r		x		
Urinalysis ^s	x	As clinically indicated	x	
HIV, HCV, HBV serology ^t	Within 2 months			
Tuberculosis test ^t	Within 3 months			

Appendix 2: Schedule of Activities: Treatment Phase

	Arm A (Atezolizumab) and Arm B (Placebo) ^a			
	Screening ^b	Treatment Cycles (28-day cycles)	Treatment Follow-Up	
	Days – 28 to – 1	Day 1 (± 3 Days for Cycles ≥ 2)	Discontinuation ^c ≤ 30 Days after Final Dose	Follow-Up
Serum sample for ADA assessment		<i>From Protocol Version 10 onwards, these samples are no longer to be collected.</i>		
Serum sample for PK sampling		<i>From Protocol Version 10 onwards, these samples are no longer to be collected.</i>		
Blood and urine samples for exploratory biomarkers		<i>See Section 4.5.6 and Appendix 5. From Protocol Version 10 onwards, only the biomarker sample collection at disease recurrence is required.</i>		
Tumor biopsy ^u		At the time of radiographic confirmation of disease recurrence		
Tumor assessments for UC recurrence ^v	x ^w	Every 9 weeks following randomization (± 7 days; at approximately every three cycles) in the first 2 years; every 12 weeks (± 10 days) for Year 3; and every 24 weeks for Years 4 and 5 (± 10 days); and at Year 6 (± 10 days), until death, unequivocal radiographic evidence of disease recurrence, loss to follow-up, end of Year 6, withdrawal of consent, or study termination by the Sponsor ^w		
Blood for plasma ctDNA testing ^x		<i>See Section 4.5.6 and Appendix 5. From Protocol Version 10 onwards, these samples are no longer to be collected; only the blood for plasma ctDNA sample collection at disease recurrence is required.</i>		
Concomitant medications ^y	x	x	x	
Adverse events ^z	x	x	x	
Study drug administration ^{aa}		x		
Survival follow-up and anti-cancer treatment				x ^{bb}

ADA=anti-drug antibody; C=cycle; C1D1=Cycle 1 Day 1; CT=computed tomography; ctDNA=circulating tumor DNA; D=day; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-5L=EuroQol 5-Dimension, 5-Level Questionnaire; HBV=hepatitis B virus; HCV=hepatitis C virus; HRQoL=health-related quality of life; IHC=immunohistochemistry; IL46=item library 46; MRI=magnetic resonance imaging; PK=pharmacokinetic; PRO=patient-reported outcome; QLQ-C30=Quality of Life–Core 30 Questionnaire; RBR=Research Biosample Repository; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; UC=urothelial carcinoma.

Appendix 2: Schedule of Activities: Treatment Phase

- ^a *At any time during the study, patients may choose to withdraw consent for specific protocol-mandated assessments without fully withdrawing from the study. In this situation, the specific assessments that the patient agrees to participate in should be documented in the source documents. The study staff may use medical records to obtain information about health status and non-protocol anti-cancer therapies for patients who choose to partially withdraw consent unless the patient specifically withdraws consent for this activity. If a patient requests to be fully withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced. If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.*
- ^b Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to C1D1 may be used (except where otherwise specified); such tests do not need to be repeated for screening.
- ^c Patients who discontinue or complete 12 cycles or 1 year of study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the final dose of study treatment. The visit at which response assessment shows recurrent or progressive disease may be used as the treatment discontinuation visit.
- ^d Treatment informed consent must be documented before any Treatment Phase-specific screening procedure is performed and may be obtained more than 28 days before.
- ^e Inclusion and exclusion criteria for the Treatment Phase as described in Sections 4.1.1.2, 4.1.2.3, and 4.1.2.4 will be reviewed to confirm the eligibility of the patient.
- ^f The PRO instruments (EORTC QLQ-C30, EORTC IL46, EQ-5D-5L) will be completed by the patients at the investigational site. If the patient is unable to complete the measure on her or his own, interview assessment is allowed but can only be conducted by site staff (see Section 4.5.8.1). All PRO instruments are required to be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified. In scenarios where laboratory assessments (e.g., blood draws) are done at a different location than the one providing treatment or when they are done on a different day than study treatment administration, laboratory assessments can be completed before the completion of PRO instruments as long as results have not been discussed with patients. 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. Reasons for non-completion should be recorded in the eCRF. *As of BO42843 Protocol Version 10, PRO instruments will no longer be administered.*
- ^g Includes respiratory rate, pulse rate, systolic and diastolic blood pressure in the seated position, and temperature. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (± 5) minutes during and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (± 10) minutes after the infusion.

Appendix 2: Schedule of Activities: Treatment Phase

- ^h Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Ongoing use of tobacco (smoking and smokeless) must also be recorded. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Complete physical examinations are defined in Section 4.5.3.
- ⁱ Perform a limited, symptom-directed examination at every cycle and as clinically indicated. Ongoing use of tobacco (smoking and smokeless) must also be recorded. Limited physical examinations are defined in Section 4.5.3.
- ^j If screening laboratory assessments were performed within 96 hours prior to C1D1, laboratory assessments do not have to be repeated at C1D1. At all cycles subsequent to C1D1, laboratory assessments, ECOG Performance Status, and limited physical examination must be performed within 96 hours prior to administration of drug.
- ^k ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.
- ^l Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).
- ^m Specified screening laboratory test results must be obtained prior to randomization and within 14 days prior to initiation of study treatment.
- ⁿ Chemistry panel (serum or plasma) includes serum troponin (at baseline, if considered standard of care/required per local clinical practice, and as clinically indicated during the study), sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH.
- ^p 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 C1D1. Either urine or serum pregnancy tests must be performed within 96 hours prior to administration of study drug at every cycle during study treatment, at treatment discontinuation, and as clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^q TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on C1D1 and every fourth cycle thereafter (i.e., Cycle 1, 5, 9, etc.).
- ^r Baseline samples are to be collected on C1D1 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.
- ^s Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. Urinalysis should be performed as clinically indicated during study treatment.
- ^t See Section 4.5.6 for serology tests. HIV testing should be performed in accordance with national and/or institutional guidelines. Patients with a positive HIV result are eligible provided their CD4 count $\geq 200/\mu\text{L}$, and they have an undetectable viral load. HBV DNA must be collected before enrollment in patients who have negative serology for hepatitis B surface antigen and positive serology for anti-HBc.

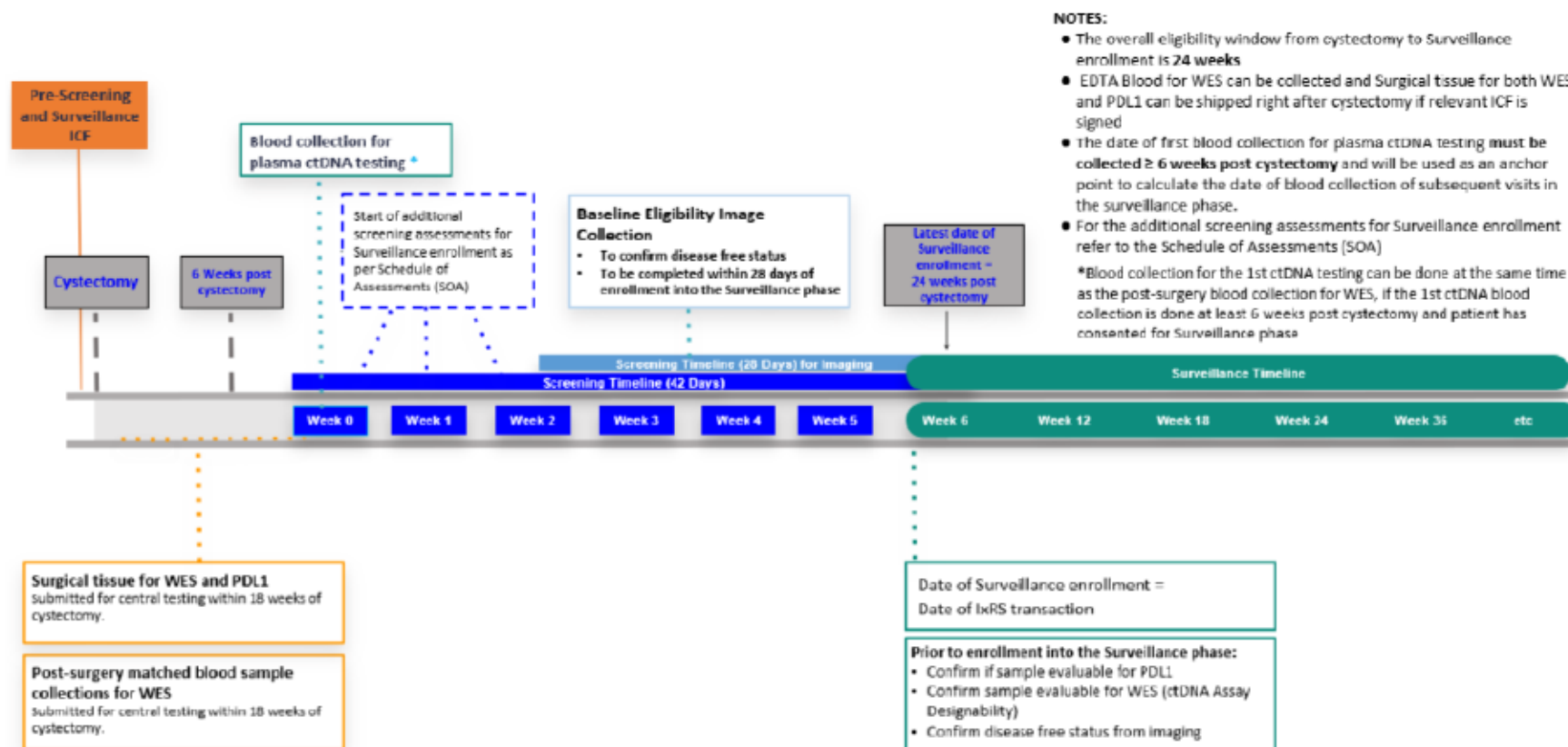
Appendix 2: Schedule of Activities: Treatment Phase

- ^u All patients *are requested to undergo* tumor biopsy sample collection, if *clinically feasible*, at the time of radiographic confirmation of disease recurrence (see Section 4.5.5) *to provide histological confirmation of recurrence. As of Protocol Version 10, biopsy tissue samples no longer need to be sent to the central lab.*
- ^v Monitoring for tumor recurrence must include physical examination and imaging studies of the chest, abdomen, upper urinary tracts, and pelvis. Other examinations such as laboratory or urine cytology should be performed as clinically indicated. Recurrence assessment at Year 6 will be performed at approximately 48 weeks after the last one in Year 5. See Section 4.5.5 for details of assessment requirements.
- ^w Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of randomization do not have to be repeated at screening. Screening assessments must include CT scans with IV and oral contrast (oral contrast can be omitted depending on local practice) or MRI of the chest, abdomen, and pelvis at screening for the Surveillance Phase and/or Treatment Phase. Eligibility into the Treatment Phases will be confirmed by an IRF review of imaging data, pathology reports if available, as well as any historical scans that may support the interpretation of benign radiographic objects. In patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance), MRIs of the abdomen and pelvis with a non-contrast CT scan of the chest may be used. For patients with renal impairment or contrast allergy, upper tract medical imaging is still required. For patients with renal impairment, CT urography with a reduced contrast agent or a non-contrasted MRI is recommended. For patients with a contrast allergy, non-contrasted MRI urogram or ureteroscopy is recommended. If a CT scan for tumor assessment is performed in a positron emission tomography/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.
- ^x Sample analysis may also include exploratory biomarker research including biomarker assay development.
- ^y Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

Appendix 2: Schedule of Activities: Treatment Phase

- ^z After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention and serious adverse events considered related to Signatera™ (Natera, Inc.) assay (including any device-related procedures) should be reported immediately (i.e., no more than 24 hours after the investigator becomes aware of the event). In addition, non-serious adverse events considered related to Signatera™ (Natera, Inc.) assay (including any device-related procedures and adverse events that may be a consequence of device deficiencies) should be reported within 5 days after the investigator becomes aware of the event. After initiation of study treatment, all adverse events will be recorded until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. In addition, non-serious adverse events considered related to Signatera™ (Natera, Inc.) assay (including any device-related procedures and adverse events that may be a consequence of device deficiencies) will be reported within 5 days after the investigator becomes aware of the event. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.
- ^{aa} 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 4 days after randomization. The initial infusion of study drug will be delivered over 60 ($\pm$ 15) minutes. Subsequent infusions will be delivered over 30 ($\pm$ 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 ($\pm$ 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. *For Cycle 2 and subsequent cycles, atezolizumab may be infused over a longer period of time at the investigator's discretion.*
- ^{bb} Survival follow-up information will be recorded via telephone calls, patient medical records, and/or clinic visits approximately every 3 months ($\pm$ 7 days) *from the date of disease recurrence* until death, loss to follow-up, or study termination by the Sponsor. All patients (irrespective of which arm they are randomized to) 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. If the patient withdraws *from the study during survival follow-up*, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 3 Surveillance Screening Assessment Timeline



ctDNA = circulating tumor DNA; ICF = Informed Consent Form; TAT = turnaround time; WES = whole exome sequencing.

Appendix 4

Schedule of Pharmacokinetic and Immunogenicity Samples in Arms A and B

<i>From Protocol Version 10 onwards, all samples below are no longer to be collected.</i>		
Visit	Timepoint	Sample Type
Day 1 of Cycle 1	Prior to the first infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
	30 min after the end of atezolizumab infusion	• Atezolizumab PK (serum)
Day 1 of Cycles 2, 3, 4, 8, and 12	Predose of atezolizumab infusion (the same day as atezolizumab administration)	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤30 days after final dose)	NA	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)

ADA=anti-drug antibody; NA=not applicable; PK=pharmacokinetic.

Notes: 1. On the basis of emerging safety, activity, or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted.

2. Assessments during non-treatment visits (screening, discontinuation, and disease progression) should be performed within ±3 days of the scheduled visit, unless otherwise specified. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

Appendix 5 Schedule of Biomarker Samples

Visit	Timepoint	Sample Type
Prescreening <i>From Protocol Version 10 onwards, these Prescreening samples are no longer to be collected.</i>		
After patient has signed Prescreening Informed Consent Form		- Surgical tumor tissue for WES and PD-L1 analysis and exploratory biomarkers ^b - Matched blood for WES - Blood for exploratory biomarkers ^b
Surveillance Phase ^a <i>From Protocol Version 10 onwards, these Surveillance Phase samples are no longer to be collected.</i>		
After patient has signed Surveillance Informed Consent Form		- Blood for plasma for ctDNA testing ^{b, c} - Blood for plasma for exploratory biomarkers ^b - Optional blood for RBR baseline visit ^a
Treatment Phase <i>From Protocol Version 10 onwards, these Treatment Phase samples are no longer to be collected with the exception of the biomarker samples at the time of disease recurrence.</i>		
After patient has signed Treatment Informed Consent Form		See below for all relevant collections
Day 1 of Cycles 1, 2, 3, 5, 7, 9, and 11 (±3 Days for ≥ Cycle 2)	Pre-dose	- Blood for plasma for ctDNA testing ^b - Blood for plasma for exploratory biomarkers ^b
Day 1 of Cycles 1, 2, 3, and 11 (±3 Days for ≥ Cycle 2)	Pre-dose	- Blood for plasma exploratory biomarkers ^b - Blood for PBMC preparation ^b
Day 1 of Cycle 1 (+3 days) and Day 1 of Cycle 3 (±3 Days)	Pre-dose	Urine for exploratory biomarkers ^b
Treatment Discontinuation Visit (≤30 days after final dose)	NA	- Blood for plasma for ctDNA testing ^b - Blood for plasma for exploratory biomarkers ^b - Blood for plasma exploratory biomarkers ^b - Blood for PBMC preparation ^b - Urine samples for exploratory biomarkers ^b
Disease Status Follow-Up	Year 2: every 9 weeks Year 3: every 12 weeks Years 4–5: every 24 weeks Year 6: 48 weeks after last follow-up	- Blood for plasma for ctDNA testing ^b - Blood for plasma for exploratory biomarkers ^b - Blood for plasma exploratory biomarker ^b - Blood for PBMC preparation ^b

Appendix 5: Schedule of Biomarker Samples

Disease Recurrence ^d	NA	• Blood for plasma for ctDNA testing ^b • Blood for plasma for exploratory biomarkers ^b • Blood for plasma exploratory biomarker ^b • Blood for PBMC preparation ^b • Urine for exploratory biomarkers ^b
---------------------------------	----	--

ctDNA=circulating tumor DNA; IxRS=interactive voice or web-based response system; NA=not applicable; PBMC=peripheral blood mononuclear cells; WES=whole exome sequencing.

- ^a To be collected during initial visit. If optional blood sample for RBR was not collected on initial visit of Surveillance Phase, it can be collected at any other time during the study after RBR optional consent has been signed.
- ^b Sample analysis may also include exploratory biomarker research including biomarker assay development.
- ^c The date of the first blood collection for plasma ctDNA to determine presence of ctDNA in the patients' blood will occur prior to enrollment into the Surveillance Phase and then occur every 6 weeks (± 5 days) from the date the first blood collection for ctDNA testing until 36 weeks from the date of the patient's cystectomy have passed. After the latest blood collection prior to 36 weeks from cystectomy has been reached, blood collection should follow the surveillance imaging schedule going forward. The date the patient has moved to surveillance in IxRS (IxRS transaction date) will be used as date of enrollment into Surveillance Phase, after meeting all inclusion/exclusion criteria for Surveillance Phase. The date of the first blood collection for plasma ctDNA testing will be used as an anchor point to calculate the date of blood collection of subsequent visits in the Surveillance Phase. Patients will enter the Treatment Phase of the study at the first plasma sample that is ctDNA positive. Based on the testing frequency, a patient's last scheduled ctDNA test will occur anywhere between 42 and 52 weeks from cystectomy. Patients whose last scheduled ctDNA test occurs more than 4 weeks prior to surveillance completion may have an optional unscheduled ctDNA test performed before the 12 months are complete.
- ^d If the disease recurrence visit is at the same time as the treatment discontinuation visit, collect the disease recurrence biomarker samples, since only one set of biomarker samples needs to be collected.

Appendix 6

Guidelines for the Assessment of Muscle-Invasive Bladder Cancer at Screening and Disease Recurrence

Assessment of muscle-invasive bladder cancer (MIBC) at screening and disease recurrence will be made on the basis of radiographic evidence and whenever possible supported/confirmed by biopsy results. The following are intended as general radiographic assessment guidelines, which are adapted from a recent publication based on an FDA-NCI public workshop on eligibility and radiologic assessment in adjuvant clinical trials in bladder cancer (Apolo AB et al. 2019).

Patients will undergo tumor recurrence assessments at baseline, within 28 days of enrollment into the surveillance and randomization in the Treatment Phases, and then every 9 weeks (± 7 days) for the next 24 months, regardless of dose delays, or until radiographic disease recurrence.

MIBC ASSESSMENT AT SCREENING

Determination of absence of residual disease and absence of metastasis will be made on the basis of radiographic evidence, supported/confirmed by biopsy results (from biopsies performed before or during the screening period) and/ or historical scans (if available). Disease-free status by imaging is defined as meeting all of the following criteria:

- Lymph nodes must be non-pathologic, which is defined as less than 1.0 cm in short axis.
- Absence of non-nodal lesions (e.g., no skin or subcutaneous lesions and no presence of CNS metastases or leptomeningeal disease), with the exception of non-nodal lesions that are diagnosed as histologically benign.

Non-nodal lesions measuring 1.0 cm or greater in long axis, which are not feasible for biopsy, must demonstrate radiographic stability across imaging tests at least 6 weeks apart.
- Presence of stable pulmonary nodules is acceptable, provided either of the following conditions are met:

Patients who have stable pulmonary nodules 6 mm or less are considered eligible for enrollment in the study provided that the pulmonary nodules are clinically not suspected of being malignant.

Pulmonary nodules greater than 6 mm in diameter require either evidence that the lesion is histologically benign or demonstration of radiographic stability across imaging tests at least 4 weeks apart.
- Surgical bed: There is potential for some radiographic changes in the postoperative setting to be related to inflammation. If an indeterminate soft tissue lesion of any size is observed in the surgical bed, biopsy is recommended, if feasible. If biopsy is not feasible, lesions that are radiographically consistent with urothelial malignancy,

Appendix 6: Guidelines for the Assessment of Muscle-Invasive Bladder Cancer at Screening and Disease Recurrence

or demonstrating growth over at least two sequential imaging tests (either computed tomography [CT] or magnetic resonance imaging [MRI]) at least 4 weeks apart should be considered recurrence.

Pleural effusion should not be considered as disease presence unless there is a suspicion for underlying pulmonary/pleural malignancy based on CT or additional imaging. In the absence of coexisting nonmalignant clinical disease, indeterminate fluid should be sampled.

For patients enrolled under Protocol Version 4 onwards, the confirmation of disease-free status will be assessed by an independent central radiologic review of imaging data only prior to entering the Treatment Phase. For patients enrolled under Protocol Versions 1 to 3, confirmation of disease-free status will be assessed by an independent central radiologic review of imaging data prior to entering the surveillance and Treatment Phases. All imaging data and supportive data (e.g., historical images and pathology report forms) must be submitted to the imaging vendor. For all versions, investigators must confirm absence of residual disease or metastasis before submitting data to imaging vendor for confirmation.

ASSESSMENT OF MIBC DISEASE RECURRENCE AFTER SCREENING

Determination of disease recurrence should be based on presence of unequivocal disease. As a general guideline for recurrence, if a suspected lesion is equivocal, for example because of its small size, continue study treatment (if applicable) and follow-up with imaging assessment expeditiously as needed. If at the next visit, the presence of new lesions or intervening growth turns unequivocal as defined by the criteria outlined in the Apolo et al. 2019 publication based on the FDA-NCI workshop, then recurrence should be declared from the date of unequivocal recurrence only. Equivocal scans should only be used as date of recurrence if followed by biopsy confirming recurrence.

Findings qualifying as unequivocal disease recurrence as per the Apolo criteria are as follows:

1. Any new lesion or nodule ≥ 1.0 cm that was absent on initial evaluation.
2. Any preexisting lesion < 1.0 cm demonstrating $> 50\%$ growth on 2 consecutive radiologic examinations with ≥ 5 mm absolute increase.
3. If ≥ 1.0 cm on previous examination, demonstrating $> 50\%$ growth in long axis on a single examination.
4. Multifocal lesions measuring < 1.0 cm that demonstrate geographic distribution or radiographic and/or metabolic features that are pathognomonic for metastatic disease.

Appendix 6: Guidelines for the Assessment of Muscle-Invasive Bladder Cancer at Screening and Disease Recurrence

Radiologic Considerations for Evaluating Patient Eligibility During Initial Evaluation and Unequivocal Disease Recurrence During Adjuvant Trial Imaging Surveillance

Anatomic Location	Initial Evaluation: Findings Warranting Customized Radiologic Workup, Repeat Radiographic Evaluation, or Biopsy Prior to Enrollment	Adjuvant Trial Surveillance: Findings Qualifying as Unequivocal Disease Recurrence	Additional Workshop Discussion Points
Lung	Indeterminate pulmonary nodule ≥ 1.0 cm long axis	- New nodule ≥ 1.0 cm that was absent on initial evaluation - Preexisting nodule: - If < 1.0 cm in previous examination, demonstrating $> 50\%$ growth in long axis on 2 consecutive examinations with ≥ 5 mm absolute increase - If ≥ 1.0 cm in previous examination, demonstrating $> 50\%$ growth in long axis on a single examination - Multifocal nodules measuring < 1.0 cm that demonstrate geographic distribution or radiographic and/or metabolic features pathognomonic for metastatic disease	Guidelines such as those published by the Fleischner Society²⁷ and the American College of Radiology Incidental Findings Committee²⁸ should be reviewed and may be helpful when evaluating indeterminate lesions on a retrospective basis on imaging performed prior to initial evaluation for trial, with the understanding that these guidelines were designed with the assumption that the patient has no underlying cancer.
Lymph nodes	Lymph node ≥ 1.0 cm short axis	- New lymph node ≥ 1.0 cm that was absent on initial evaluation - Preexisting lymph node: - If < 1.0 cm in previous examination, demonstrating $> 50\%$ growth in short axis on 2 consecutive examinations with ≥ 5 mm absolute increase - If ≥ 1.0 cm in previous examination, demonstrating $> 50\%$ growth in short axis on a single examination	- Lymph nodes ≥ 1.0 cm but < 1.5 cm in the short axis are suspicious; however, they can be difficult to interpret, and may not be convincing enough to call recurrence on imaging alone. - Nodes ≥ 1.5 cm in the short axis are considered highly suspicious for malignant disease involvement, especially when exhibiting growth on multiple scans.
Liver	Indeterminate lesion ≥ 1.0 cm long axis	- New lesion ≥ 1.0 cm that was absent on initial evaluation - Preexisting lesion: - If < 1.0 cm in previous examination, demonstrating $> 50\%$ growth in long axis on 2 consecutive examinations with ≥ 5 mm absolute increase - If ≥ 1.0 cm in previous examination, demonstrating $> 50\%$ growth in long axis on a single examination - Multifocal lesions measuring < 1.0 cm that demonstrate geographic distribution or radiographic and/or metabolic features pathognomonic for metastatic disease	Any new enhancing lesions, even those < 1.0 cm, are considered suspicious.
Other solid visceral organs (including spleen, pancreas, adrenal glands, and kidneys) and peritoneum, omentum, or mesentery	Indeterminate lesion ≥ 1.0 cm long axis	- New lesion ≥ 1.0 cm that was absent on initial evaluation - Preexisting lesion: - If < 1.0 cm in previous examination, demonstrating $> 50\%$ growth in long axis on 2 consecutive examinations with ≥ 5 mm absolute increase - If ≥ 1.0 cm on previous examination, demonstrating $> 50\%$ growth in long axis on a single examination - Multifocal lesions measuring < 1.0 cm that demonstrate geographic distribution or radiographic and/or metabolic features pathognomonic for metastatic disease	Any new and/or enhancing mass in the abdominal cavity on CT imaging or MRI is considered suspicious, especially when associated with lymphadenopathy.
Tumor resection bed	Indeterminate soft tissue lesion of any size	- New lesion ≥ 1.0 cm that was absent on initial evaluation - Preexisting lesion: - If < 1.0 cm on previous examination, demonstrating $> 50\%$ growth in long axis on 2 consecutive examinations with ≥ 5 mm absolute increase - If ≥ 1.0 cm on previous examination, demonstrating $> 50\%$ growth in long axis on a single examination	Imaging should be performed > 4 wk after surgical resection to allow for resolution of postsurgical inflammation.
Pleural effusion or ascites	No radiologic study can definitively differentiate between benign vs malignant processes. In the absence of coexisting nonmalignant clinical disease, indeterminate fluid should be sampled.	No radiologic study can definitively differentiate between benign vs malignant processes. In the absence of coexisting nonmalignant clinical disease, indeterminate fluid should be sampled.	In the absence of coexisting nonmalignant clinical disease, indeterminate pleural and ascitic fluid should have cytologic evaluation, if safe and feasible.
Bone	Indeterminate bone lesion	- New lytic or sclerotic bone lesion that was absent on initial evaluation - Multifocal lesions demonstrating geographic distribution or radiographic and/or metabolic features pathognomonic for metastatic disease	Osseous metastases commonly demonstrate nonspecific features on CT imaging. In the absence of multifocal stereotypical features of osteolytic or osteoblastic metastases, indeterminate lesions should be further evaluated by radiography, MRI, or nuclear medicine imaging.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

Appendix 6: Guidelines for the Assessment of Muscle-Invasive Bladder Cancer at Screening and Disease Recurrence

REFERENCES

Apolo AB, Milowsky MI, Kim L, et al. Eligibility and radiologic assessment in adjuvant clinical trials in bladder cancer. *JAMA Oncol* 2019;5;1790–98.

Naidich DP, Bankier AA, MacMahon H, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: A statement from the Fleischner Society. *Radiology* 2013;266;304–17.

Appendix 7 EORTC QLQ-C30

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.



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.

Today's date (Day, Month, Year): 31

--	--	--	--	--	--	--	--	--	--

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

During the past week:

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

Please go on to the next page

Appendix 7: EORTC QLQ-C30

During the past week:		Not at All	A Little	Quite a Bit	Very Much
16.	Have you been constipated?	1	2	3	4
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 Study Group on Quality of Life. All rights reserved. Version 3.0

Appendix 8

European Organisation for Research and Treatment of Cancer Item Library 46 (EORTC IL46)

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.



EORTC IL46

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
1. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4

Appendix 9

EQ-5D-5L

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.



Health Questionnaire

English version for the USA

USA (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Appendix 9: EQ-5D-5L

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

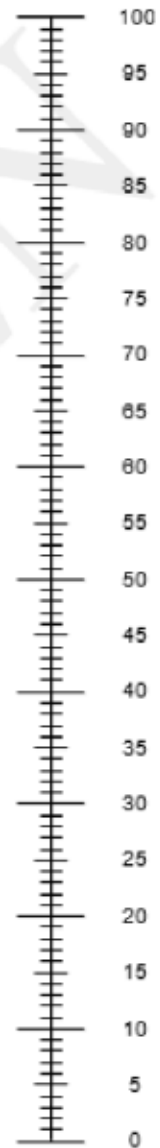
- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

Appendix 9: EQ-5D-5L

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

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine

Appendix 10

Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anticancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myelitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome	• Crohn disease • Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Granulomatosis with polyangiitis • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea	• Multiple sclerosis • Myasthenia gravis • Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cholangitis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease
--	---	--

Appendix 11

Anaphylaxis Precautions

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

REQUIRED EQUIPMENT AND MEDICATION

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

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

PROCEDURES

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

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

Appendix 12

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

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

Although toxicities observed with atezolizumab have been mild and self-limiting, they 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.

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. Management guidelines for patients who experience adverse events associated with atezolizumab are provided in [Table 1](#). Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab

GENERAL GUIDANCE

Early Recognition and Close Monitoring:

Timely and up-to-date information about the risks associated with atezolizumab should be shared with patients and family caregivers prior to initiating atezolizumab and throughout treatment and survival follow-up. Patients and caregivers should be instructed to have a high level of suspicion that new symptoms are treatment-related. Patients should be assessed for signs and symptoms of organ dysfunctions throughout the study, including monitoring of results of thyroid function, liver function, and other laboratory tests as appropriate (e.g., blood glucose, creatinine, amylase, lipase, urine protein). Patients presenting with adverse events of any severity grade should be monitored closely and referred promptly to specialists for evaluation. Treatment and supportive care measures should be initiated as per institutional guidelines.

Monitoring of high-risk cardiac patients:

In high-risk cardiac patients (including those with abnormal baseline cardiac troponin levels, when available), TTE monitoring should be performed on a regular basis, if clinically indicated and considered appropriate per institutional practice.

Monitoring for Myocarditis, Myositis, and Myasthenia Gravis:

Myocarditis symptoms are nonspecific and may occur as early as days or weeks after the first or second dose of atezolizumab. Although myocarditis events are rare, myocarditis is often severe and associated with myositis or myasthenia gravis. All patients with possible myocarditis should be urgently evaluated by performing a cardiac enzyme assessment, an ECG, a chest X-ray, a TTE for evaluation of left ventricular ejection fraction and global longitudinal strain, and a cardiac MRI as appropriate per institutional practice. A cardiologist should be consulted. An endomyocardial biopsy may be performed to enable a definitive diagnosis and appropriate treatment, if clinically indicated. For suspicion of myositis, myocarditis, and/or myasthenia gravis, there is a possibility of overlapping symptoms, and patients should therefore be evaluated with a shared set of diagnostics, including erythrocyte sedimentation rate, C-reactive protein, creatine kinase, antibody tests (acetylcholine, muscle-specific kinase, striational), aldolase, troponin, ECG, nerve conduction, and electromyography. Such patients should undergo frequent pulmonary evaluations.

Use of Corticosteroids and Immunosuppressants for Managing Adverse Events:

In the guidance for specific events below, treatment with high-dose corticosteroids refers to 1–2 mg/kg/day oral prednisone (or equivalent) or IV methylprednisolone (or equivalent), and an additional immunosuppressive agent can be added if symptoms do not improve within 48 hours after initiating high-dose corticosteroids. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day of oral prednisone before atezolizumab can be resumed.

Action to be Taken with Atezolizumab:

Treatment with atezolizumab may be withheld or permanently discontinued because of toxicities, as specified below. If atezolizumab is withheld, treatment can be resumed if the event resolves to Grade 1 or better, or when symptoms improve as specified below. As a general rule, atezolizumab can be withheld for up to 12 weeks after event onset. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment.

If an event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical

Appendix 12: Risks Associated with Atezolizumab and Guidelines for the Management of Adverse Events Associated with Atezolizumab

Monitor. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from an immune-mediated event, except when resumption of atezolizumab is expressly prohibited as described below. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and should be documented by the investigator. The Medical Monitor is available to advise as needed.			
Event	Symptoms or CTCAE Severity Grade	Action to be Taken with Atezolizumab	Adverse Event Management [To Be Implemented in Combination with Above General Guidance]
Pulmonary event	Grade 1	Continue with one exception: For pneumonitis, consider withholding and resuming on radiographic evidence of improvement.	- Re-evaluate on serial imaging. - Closely monitor patients, including asymptomatic patients.
	Grade 2	Withhold.	- Consider bronchoscopy or BAL with or without transbronchial biopsy. - Initiate treatment with high-dose oral corticosteroids.
	Recurrent Grade 2 or Grade 2 event not improving after 48–72 hours of corticosteroids or Grade 3 or 4	- Permanently discontinue. - In case of pneumonitis, atezolizumab should not be resumed under any circumstances.	- Bronchoscopy or BAL with or without transbronchial biopsy is recommended. - Initiate treatment with oral or IV broad-spectrum antibiotics and high-dose IV corticosteroids. - If event does not improve, consider adding an immunosuppressive agent.

Appendix 12: Risks Associated with Atezolizumab and Guidelines for the Management of Adverse Events Associated with Atezolizumab

Hepatic event	Guidelines for patients without hepatocellular carcinoma		
	Grade 1	Continue.	Closely monitor patient.
	Grade 2	Events of > 5 days' duration: Withhold.	All events: - Monitor liver function tests more frequently until return to baseline values. Events of > 5 days' duration: - Initiate treatment with high-dose oral corticosteroids.
	Grade 3 or 4	Permanently discontinue.	- Consider liver biopsy to establish etiology of hepatic injury. - Initiate treatment with high-dose oral corticosteroids. - If event does not improve, consider adding an immunosuppressive agent. <i>Consider an urgent GI/hepatology referral if no improvement after 7 days of treatment or if two immunosuppressive agents do not yield adequate response within an additional 7 days.</i>
	Guidelines for patients with hepatocellular carcinoma		
	AST/ALT is within normal limits at baseline and increases to $> 3 \times \text{ULN}$ to $\leq 10 \times \text{ULN}$ <u>or</u> AST/ALT is $> \text{ULN}$ to $\leq 3 \times \text{ULN}$ at baseline and increases to $> 5 \times \text{ULN}$ to $\leq 10 \times \text{ULN}$ <u>or</u>	Withhold.	- Monitor liver function tests more frequently until return to baseline values. - For events of > 5 days' duration, consider initiating treatment with high-dose oral corticosteroids.

Appendix 12: Risks Associated with Atezolizumab and Guidelines for the Management of Adverse Events Associated with Atezolizumab

	AST/ALT is $>3 \times \text{ULN}$ to $\leq 5 \times \text{ULN}$ at baseline and increases to $>8 \times \text{ULN}$ to $\leq 10 \times \text{ULN}$		
	AST or ALT increases to $>10 \times \text{ULN}$ or total bilirubin increases to $>3 \times \text{ULN}$	• Permanently discontinue.	• Consider liver biopsy to establish etiology of hepatic injury. • Initiate treatment with high-dose oral corticosteroids. • If event does not improve, consider adding an immunosuppressive agent.
Diarrhea or colitis	Grade 1	• Continue.	• Closely monitor patient. • For events of >7 days duration, endoscopy is recommended.
	Grade 2	• Withhold.	• Endoscopy is recommended. • If strong clinical suspicion for immune-mediated colitis, initiate empiric IV corticosteroids while waiting for definitive diagnosis. • For recurrent events or events that persist >5 days, initiate treatment with high-dose oral corticosteroids. • If event does not improve, consider adding an immunosuppressive agent.
	Grade 3	• Withhold.	• Order confirmatory biopsy. • Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement. • If event does not improve or patient is unable to transition to oral corticosteroids, consider adding an immunosuppressive agent.
	Grade 4	• Permanently discontinue.	

Appendix 12: Risks Associated with Atezolizumab and Guidelines for the Management of Adverse Events Associated with Atezolizumab

Hypothyroidism	Grade 1	Continue.	Closely monitor patient.
	Grade 2	- Consider withholding. - If withheld, resume when symptoms are controlled and thyroid function is improving.	Initiate treatment with thyroid replacement hormone.
	Grade 3 or 4	- Withhold. - Resume when symptoms are controlled and thyroid function is improving. - Permanently discontinue for life-threatening immune-mediated hypothyroidism.	- Initiate treatment with thyroid replacement hormone. - Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status).
Hyperthyroidism	Grade 1, TSH ≥ 0.1 mU/L and < 0.5 mU/L	Continue.	Monitor TSH every 4 weeks.
	Grade 1, TSH < 0.1 mU/L or Grade 2	- Consider withholding. - Resume when symptoms are controlled and thyroid function is improving.	Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed.
	Grade 3 or 4	- Withhold. - Resume when symptoms are controlled and thyroid function is improving. - Permanently discontinue for life-threatening immune-mediated hyperthyroidism.	

Appendix 12: Risks Associated with Atezolizumab and Guidelines for the Management of Adverse Events Associated with Atezolizumab

Symptomatic adrenal insufficiency	Grade 2, 3, or 4	• Withhold. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume. • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding, permanently discontinue.	• Perform appropriate imaging. • Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement. • Monitor for signs of adrenal crisis, such as hemodynamic instability.
Hyperglycemia	Grade 1 or 2 without Type 1 diabetes	• Continue.	• Closely monitor patient.
	Grade 3 or 4 or Type 1 diabetes	• Withhold. • Resume when symptoms resolve and glucose levels are stable.	• Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis.
Hypophysitis (pan-hypopituitarism)	Grade 1	• Continue.	• Closely monitor patient.
	Grade 2 or 3	• Withhold.	• Perform brain MRI (pituitary protocol). • Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement. • Initiate other hormone replacement if clinically indicated, only after corticosteroid replacement to avoid adrenal crisis.
	Recurrent hypophysitis Grade 2 or 3 or Grade 4	• Permanently discontinue.	

Appendix 12: Risks Associated with Atezolizumab and Guidelines for the Management of Adverse Events Associated with Atezolizumab

Ocular event	Grade 1	Continue.	Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.
	Persistent Grade 1 despite treatment or Grade 2	Withhold.	
	Grade 3 or 4	Permanently discontinue.	Initiate treatment with high-dose oral corticosteroids.
Myocarditis or pericardial disorders	Grade 1	Withhold.	Conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.
	Grade 2, 3, or 4	- Permanently discontinue. - Atezolizumab should not be resumed under any circumstances.	- Consider anti-arrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. - Initiate treatment with higher-dose IV corticosteroids equivalent to 1 g/day IV methylprednisolone for 3–5 days and convert to high-dose oral corticosteroids upon improvement. - If event does not improve within 24 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
Amylase and/or lipase elevation	Grade 1	Continue.	Closely monitor patient.
	Grade 2	Continue.	- Evaluate for pancreatitis. - If persistent moderate to severe amylase and/or lipase elevation, consider performing abdominal CT scan with contrast or magnetic resonance cholangiopancreatography. - Consider other causes for elevated amylase/lipase. - If evidence of pancreatitis, manage according to pancreatitis algorithm.
	Grade 3 or 4	- Withhold. - For recurrent events, permanently discontinue.	

Appendix 12: Risks Associated with Atezolizumab and Guidelines for the Management of Adverse Events Associated with Atezolizumab

Pancreatitis	Grade 2	Withhold.	Manage as per elevation in amylase/lipase (asymptomatic) above.
	Grade 3	- Withhold. - For recurrent events, permanently discontinue.	Consider treatment with high-dose IV corticosteroids only if no improvement with hydration and pain control, and convert to oral corticosteroids upon improvement.
	Grade 4	Permanently discontinue.	- Consider treatment with high-dose IV corticosteroids only if no improvement with hydration and pain control, and convert to oral corticosteroids upon improvement. - If event does not improve, consider adding an immunosuppressive agent.
Dermatologic event	Grade 1	Continue.	Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
	Grade 2	Continue.	- Consider biopsy, if indicated. - Initiate treatment with topical corticosteroids. - Consider treatment with higher-potency topical corticosteroids if the event does not improve. - If unresponsive to topical corticosteroids, consider oral corticosteroids equivalent to 0.5 mg/kg/day prednisone.
	Grade 3	Withhold.	- Order a biopsy, if indicated. - Initiate treatment with oral corticosteroids equivalent to 10 mg/day prednisone, increasing to high-dose oral corticosteroids if event does not improve within 48–72 hours.
	Grade 4	Permanently discontinue.	
Stevens-Johnson syndrome or toxic epidermal necrolysis	Suspected event, any grade	Withhold.	- Order a biopsy, if indicated. - Follow the applicable treatment/management guidelines for dermatologic events above.
	Confirmed event, any grade	- Permanently discontinue. - Atezolizumab should not be resumed under any circumstances.	

Appendix 12: Risks Associated with Atezolizumab and Guidelines for the Management of Adverse Events Associated with Atezolizumab

Myasthenia gravis and Guillain-Barré syndrome	Any grade	• Permanently discontinue. • Atezolizumab should not be resumed under any circumstances.	• Consider initiation of high-dose oral or IV corticosteroids. • Consider IVIG or plasmapheresis in patients with rapid progression with development of bulbar and/or respiratory symptoms. • In life-threatening cases, consider higher-dose IV methylprednisolone 1 g/day for 3–5 days and other immunosuppressive agents.
Facial paresis	Grade 1 or 2	• Withhold. • If event resolves fully, resume. • If event does not resolve fully while withholding, permanently discontinue.	• Investigate etiology. • Closely monitor patient or initiate high-dose oral corticosteroids (if progressing from mild). • Initiate non-opioid treatment (e.g., gabapentin, pregabalin, duloxetine) for pain.
	Grade 3 or 4	• Permanently discontinue.	• Follow guidelines for management of myasthenia gravis and Guillain-Barré syndrome.
Other cranial nerve disorder (excluding facial paresis)	Grade 1 or 2	• Withhold.	• Investigate etiology.
	Grade 3 or 4	• Permanently discontinue.	• Follow guidelines for management of myasthenia gravis and Guillain-Barré syndrome.
Other neuropathy (excluding myasthenia gravis, Guillain-Barré syndrome, facial paresis, and other cranial nerve disorders)	Grade 1	• Continue.	• Closely monitor patient.
	Grade 2	• Withhold.	• Investigate etiology.
	Grade 3 or 4	• Permanently discontinue.	• Follow guidelines for management of myasthenia gravis and Guillain-Barré syndrome.

Appendix 12: Risks Associated with Atezolizumab and Guidelines for the Management of Adverse Events Associated with Atezolizumab

Myelitis	Grade 1	Continue unless symptoms worsen or do not improve.	Investigate etiology.
	Grade 2	- Permanently discontinue. - Atezolizumab should not be resumed under any circumstances.	- Investigate etiology and rule out infection. - Initiate treatment with high-dose oral corticosteroids.
	Grade 3 or 4	- Permanently discontinue. - Atezolizumab should not be resumed under any circumstances.	- Initiate non-opioid treatment (e.g., gabapentin, pregabalin, duloxetine) for pain. - Hospitalize patient. - Initiate treatment with IV corticosteroids equivalent to 1 g/day methylprednisolone. - If event does not improve or there is worsening of symptoms within 48 hours, consider IVIG or plasmapheresis and manage as per institutional practice.
Meningoencephalitis	Any grade	- Permanently discontinue. - Atezolizumab should not be resumed under any circumstances.	- Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement. - If event does not improve, consider adding an immunosuppressive agent.
Renal event	Grade 1	Continue.	Closely monitor patient.
	Grade 2	Withhold.	Initiate treatment with high-dose oral corticosteroids.
	Grade 3 or 4	Permanently discontinue.	- Consider renal biopsy. - Initiate treatment with high-dose oral corticosteroids. - If event does not improve, consider adding an immunosuppressive agent.

Appendix 12: Risks Associated with Atezolizumab and Guidelines for the Management of Adverse Events Associated with Atezolizumab

Myositis	Grade 1	Continue.	Closely monitor patient.
	Grade 2	Withhold.	- Consider treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement. - If the event does not improve, consider adding an immunosuppressive agent.
	Grade 3	- Withhold. - If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and atezolizumab should not be resumed under any circumstances.	- Initiate treatment with high-dose IV corticosteroids, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to oral corticosteroids upon improvement. - If event does not improve within 24–48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - Consider IVIG or plasmapheresis.
	Recurrent Grade 3 or Grade 4	- Permanently discontinue. - Atezolizumab should not be resumed under any circumstances.	
Suspected HLH ^a	Any grade	- Permanently discontinue. - Atezolizumab should not be resumed under any circumstances.	- Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. - If the event does not respond to treatment within 24 hours, contact the Medical Monitor and initiate treatment as appropriate according to published guidelines. ^b

Appendix 12: Risks Associated with Atezolizumab and Guidelines for the Management of Adverse Events Associated with Atezolizumab

IRR and CRS	Grade 1 ^c : Fever ^d with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose.	• In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS.
	Grade 2 ^c : Fever ^d with hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen ^e by nasal cannula or blow-by	• If event occurs during infusion, immediately discontinue. Do not restart infusion. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. • Permanently discontinue atezolizumab for patients with Grade ≥ 3 wheezing, bronchospasm, or urticaria. • If event occurs during or within 24 hours after infusion, administer next dose at $\leq 50\%$ of initial infusion rate.	• For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy if the patient is not responding as expected after initiating corticosteroids. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact the Medical Monitor. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Medical Monitor.

Appendix 12: Risks Associated with Atezolizumab and Guidelines for the Management of Adverse Events Associated with Atezolizumab

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

Appendix 12: Risks Associated with Atezolizumab and Guidelines for the Management of Adverse Events Associated with Atezolizumab

	mechanical ventilation)		may be considered at the discretion of the investigator and in consultation with the Medical Monitor. Hospitalize patient until complete resolution of symptoms.
Atezolizumab-related event not described above	Grade 1	Continue.	Closely monitor patient.
	Grade 2	Consider withholding and resuming when event resolves to Grade 1 or better.	Refer to current standard guidelines for management of immune checkpoint inhibitor-related toxicities, such as those provided by a professional society (e.g., NCCN, ESMO, SITC, ASCO).
	Grade 3	Withhold.	
	Grade 4	Permanently discontinue.	

ASCO=American Society of Clinical Oncology; ASTCT=American Society for Transplantation and Cellular Therapy; BAL=bronchoscopic alveolar lavage; BiPAP=bi-level positive airway pressure; CPAP=continuous positive airway pressure; CRS=cytokine release syndrome; CT= *computed tomography*; CTCAE=Common Terminology Criteria for Adverse Events; ECMO=extracorporeal membrane oxygenation; eCRF=electronic Case Report Form; ESMO=European Society for Medical Oncology; GI= *gastrointestinal*; HLH=hemophagocytic lymphohistiocytosis; ICU=intensive care unit; IRR=infusion-related reaction; IVIG=intravenous immunoglobulin; MRI=magnetic resonance imaging; NCCN=National Comprehensive Cancer Network; NCI=National Cancer Institute; SITC=Society for Immunotherapy of Cancer; TTE=transthoracic echocardiogram; VAD=ventricular assist device; ULN=upper limit of normal.

Appendix 12: Risks Associated with Atezolizumab and Guidelines for the Management of Adverse Events Associated with Atezolizumab

- ^a Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014).
- ^b Refer to La Rosée (2015); Schram and Berliner (2015); La Rosée et al. (2019).
- ^c Grading system for these management guidelines is based on ASTCT Consensus Grading Scale for CRS. NCI CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
- ^d Fever is defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause. In patients who develop CRS and then receive antipyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
- ^e Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.
- ^f For subsequent infusions, administer oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit-risk ratio.
- ^g Refer to Riegler et al. (2019).

REFERENCES

- La Rosée P. Treatment of hemophagocytic lymphohistiocytosis in adults. *Hematology Am Soc Hematol Educ Program* 2015;1:190–6.
- La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood* 2019;133:2465–77.
- McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: <https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis>.
- Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. *Ther Clin Risk Manag* 2019;15:323–35.
- Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. *Blood* 2015;125:2908–14.

Appendix 13

Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table 1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product)	Authorized	No ^a
RO5541267 placebo	IMP (placebo)	Unauthorized	Not applicable

AxMP=auxiliary medicinal product; EEA=European Economic Area; IMP=investigational medicinal product.

^a Atezolizumab as monotherapy is approved for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma:

- After prior platinum-containing chemotherapy, or
- Who are considered cisplatin ineligible, and whose tumors have a PD-L1 expression $\geq 5\%$.

But it is not approved as an adjuvant treatment for patients with muscle-invasive bladder cancer who are at high risk for recurrence following cystectomy.

Table 2 Investigational and Non-Investigational Medicinal Product Designations for United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in UK	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product)	Authorized	No ^a
RO5541267 placebo	IMP (placebo)	Unauthorized	Not applicable

IMP=investigational medicinal product; NIMP=non-investigational medicinal product; UK=United Kingdom.

^a Atezolizumab as monotherapy is approved for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma:

- After prior platinum-containing chemotherapy, or
- Who are considered cisplatin ineligible, and whose tumors have a PD-L1 expression $\geq 5\%$.

But it is not approved as an adjuvant treatment for patients with muscle-invasive bladder cancer who are at high risk for recurrence following cystectomy.

Signature Page for Protocol - BO42843 - TECENTRIQ - v10 - Global/Core - Published

System identifier: RIM-CLIN-1118757

Approval Task	Company Signatory 10-Nov-2025 17:51:06 GMT+0000
---------------	--