Official Title: A Phase Ib/II, Open-Label, Multicenter, Randomized Umbrella Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatments and Combinations in Patients with Urothelial Carcinoma (MORPHEUS-UC)

NCT Number: NCT03869190

Document Date: Protocol Amendment Version 22: 08-May-2024

PROTOCOL

PROTOCOL TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENTS AND COMBINATIONS IN PATIENTS WITH UROTHELIAL CARCINOMA (MORPHEUS-UC)**
PROTOCOL NUMBER:	WO39613
VERSION NUMBER:	22
TEST COMPOUNDS:	Atezolizumab (RO5541267), enfortumab vedotin, niraparib, magrolimab (Hu5F9-G4), tiragolumab (RO7092284), sacituzumab govitecan, tocilizumab (RO4877533), RO7122290 (FAP-4-1BBL), cisplatin, and gemcitabine
STUDY PHASE	Ib/II
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 136,754 EudraCT Number: 2017-004634-28 CIV ID: Not applicable NCT Number: NCT03869190
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

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PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
22	See electronic date stamp on the final page of this document.	—	—	—
20	26 October 2023	France	21	14 December 2023
18	21 December 2022	France	19	18 January 2023
15	28 September 2021	United Kingdom	17	9 February 2022
		France	16	28 September 2021
13	13 November 2020	France	14	12 April 2021
11	20 July 2020	United Kingdom	12	13 November 2020
8	4 February 2020	United Kingdom	10	8 February 2020
		France	9	8 February 2020
5	29 July 2019	United Kingdom	7	13 August 2019
		France	6	9 August 2019
2	13 November 2018	France	4	12 April 2019
		United Kingdom	3	19 February 2019
1	4 May 2018	—	—	—

PROTOCOL AMENDMENT, VERSION 22:
RATIONALE

Rationale of Changes from Version 20 (Global) to Version 22 (Global)

Protocol WO39613, Version 20 (Global) has been amended to consolidate Protocol WO39613, Version 21 (France) into Protocol WO39613, Version 22 (Global) to harmonize under the Common Technical Document ahead of the switch to submission under the Clinical Trials Regulation. The specific changes are described below:

- Language has been added to state that all information describing the muscle invasive bladder cancer (MIBC) cohorts is not applicable to France (synopsis, Sections 1.4, 3.1, and 4.1; Appendices 7, 8, and 12).
- Statements have also been added to clarify that specific sections (Sections 2.2, 3.1.3 and associated subsections, 3.1.4.2, 3.3.8–3.3.10, 3.3.12–3.3.14, 4.1.3, 4.1.4 and associated subsections, 4.5.2, 4.5.7, 6.4.4–6.4.6, 6.9.2) and appendices (Appendices 16 and 17) are not applicable to France as these only apply to patients enrolled in the MIBC cohorts.
- For additional clarity, a section on this France-specific stipulation has been made to list the sections and appendices not applicable to France (Section 3.1.7).

An additional minor error has been corrected below:

- A discrepancy in the timing of the final tumor assessment visit in the MIBC cohorts has been corrected from 24 months (104 weeks) after the last study treatment dose to 24 months (104 weeks) after the treatment discontinuation visit to align with Table A12-8 (Section 4.5.7)

Rationale of Changes from Version 21 (France) to Version 22 (Global)

The change summarized below was introduced in Protocol WO39613, Version 20 (Global), but was not included in Protocol WO39613, Version 21 (France). As of Protocol WO39613, Version 22 (Global), this change applies to France. This change will be shown in italics throughout the protocol.

- Analysis of serum troponin (at baseline, if considered standard of care/required per local clinical practice, and as clinically indicated during the study) has been added to aid in the monitoring for cardiotoxicity (Section 4.5.8, Appendix 7 [Tables A7-1 and A7-2], and schedules of activities for all cohorts with patients with metastatic urothelial carcinoma [i.e., Appendices 8, 9, 10, 11, 12, 13, 14, and 15]).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENTS AND COMBINATIONS IN PATIENTS WITH UROTHELIAL CARCINOMA (MORPHEUS-UC)**
PROTOCOL NUMBER:	WO39613
VERSION NUMBER:	22
TEST COMPOUNDS:	Atezolizumab (RO5541267), enfortumab vedotin, niraparib, magrolimab (Hu5F9-G4), tiragolumab (RO7092284), sacituzumab govitecan, tocilizumab (RO4877533), RO7122290 (FAP-4-1BBL), cisplatin, and gemcitabine
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 signed copy as instructed by Labcorp.

PROTOCOL SYNOPSIS

PROTOCOL TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENTS AND COMBINATIONS IN PATIENTS WITH UROTHELIAL CARCINOMA (MORPHEUS-UC)**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 136,754 EudraCT Number: 2017-004634-28 CIV ID: Not applicable NCT Number: NCT03869190

STUDY RATIONALE

The purpose of this study is to evaluate the efficacy, safety, and pharmacokinetics of cancer immunotherapy combinations in patients with locally advanced or metastatic urothelial carcinoma (UC) or muscle-invasive bladder cancer (MIBC). For patients with advanced UC who have progressed following a platinum-containing regimen, single-agent checkpoint inhibitors (CPIs) have shown promising objective response rates and led to improvements in overall survival. However, a significant fraction of patients either do not respond to single-agent CPIs or develop resistance to these treatments. For patients with MIBC, cisplatin-based neoadjuvant chemotherapy is associated with modest improvements in overall survival; however, most patients are not eligible to receive cisplatin, and for those who are eligible, a large proportion do not experience durable benefit. Therefore, there is a high unmet need for improved therapies for patients with metastatic UC and MIBC.

OBJECTIVES AND ENDPOINTS

Table 1 Objectives and Corresponding Endpoints for mUC Cohort Stage 1

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• Objective response rate, defined as the proportion of patients with a CR or PR on two consecutive occasions ≥4 weeks apart during Stage 1, as determined by the investigator according to RECIST v1.1

CR = complete response; DOR = duration of response; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Table 1 Objectives and Corresponding Endpoints for mUC Cohort Stage 1 (cont.)

Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• PFS after randomization, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • OS after randomization, defined as the time from randomization to death from any cause • OS rate at specific timepoints (e.g., 12 months), defined as the proportion of patients who have not experienced death from any cause at that timepoint • DOR, defined as the time from the first occurrence of a documented objective response during Stage 1 to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • Disease control, defined as stable disease ≥ 18 weeks or a CR or PR, as determined by the investigator according to RECIST v1.1
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 1	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in vital signs • Change from baseline in targeted clinical laboratory test results

CR = complete response; DOR = duration of response; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Table 2 Objectives and Corresponding Endpoints for mUC Cohort Stage 2

Safety Objective	Corresponding Endpoints
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 2	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• Plasma or serum concentration of each drug (as appropriate) at specified timepoints

ADA = anti-drug antibody; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PK = pharmacokinetic.

Table 2 Objectives and Corresponding Endpoints for mUC Cohort Stage 2 (cont.)

Immunogenicity Objective	Corresponding Endpoint
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline

ADA = anti-drug antibody; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PK = pharmacokinetic.

Table 3 Objectives and Corresponding Endpoints for MIBC Cohorts

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of treatment in patients treated perioperatively for MIBC	• pCR, defined as the proportion of patients with an absence of residual invasive cancer of the complete resected specimen
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of treatment in patients treated perioperatively for MIBC	• Landmark RFS, defined as RFS at specific timepoints (e.g., 12, 18, 24 months) • Landmark EFS, defined as EFS at specific timepoints (e.g., 12, 18, 24 months) • Landmark OS, defined as OS at specific timepoints (e.g., 12, 18, 24 months)
Safety Objective	**Corresponding Endpoint**
• To evaluate the safety of treatment in patients treated perioperatively for MIBC	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0

EFS = event-free survival; MIBC = muscle invasive bladder cancer; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; pCR = pathological complete response; RFS = recurrence-free survival.

Note: This table is not applicable to France.

OVERALL DESIGN AND STUDY POPULATION

This is a Phase Ib/II, open-label, multicenter, randomized, umbrella study in patients with MIBC and in patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status). Eligible patients will initially be assigned to one of several treatment arms (for mUC [metastatic UC] Cohort Stage 1). Patients in the mUC Cohort who experience loss of clinical benefit or unacceptable toxicity during Stage 1 may be eligible to continue treatment with a different treatment regimen for Stage 2. Patients with cisplatin-ineligible MIBC will be enrolled in either MIBC Cohort 1 or MIBC Cohort 2 based on programmed death ligand-1 (PD-L1) expression status, while patients with cisplatin-eligible MIBC will be enrolled in MIBC Cohort 3 regardless of PD-L1 expression status. When additional treatment options become available for MIBC, patients may be eligible to receive treatment with a different treatment combination in an additional study stage (Stage 2).

Information on the MIBC cohorts is not applicable to France.

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

Table 4 Study Design and Study Population

Phase:	Phase Ib/II	**Population Type:**	Adult patients
Control Method:	Active comparator	**Population Diagnosis or Condition:**	Metastatic urothelial carcinoma (mUC), muscle invasive bladder cancer (MIBC)
Interventional Model:	Parallel group	**Population Age:**	≥ 18 years
Test Compound{s}:	Enfortumab vedotin, niraparib, magrolimab (Hu5F9-G4), tiragolumab, sacituzumab govitecan, tocilizumab, RO7122290 (FAP-4-1BBL)	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Atezolizumab, cisplatin, gemcitabine	**Study Intervention Assignment Method:**	Randomization (mUC Cohort) Randomization and stratification (MIBC cohorts)
Number of Arms:	16	**Number of Participants to Be Enrolled:**	Approximately 145–345 in Stage 1 (mUC Cohort) Approximately 150–300 (MIBC cohorts)

Note: Information on the MIBC cohorts is not applicable to France.

STUDY TREATMENT

Table 5 Study Treatments

Treatment Regimen	Cycle Length	Dose, Route, and Regimen
Atezolizumab	21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle
Atezolizumab and enfortumab vedotin	21 days	• Enfortumab vedotin 1.25 mg/kg IV on Days 1 and 8 • Atezolizumab 1200 mg IV on Day 1
Atezolizumab and niraparib	21 days	• Atezolizumab 1200 mg IV on Day 1 • Niraparib 200 mg by mouth once daily
Atezolizumab and magrolimab	Cycle 1 28 days	• Atezolizumab 840 mg IV on Days 1 and 15 • Magrolimab 1 mg/kg IV on Day 1 • Magrolimab 30 mg/kg IV on Days 8, 15, and 22
	Cycle 2 28 days	• Atezolizumab 840 mg IV on Days 1 and 15 • Magrolimab 30 mg/kg IV on Days 1, 8, 15, and 22
	Cycle 3+ 28 days	• Atezolizumab 840 mg IV on Days 1 and 15 • Magrolimab 30 mg/kg IV on Days 1 and 15
Atezolizumab and tiragolumab	21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Tiragolumab 600 mg IV on Day 1 of each cycle
Atezolizumab and sacituzumab govitecan	21 days	• Sacituzumab govitecan 10 mg/kg by IV infusion on Days 1 and 8 • Atezolizumab 1200 mg by IV infusion on Day 1

Table 5 Study Treatments (cont.)

Treatment Regimen	Cycle Length	Dose, Route, and Regimen
Atezolizumab and tocilizumab	28 days	• Tocilizumab 8 mg/kg IV on Day 1 • Atezolizumab 840 mg IV on Days 1 and 15
Atezolizumab and RO7122290	21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • RO7122290 [redacted]
Atezolizumab, gemcitabine, and cisplatin [a]	Cycles 1–3 Before Surgery 21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Gemcitabine 1000 mg/m^2 IV on Days 1 and 8 of each cycle • Cisplatin 70 mg/m^2 IV on Day 1 of each cycle
	Cycles 4–17 After Surgery 21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle
Atezolizumab, tiragolumab, gemcitabine, and cisplatin [a]	Cycles 1–3 Before Surgery 21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Tiragolumab 600 mg IV on Day 1 of each cycle • Gemcitabine 1000 mg/m^2 IV on Days 1 and 8 of each cycle • Cisplatin 70 mg/m^2 IV on Day 1 of each cycle
	Cycles 4–17 After Surgery 21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Tiragolumab 600 mg IV on Day 1 of each cycle

[a] *These treatment regimens are not applicable to patients in France.*

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

Dose reduction for enfortumab vedotin-associated toxicity is allowed depending on the type and severity of toxicity. Patients should initially dose reduce to 1.0 mg/kg (dose level –1). If additional dose reduction is needed, an additional dose reduction to 0.75 mg/kg (dose level –2) may occur.

Niraparib dose reduction will be allowed based on treatment side effects. Dose reductions to 1 capsule once daily (100 mg) will be allowed. No further dose reductions will be allowed.

The dose of magrolimab may be decreased to 20 mg/kg at the investigator's discretion. The Medical Monitor is available to advise as needed.

Dose modification or discontinuation of tocilizumab is required for serious infections, anaphylaxis, serious hypersensitivity, gastrointestinal perforations, demyelinating disorders, elevated liver enzymes, neutropenia, and thrombocytopenia. Guidelines are presented in Section A14–5.1.4.

The dose of RO7122290 may be decreased to [redacted] at the investigator's discretion if considered in the best interest of the participant. The Medical Monitor is available to advise as needed.

For management of drug-related toxicities, the dose of sacituzumab govitecan can be reduced by 2.5 mg/kg (i.e., one dose level) up to two times , the dose of cisplatin may be reduced by 10 mg/m^2 (i.e., one dose level) up to two times, and the dose of gemcitabine may be reduced by 100 mg/m^2 (i.e., one dose level) up to two times.

Guidelines for sacituzumab govitecan, gemcitabine and cisplatin dose modifications are shown in Table 6.

Table 6 Dose-Modification Levels for Sacituzumab Govitecan, Gemcitabine, and Cisplatin

	Starting Dose	Dose Level −1	Dose Level −2
Sacituzumab govitecan	10 mg/kg	7.5 mg/kg	5 mg/kg
Cisplatin	70 mg/m^2	60 mg/m^2	50 mg/m^2
Gemcitabine	1000 mg/m^2	900 mg/m^2	800 mg/m^2

DURATION OF PARTICIPATION

For the mUC Cohort, treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator. For MIBC cohorts, up to 17 cycles of treatment will be given. Treatment will be stopped if patients experience unacceptable toxicity or loss of clinical benefit as determined by the investigator. The total duration of the study, from screening of the first patient to the end of the study, is expected to be approximately 5−7 years.

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Internal Monitoring Committee, Scientific Oversight Committee

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody, also known as anti-therapeutic antibody
ADP	adenosine diphosphate
ALP	alkaline phosphatase
ASTCT	American Society for Transplantation and Cellular Therapy
Atezo	atezolizumab
CarboGem	carboplatin and gemcitabine
Cis	cisplatin
CIT	cancer immunotherapy
COVID-19	coronavirus 2019
CPI	checkpoint inhibitor
CPS	Combined Positive Score
CR	complete response
CrCl	creatinine clearance
CRS	cytokine release syndrome
CSR	Clinical Study Report
CT	computed tomography
ctDNA	circulating tumor DNA
DOR	duration of response
EBNA	Epstein-Barr nuclear antigen
EBV	Epstein-Barr virus
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
EOT	end of treatment
EMA	European Medicines Agency
EV	enfortumab vedotin
FAP	fibroblast activation protein
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GC	gemcitabine and cisplatin
G-CSF	granulocyte colony-stimulating factor
Gem	gemcitabine
GI	gastrointestinal
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

Abbreviation	Definition
IC	immune cell
ICH	International Council for Harmonisation
IFN	interferon
IL	interleukin
ILD	interstitial lung disease
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intent-to-treat
IxRS	interactive voice or web-based response system
KPS	Karnofsky Performance Status
MIBC	muscle invasive bladder cancer
MMAE	monomethyl auristatin
MRI	magnetic resonance imaging
mUC	metastatic urothelial carcinoma
MVAC	methotrexate, vinblastine, doxorubicin, and cisplatin
NCCN	National Comprehensive Cancer Network
NCI CTCAE v4.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
NGS	next-generation sequencing
Nira	niraparib
ORR	objective response rate
OS	overall survival
PARP	poly (ADP-ribose) polymerase
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
pCR	pathological complete response
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
P-gp	permeability glycoprotein
PK	pharmacokinetic
PR	partial response
PS	performance status
PSA	prostate-specific antigen
QW	every week
Q2W	every 2 weeks
Q3W	every 3 weeks
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1

Abbreviation	Definition
RFS	recurrence-free survival
SG	sacituzumab govitecan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	Scientific Oversight Committee
T3	triiodothyronine
T4	thyroxine
TB	tuberculosis
TCC	transitional cell carcinoma
TCZ	tocilizumab
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TIM-3	T-cell immunoglobulin and mucin domain 3
Tira	tiragolumab
TNF-α	tumor necrosis factor$-\alpha$
TURBT	transurethral resection of bladder tumor
UC	urothelial carcinoma
ULN	upper limit of normal
VCA	viral capsid antigen
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON UROTHELIAL CARCINOMA

Worldwide, urothelial carcinoma (UC) is the most common cancer of the urinary system. The majority of urothelial tumors arise in the bladder with the remainder originating in the renal pelvis, urethra, or ureter. Transitional cell carcinoma (TCC) is the most common histologic subtype associated with bladder cancer and accounts for $>$90% of all UC cases in the industrialized world (Chalasani et al. 2009). Globally, there were an estimated 429,793 new cases of bladder cancer and 165,084 deaths in 2012 (Ferlay et al. 2013). In 2017, it was estimated that there would be 79,030 new cases and 16,870 deaths from bladder cancer in the United States (American Cancer Society 2017).

UC 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). For muscle invasive bladder cancer (MIBC) radical cystectomy with bilateral pelvic lymphadenectomy is the backbone of management. Half of patients with MIBC will develop a local and/or metastatic recurrence of their disease within 2 years of cystectomy and will eventually die from the disease (Raghavan et al. 1990; Stein et al. 2001; Stenzl et al. 2009). For patients with high-risk features ($-$T4a pT3 or pN+) who have not received neoadjuvant chemotherapy, the overall 5-year survival ranges from 10% to 40% (Stein et al. 2001). The MIBC prognostic factors that have been associated with a higher risk for recurrence after surgery include 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).

Poor prognostic factors for survival in patients with metastatic urothelial carcinoma (mUC) include advanced stage of disease at the time of initial diagnosis, Karnofsky Performance Status (KPS) $<$80%, and visceral metastasis (i.e., lung, liver, or bone; Bajorin et al. 1999). The presence of these unfavorable features was associated with a median survival of 4 months compared with 18 months in patients without these features (Loehrer et al. 1992; Bellmunt et al. 2010). The overall 5-year survival rate for mUC is approximately 5.2% (Howlader et al. 2016).

1.2 FIRST-LINE TREATMENT OF METASTATIC UROTHELIAL CARCINOMA

Historically, platinum-based chemotherapy has been the standard of care for patients with previously untreated mUC. The first evidence that chemotherapy produced a significant survival benefit in patients with mUC came in the mid-1980s with two studies that showed that the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) produced overall response rates $>$70% (Sternberg et al. 1985; Sternberg et al. 1989).

In an effort to develop a less toxic regimen, the combination of gemcitabine and cisplatin (GC) was subsequently developed. In a Phase III study comparing MVAC and GC, the two regimens were found to have similar overall survival (OS; 14.0 months for GC vs. 15.2 months for MVAC; hazard ratio = 1.09; 95% CI: 0.88, 1.34; p = 0.66) with GC having less Grade 3 or 4 toxicity (including neutropenia, neutropenic sepsis, and mucositis). As a result, GC has largely displaced MVAC as the standard of care (von der Maase et al. 2005).

Despite the observed efficacy of cisplatin-based combination chemotherapy, up to 50% of patients are ineligible to receive cisplatin because of baseline comorbidities and impaired functional status (Sonpavde et al. 2014; Thompson et al. 2014).

A consensus working group has defined cisplatin-ineligible patients using the following specific criteria (Galsky et al. 2011):

- WHO/Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≥ 2 or a KPS of 60%–70%
- Creatinine clearance < 60 mL/min
- A hearing loss of 25 dB at two contiguous frequencies
- Grade ≥ 2 peripheral neuropathy
- New York Heart Association Class III or greater heart failure

The benefit of carboplatin-based therapy in cisplatin-ineligible patients was demonstrated in the European Organisation for the Research and Treatment of Cancer Trial 30986. In this study, 238 cisplatin-ineligible patients were enrolled to gemcitabine and carboplatin (CarboGem) or methotrexate, carboplatin, and vincristine (De Santis et al. 2012). The objective response rate (ORR) for the CarboGem arm was 41% versus 30% for the methotrexate, carboplatin, and vincristine arm with an improved toxicity profile, effectively identifying CarboGem as the standard of care in these patients, although there was no difference in median OS (9.3 vs. 8.1 months). Notably, those patients with both impaired renal function and poor performance status had especially poor outcomes and increased acute toxicity with combination chemotherapy in this trial. In addition, a posthoc analysis of OS by the Bajorin-risk groups showed that, as the number of risk factors increased, OS decreased significantly (De Santis et al. 2012).

Until recently, carboplatin-based regimens remained the standard of care for cisplatin-ineligible patients. However, the treatment paradigm for mUC, and cisplatin-ineligible mUC in particular, has changed drastically with the recent advances in immunotherapy, specifically checkpoint inhibitors (CPIs). Response rates with single-agent CPIs in mUC platinum-refractory and cisplatin-ineligible patients compare favorably with historical controls (Katz et al. 2017). As a class of agents, CPIs have shown durable long-term responses infrequently observed with historical chemotherapy regimens in 15%–30% of patients. Additionally, these agents have a generally favorable safety profile and have become a preferred treatment option for patients with previously

untreated mUC who are cisplatin ineligible (National Comprehensive Cancer Network [NCCN] 2017). Currently, both pembrolizumab and atezolizumab are approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of first-line cisplatin-ineligible bladder cancer, which provides two new therapies for a patient population that has a significant need for more tolerable treatment options. See Section 3.3.1 for detailed atezolizumab data in this population.

1.2.1 Second-Line Treatment of Metastatic Urothelial Carcinoma

Despite the efficacy of first-line regimens for patients with advanced UC, nearly all patients experience disease progression and will require second-line therapy. Atezolizumab was the first CPI to be approved in the United States (conditional approval) for use in the mUC setting after prior therapy with a platinum-based regimen on the basis of the results of a Phase II, single-arm trial (IMvigor210, Cohort 2), which was followed by a full approval in the same indication in Europe based on results from both IMvigor210 and a Phase III study, IMvigor211 (Powles et al. 2018).

Other second-line treatment CPI options for patients with bladder cancer currently include pembrolizumab, nivolumab, durvalumab, avelumab, as well as several other single-agent chemotherapy regimens (NCCN 2017). It is unclear how the second-line treatment space will evolve and what role CPIs will play as more patients receive CPIs as first-line treatment. One treatment possibility is that many commonly used first-line chemotherapy combinations will move into the second-line space.

A summary of second-line CPI therapy from Phase Ib, Phase II, and Phase III studies is provided in Table 1.

Table 1 Summary of Second-Line Checkpoint Inhibitor Therapy (Phase Ib, Phase II, and Phase III)

Second-Line Therapy Regimen	ORR (%)	PFS (months)	OS (months)
Atezolizumab (n = 931)	13.4	2.1	8.6
Pembrolizumab (n = 542)	21.1	2.1	10.3
Nivolumab (n = 270)	19.6	2.0	8.74
Durvalumab (n = 191)	17.8	1.5	18.2
Avelumab (n = 249)	17	1.6	6.7

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

1.3 NEOADJUVANT TREATMENT OF MUSCLE INVASIVE BLADDER CANCER

MIBC has a 5-year survival rate of 25%–50% (EAU guidelines 2013), with little improvement seen over the past 30 years because of a lack of effective new treatments in this disease area (SEER 2020).

The time from diagnosis to cystectomy is typically 4–8 weeks, providing a window of opportunity to provide patients with neoadjuvant chemotherapy to improve rates of recurrence and OS. The benefits of neoadjuvant chemotherapy are modest, with a 5% increase in OS in patients treated with neoadjuvant chemotherapy as compared to cystectomy alone (Vale 2005). A meta-analysis of data from 11 randomized trials has demonstrated that MIBC is most sensitive to cisplatin-based neoadjuvant chemotherapy (Advanced Bladder Cancer Meta-Analysis Collaboration 2003). EAU and NCCN clinical practice guidelines recommend cisplatin-based neoadjuvant chemotherapy 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 neoadjuvant chemotherapy 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). Patients who achieve a pCR benefit the most from having received neoadjuvant cisplatin-based chemotherapy, with 80%–90% alive at 5 years follow up; however, up to 50% of patients may have residual high-risk disease (pT2 or higher) at the time of surgery, with less than 50% survival at 5 years (Rosenblatt et al. 2012; Bhindi et al. 2017). Therefore, pCR could be a surrogate marker for efficacy and increased survival in neoadjuvant therapies for MIBC.

Only approximately 50% of patients are eligible for cisplatin-based chemotherapy. Factors rendering patients ineligible for cisplatin therapy include an Eastern Cooperative Oncology Group (ECOG) Performance Status of 2, impaired renal function, hearing loss, and neuropathy (Dash et al. 2006; Jiang et al. 2021). There is no evidence that non-cisplatin-based regimens (e.g., carboplatin-based chemotherapy) are as effective as cisplatin-based chemotherapy. Based on 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 is no alternative treatment available to them.

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

This randomized Phase Ib/II umbrella study is designed to accelerate the development of cancer immunotherapy (CIT) combinations by identifying early signals and establishing proof-of-concept clinical data in patients with MIBC and patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen. Single-agent CPIs have shown promising ORRs and OS and are approved for use in patients with mUC who have progressed following a platinum-containing regimen (Rosenberg et al. 2016; Powles et al. 2018).

Platinum-based neoadjuvant chemotherapy is associated with an improvement in OS, but it has only demonstrated durable benefits in a minority of patients. Given the relatively limited treatment options for patients with cisplatin-ineligible MIBC, the small number of patients achieving a pCR after cisplatin-based chemotherapy, and additionally the poor prognosis and potential toxicities associated with treatments for locally advanced or metastatic UCs, these populations are in need of treatment options and are therefore considered appropriate for trials of novel therapeutic candidates. The currently prevailing CIT approach is to circumvent immune evasion mechanisms and reinvigorate anti-tumor responses by targeting T-cell inhibitory factors, such as programmed death-ligand 1 (PD-L1)/programmed death-1 (PD-1).

CIT has demonstrated clear clinical efficacy, with significant survival benefit observed across multiple advanced malignancies, and there is evidence that PD-1/PD-L1 checkpoint blockade can generate pCR and durable responses in patients with UC (Powles et al. 2019; Necchi et al. 2018). Although these targets have resulted in remarkable clinical therapeutic success for various cancer indications, ongoing research indicates that a series of stepwise events is necessary for the generation of an effective anti-tumor immune response (Chen and Mellman 2013). Each event is critical for an effective response, and each is also susceptible to several tumor immune-evasion mechanisms. Thus, the need to identify and circumvent the various factors that account for the absence of, or escape from, an effective anti-cancer immune response will be critical for propagating cancer immunity and advancing the field of CIT. The combination of atezolizumab with agents targeting different immune-evasion mechanisms or novel second-generation CPIs may increase response rates and decrease rates of disease recurrence in this population further.

The potential risks for patients with MIBC will be related to the adverse events associated with study treatments. In most countries, patients wait an average of 4–8 weeks between establishing the diagnosis of urothelial cancer and surgery. Participation in this trial that includes preoperative treatment is not expected to result in relevant delays of surgery for participants. Furthermore, atezolizumab did not have an impact on operability or increases the risks associated with surgery in the ABACUS study (Powles et al. 2019).

The study is designed with the flexibility to open new treatment arms as new treatment combinations become available and close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity. Enrollment of multiple experimental arms within a single study, rather than one or two experimental arms within multiple studies, will result in an overall reduction in the number of patients receiving comparator/control arm treatment. More importantly, this study will assess the importance of simultaneously targeting multiple mechanisms of immune escape through immune cell priming and activation, tumor infiltration, and/or recognition of tumor cells for elimination. To improve the confidence of clinical signal detection in the experimental arms, this study will include a comparator/control arm.

Moreover, patients with mUC who experience loss of clinical benefit with the initial treatment regimen (Stage 1) may be eligible to continue treatment with a different treatment regimen (Stage 2), which may advance the scientific understanding of immune-escape mechanisms in patients who fail to respond to, or experience disease progression during, treatment with a CIT or chemotherapy regimen.

The target and proposed mechanism-of-action classification for each experimental investigational medicinal product (IMP) is summarized in Table 2.
The comparator/control and experimental treatment regimens are described in Section 3.1 (see Table 6 and Table 7). Background information and a rationale for each treatment combination, including a benefit–risk assessment for experimental agents, are provided in the respective appendix for that treatment arm, as outlined in Table 6 and Table 7 for the mUC cohort and in Table 8 for the MIBC cohorts. *Information on the MIBC cohorts is not applicable to France.*

Table 2 Target and Proposed Mechanism-of-Action Classification for Investigational Medicinal Products

Experimental IMP	Target(s)	Proposed Mechanism-of-Action Classification
Atezolizumab	PD-L1	Immune checkpoint inhibitor
Enfortumab vedotin	Nectin-4	Antibody–drug conjugate with anti–nectin-4 monoclonal antibody linked to MMAE (Challita-Eid et al. 2016)
Niraparib	PARP	PARP inhibitor; increases PD-L1 expression and immune activation (Jiao et al. 2017)
Magrolimab (also known as Hu5F9-G4)	CD47	Stimulation of macrophage phagocytosis with subsequent cross-presentation of tumor antigens and immune activation (Tseng et al. 2013; Yanagita et al. 2017)
Sacituzumab govitecan	Trop 2	Tumor cell-targeted topoisomerase-I inhibitor, causes tumor cell death
Tocilizumab	IL-6R	IL-6R inhibitor; decreases tumor-associated macrophages, T-regulatory cells, and myeloid-derived suppressor cells
Tiragolumab	TIGIT	TIGIT antagonist, improves the activation and effectiveness of T-cell and NK-cell tumor-killing activity
RO7122290	FAP 4-1BBL	Fibroblast activation protein-α-targeted split 4-1BB ligand bispecific antibody-like fusion protein; induces co-stimulation of immune cells including CD8+ T and NK cells within the tumor microenvironment
Cisplatin	DNA	Anti-neoplastic (alkylating agent)
Gemcitabine	DNA	Anti-neoplastic (antimetabolite)

ADP = adenosine diphosphate; FAP = fibroblast activation protein; IL-6R = interleukin-6 receptor; IMP = investigational medicinal product; MMAE = monomethyl auristatin; NK = natural killer; PARP = poly (ADP-ribose) polymerase; PD-L1 = programmed death-ligand 1; TIGIT = T-cell immunoreceptor with Ig and ITIM domains.

1.5 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 immune checkpoint inhibition may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses (Wykes and Lewin 2018). 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 CIT.

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 acute SARS-CoV-2 infection while receiving immune CPI therapies (e.g., atezolizumab). At this time, there is insufficient evidence for causal association between immune CPI therapies 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 immune CPI therapies 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 CIT 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 CPIs), 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 CIT (SITC 2020). For patients

enrolling in this study and receiving CIT, 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 CIT 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).

2. OBJECTIVES AND ENDPOINTS

2.1 OBJECTIVES AND ENDPOINTS FOR THE METASTATIC UROTHELIAL CARCINOMA COHORT

This study will evaluate the efficacy, safety, and pharmacokinetics of immunotherapy-based treatment combinations in patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen. Specific objectives and corresponding endpoints for the study are outlined below for Stage 1 (see Table 3) and Stage 2 (see Table 4).

Table 3 Objectives and Corresponding Endpoints for mUC Cohort Stage 1

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• Objective response rate, defined as the proportion of patients with a CR or PR on two consecutive occasions ≥4 weeks apart during Stage 1, as determined by the investigator according to RECIST v1.1
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• PFS after randomization, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • OS after randomization, defined as the time from randomization to death from any cause • OS rate at specific timepoints (e.g., 12 months), defined as the proportion of patients who have not experienced death from any cause at that timepoint • DOR, defined as the time from the first occurrence of a documented objective response during Stage 1 to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • Disease control, defined as stable disease ≥18 weeks or a CR or PR, as determined by the investigator according to RECIST v1.1
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 1	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in vital signs • Change from baseline in targeted clinical laboratory test results
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	• Plasma or serum concentration of each drug (as appropriate) at specified timepoints
• To evaluate potential relationships between drug exposure during Stage 1 and the efficacy and safety of immunotherapy-based treatment combinations	• Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate, on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate, on the basis of available data) and safety endpoints

ADA = anti-drug antibody; CR = complete response; DOR = duration of response; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Table 3 Objectives and Corresponding Endpoints for mUC Cohort Stage 1 (cont.)

Exploratory Immunogenicity Objectives	Corresponding Endpoint
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline
• To evaluate potential effects of ADAs during Stage 1	• For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers during Stage 1 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; CR = complete response; DOR = duration of response; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Table 4 Objectives and Corresponding Endpoints for mUC Cohort Stage 2

Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 2	• Objective response rate, defined as the proportion of patients with a CR or PR on two consecutive occasions ≥4 weeks apart during Stage 2, as determined by the investigator according to RECIST v1.1 • PFS after initiation of Stage 2, defined as the time from initiation of Stage 2 to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • DOR, defined as the time from the first occurrence of a documented objective response during Stage 2 to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • Disease control, defined as stable disease for ≥18 weeks or a CR or PR, as determined by the investigator according to RECIST v1.1
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 2	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• Plasma or serum concentration of each drug (as appropriate) at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate potential effects of ADAs during Stage 2	• For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK, endpoints

ADA = anti-drug antibody; CR = complete response; DOR = duration of response; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Table 4 Objectives and Corresponding Endpoints for mUC Cohort Stage 2 (cont.)

Exploratory Biomarker Objective	Corresponding Endpoint
• To identify biomarkers during Stage 2 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; CR = complete response; DOR = duration of response; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

2.2 OBJECTIVES AND ENDPOINTS FOR THE MUSCLE INVASIVE BLADDER CANCER COHORTS

This study will evaluate the efficacy, safety, and pharmacokinetics of immunotherapy-based treatment combinations in patients with MIBC. Specific objectives and corresponding endpoints for the study are outlined below for the MIBC cohorts (Table 5).

This section is not applicable to France.

Table 5 Objectives and Corresponding Endpoints for MIBC Cohorts

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of treatment in patients treated perioperatively for MIBC	• pCR, defined as the proportion of patients with an absence of residual invasive cancer of the complete resected specimen
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of treatment in patients treated perioperatively for MIBC	• Landmark RFS, defined as RFS at specific timepoints (e.g., 12, 18, 24 months) • Landmark EFS, defined as EFS at specific timepoints (e.g., 12, 18, 24 months) • Landmark OS, defined as OS at specific timepoints (e.g., 12, 18, 24 months)
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of treatment in patients treated perioperatively for MIBC	• RFS, defined as the time from Day 1 in the first cycle after surgery to the first documented recurrence of disease or death from any cause • EFS, defined as the time from randomization to any of the following events (whichever occurs first): disease progression that precludes surgery, as assessed by the investigator according to RECIST v1.1; local or distant disease recurrence; or death from any cause • OS, defined as the time from randomization to death from any cause • Pathological downstaging rate, defined as the proportion of patients that reach ≤ pT2pN0 at the time of cystectomy
Safety Objective	**Corresponding Endpoint**
• To evaluate the safety of treatment in patients treated perioperatively for MIBC	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the PK profile of drugs that are administered to patients treated perioperatively for MIBC	• Plasma or serum concentration of each drug (as appropriate) at specified timepoints
• To evaluate potential relationships between drug exposure and the efficacy and safety of treatment	• Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate, on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate, on the basis of available data) and safety endpoints

ADA = anti-drug antibody; CR = complete response; DOR = duration of response; EFS = event-free survival; MIBC = muscle invasive bladder cancer; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; pCR = pathological complete response; PK = pharmacokinetic; RFS = recurrence-free survival.

Note: This table is not applicable to France.

Table 5 Objectives and Corresponding Endpoints for MIBC Cohorts (cont.)

Exploratory Immunogenicity Objectives	Corresponding Endpoint
• To evaluate the immune response to drugs that are administered to patients treated perioperatively for MIBC	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline
• To evaluate potential effects of ADAs in patients treated perioperatively for MIBC	• For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; CR = complete response; DOR = duration of response; EFS = event-free survival; MIBC = muscle invasive bladder cancer; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PK = pharmacokinetic; RFS = recurrence-free survival.

Notes: *This table is not applicable to France.*
Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1.

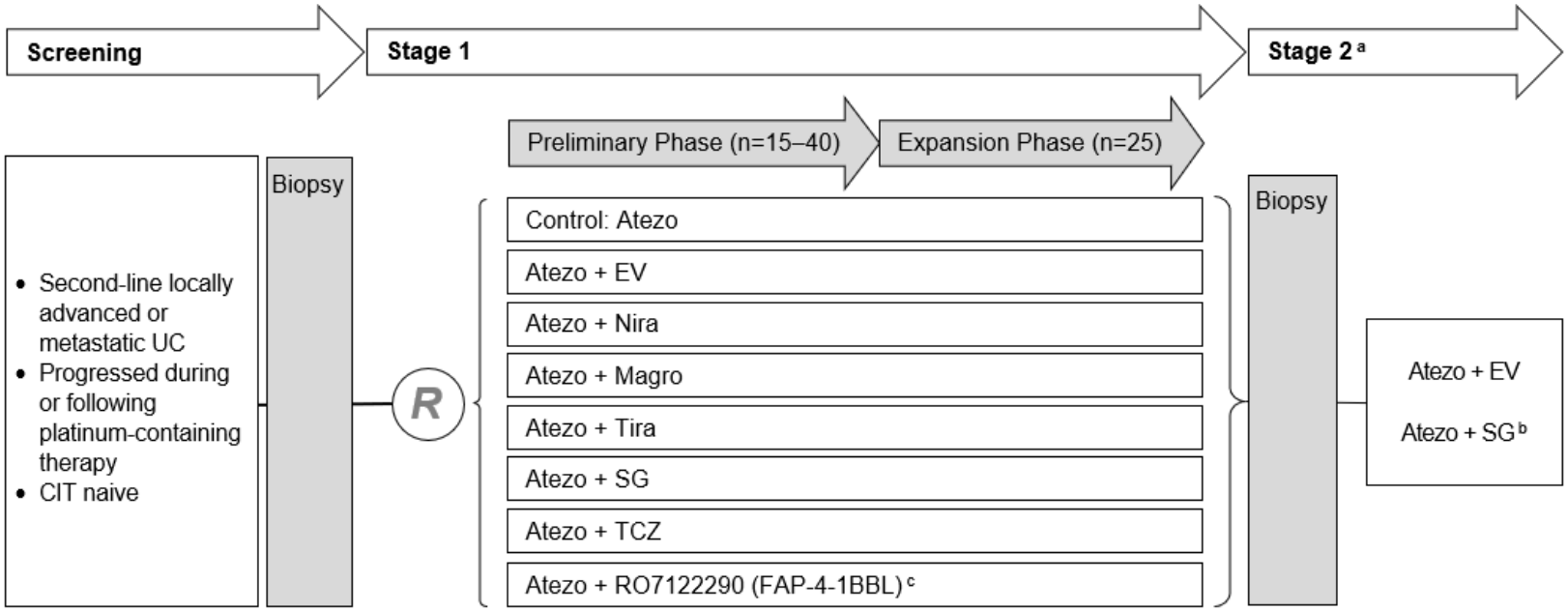
3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase Ib/II, open-label, multicenter, randomized, umbrella study in patients with MIBC and in patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status). Eligible patients will initially be assigned to one of several treatment arms (for mUC Cohort Stage 1, see Section 3.1.1). Patients in the mUC Cohort who experience loss of clinical benefit or unacceptable toxicity during

Stage 1 may be eligible to continue treatment with a different treatment regimen for Stage 2 (see Section 3.1.2). Patients with cisplatin-ineligible MIBC will be enrolled in either MIBC Cohort 1 or MIBC Cohort 2 based on PD-L1 expression status while patients with cisplatin-eligible MIBC will be enrolled in MIBC Cohort 3 regardless of PD-L1 expression status (see Section 3.1.3). When additional treatment options become available for MIBC, patients may be eligible to receive treatment with a different treatment combination in an additional study stage (Stage 2). When a Stage 2 treatment is available for MIBC, this will be introduced by amending the protocol. *Information on the MIBC cohorts is not applicable to France.* For the study design schemas, see Figure 1 and Figure 2.

Figure 1 Study Design for the mUC Cohort



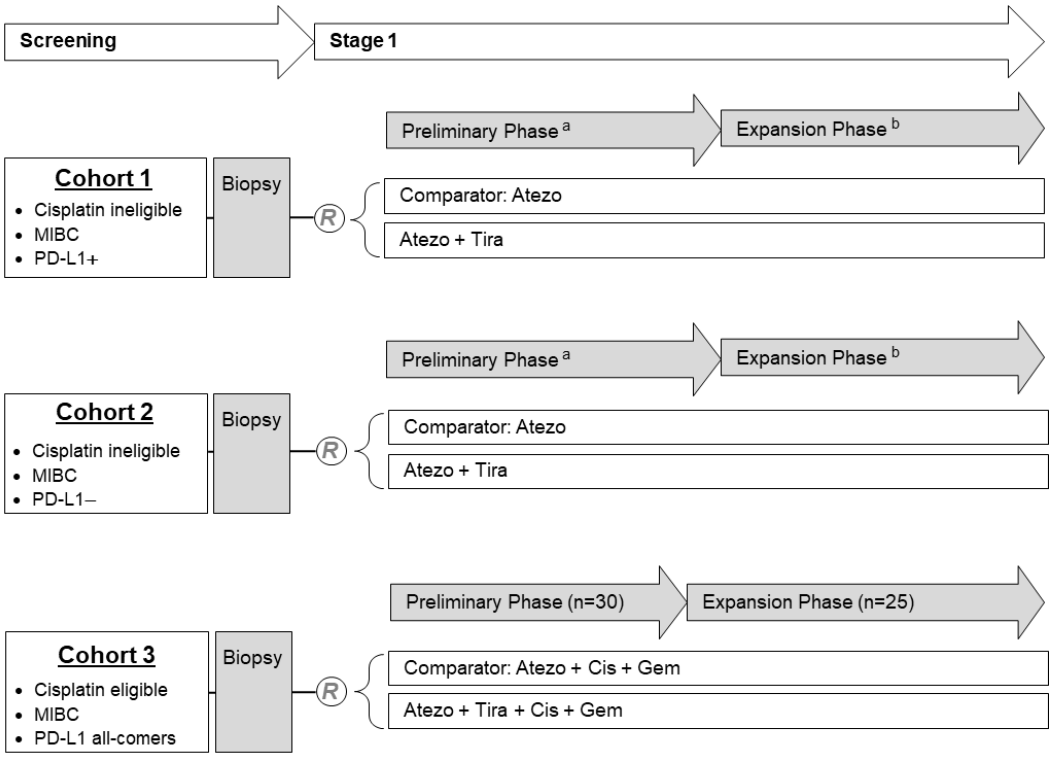
Atezo = atezolizumab; CIT = cancer immunotherapy; EV = enfortumab vedotin; Magro = magrolimab; Nira = niraparib; R = randomization; SG = sacituzumab govitecan; Tira = tiragolumab; TCZ = tocilizumab; UC = urothelial carcinoma.

[a] During Stage 1, patients who experience loss of clinical benefit, as determined by the investigator (see Section 3.1.1 for details), or unacceptable toxicity may be eligible to receive a different treatment combination during Stage 2, provided they meet the eligibility criteria. Details are provided in the respective appendix for each treatment arm (see Appendix 8 through Appendix 15).

[b] Patients who received enfortumab vedotin in Stage 1 will not receive enfortumab vedotin in Stage 2, and patients who received sacituzumab govitecan in Stage 1 will not receive sacituzumab govitecan in Stage 2; other patients who are eligible for more than one treatment arm will be assigned a treatment arm by the investigator. Once the Atezo+SG arm opens, enrollment in the Atezo+EV arm will be closed.

[c] The Atezo+RO7122290 (FAP-4-1BBL) arm will only be opened in ex-U.S. countries.

Figure 2 Study Design for the MIBC Cohorts



Atezo = atezolizumab; Cis = cisplatin; Gem = gemcitabine; MIBC = muscle invasive bladder cancer; PD-L1 = programmed death ligand-1; R = randomization; Tira = tiragolumab.

Note: This figure is not applicable to France.

[a] In the preliminary phase, approximately 90 patients will be enrolled in MIBC Cohorts 1 and 2 (cisplatin-ineligible cohorts) according to PD-L1 status. A minimum of 15 PD-L1+ patients will be enrolled in MIBC Cohort 1. If the minimum is not met by the time 90 patients have been enrolled, up to 10 additional patients may be included in total in the cisplatin-ineligible cohorts. If additional patients are enrolled in the preliminary phase, enrollment in the expansion phase will be reduced by a corresponding amount.

[b] In the expansion phase, either MIBC Cohort 1 or 2 may be expanded individually, or both cohorts may be expanded. In case both cohorts are expanded, up to 100 additional patients will be enrolled in Cohorts 1 and 2. In case only one cohort is expanded, up to 50 patients will be enrolled in that cohort.

3.1.1 Metastatic Urothelial Carcinoma Cohort Stage 1

During Stage 1, patients in the mUC Cohort will be randomly assigned to a control arm (atezolizumab [Atezo]) or an experimental arm consisting of atezolizumab in combination with enfortumab vedotin (Atezo+EV), niraparib (Atezo+Nira), magrolimab (Atezo+Magro), sacituzumab govitecan (Atezo+SG), tocilizumab (Atezo+TCZ), tiragolumab (Atezo+Tira), or RO7122290 (Atezo+RO7122290) (see Figure 1). Details on the treatment regimens for Stage 1 are provided in Appendix 8 through Appendix 15, as specified in Table 6.

Approximately 145–345 patients will be enrolled during Stage 1. Enrollment within the experimental arms will take place in two phases: a preliminary phase, followed by an expansion phase. Up to 40 patients will be enrolled in the Atezo+Nira arm during the preliminary phase to ensure a sufficient number of patients with homologous-recombination deficiency in order to facilitate the evaluation of benefit and risk within this subpopulation. Approximately 15 patients will be enrolled in all other arms during the preliminary phase. If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients may be enrolled in that arm during the expansion phase.

The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Randomization will be suspended after enrollment of a minimum of 6 patients to allow for a safety evaluation in the Atezo+EV, Atezo+Magro, Atezo+TCZ, and Atezo+SG arms (see Section 3.1.4 for details). Experimental arms with insufficient clinical activity or unacceptable toxicity will not be expanded. Additional patients may be enrolled to ensure balance among treatment arms with respect to demographic and baseline characteristics, including potential predictive biomarkers, in order to enable further subgroup analyses. New experimental arms may be added during the study by amending the protocol.

Patients will be randomly assigned to treatment arms, with the exception of the Stage 2 treatment arms. The randomization ratio will depend on the number of experimental arms that are available (e.g., if an arm is added or enrollment in an arm is suspended, pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control arm is no more than 35%. Randomization will take into account arm-specific exclusion criteria. Patients will be ineligible for a specific arm if they meet any of the exclusion criteria outlined for that arm (see Section 4.1.2). Details on treatment assignment and randomization are provided in Section 4.2.

Table 6 Stage 1 Treatment Regimens

Treatment [a, b]	Number of Patients		Appendix
	Preliminary Phase	Expansion Phase [c]	
Atezo (control)	Variable [d]	Variable [d]	Appendix 8
Atezo+EV	15	25	Appendix 9
Atezo+Nira	40	25	Appendix 10
Atezo+Magro	15	25	Appendix 11
Atezo+Tira	15	25	Appendix 12
Atezo+SG	15	25	Appendix 13
Atezo+TCZ	15	25	Appendix 14
Atezo+RO7122290 (FAP-4-1BBL) [e]	15	25	Appendix 15

Atezo = atezolizumab; EV = enfortumab vedotin; HRD = homologous recombination deficiency; Magro = magrolimab; Nira = niraparib; SG = sacituzumab govitecan; TCZ = tocilizumab; Tira = tiragolumab.

[a] The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Thus, all experimental arms may not be open for enrollment at the same time.

[b] Randomization will be suspended after enrollment of a minimum of 6 patients to allow for a safety evaluation in the Atezo+EV, Atezo+Magro, Atezo+TCZ, and Atezo+SG arms (see Section 3.1.4 for details).

[c] If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients will be enrolled in that arm during the expansion phase.

[d] The randomization ratio will depend on the number of experimental arms that are open for randomization (e.g., if an arm is added or randomization into an arm is suspended pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control arm is no more than 35%. See Section 4.2 for more information.

[e] The Atezo+RO7122290 (FAP-4-1BBL) arm will only be opened in ex-U.S. countries.

Patients in the atezolizumab control arm and the experimental arms will be treated until unacceptable toxicity or loss of clinical benefit, as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudoprogression) with CITs (such as atezolizumab), radiographic progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet the criteria for disease progression per RECIST v1.1 while receiving treatment with a CIT drug will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in ECOG PS that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

3.1.2 Metastatic Urothelial Carcinoma Cohort Stage 2

During Stage 1, patients in the mUC Cohort who experience loss of clinical benefit, as determined by the investigator (see Section 3.1.1 for details), or unacceptable toxicity may be eligible to receive a different treatment combination during Stage 2, provided they meet the eligibility criteria. Details are provided in the respective appendix for each treatment arm (see Appendix 8 through Appendix 15).

Study details specific to the Stage 2 treatment regimen are provided in Appendix 9 and Appendix 13, as specified in Table 7.

Patients in Stage 2 who are eligible for more than one treatment arm will be assigned a treatment arm by the investigator. However, patients who receive Atezo+EV in Stage 1 will not receive Atezo+EV in Stage 2, and patients who received Atezo+SG in Stage 1 will not receive Atezo+SG in Stage 2. Once the Atezo+SG arm opens, enrollment in the Atezo+EV arm will be closed.

Stage 2 treatment must begin within 3 months after a patient has experienced loss of clinical benefit or unacceptable toxicity and will continue until loss of clinical benefit or unacceptable toxicity as determined by the investigator. It is recommended that patients begin Stage 2 treatment as soon as possible.

Table 7 Stage 2 Treatment Regimens

Study Treatment	Appendix
Atezo+EV	Appendix 9
Atezo+SG	Appendix 13

Atezo = atezolizumab; EV = enfortumab vedotin; SG = sacituzumab govitecan.

If no clinical activity is observed with Atezo+EV or Atezo+SG combination during the preliminary phase of Stage 1, further enrollment in this combination during Stage 1 and Stage 2 will be stopped. The Sponsor may also decide to hold or discontinue enrollment in Stage 2 treatment arms on the basis of a review of safety data, preliminary efficacy data, and supportive information (e.g., biomarker research data), as appropriate.

3.1.3 Muscle Invasive Bladder Cancer Cohorts

Patients with MIBC will be enrolled in one of three cohorts as shown in Figure 2 and Table 8. *This section and the below subsections are not applicable to France.*

Patients with MIBC who are ineligible to receive cisplatin will be enrolled in either MIBC Cohort 1 PD-L1+ or MIBC Cohort 2 PD-L1− based on PD-L1 expression status. Patients in each cohort will be assigned to a comparator arm or an experimental arm, as detailed in Section 3.1.3.1.

Patients with cisplatin-eligible MIBC will be enrolled in MIBC Cohort 3, with PD-L1 expression status used for stratification. Patients in this cohort will be assigned to a comparator arm or an experimental arm, as detailed in Section 3.1.3.2.

Centralized PD-L1 testing of transurethral resection of bladder tumor (TURBT) samples will be performed using the VENTANA PD-L1 (SP142) assay for all patients with MIBC. A PD-L1 immune cell (IC) score of 2 or 3 (IC2/3, corresponding to the presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥5% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peritumoral stroma) will be considered PD-L1+. An IC score of 0 or 1 (IC0/1, corresponding to the presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≤5% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peritumoral stroma) will be considered PD-L1−.

Patients will receive 3 cycles of treatment pre-surgery (i.e., neoadjuvant setting) and will receive 14 cycles of treatment post-surgery (i.e., adjuvant setting) for a total of 17 cycles. After treatment discontinuation, patients will then be followed for 2 years on a 3-monthly basis. After completing 1 year of post-surgery treatment and 2 years of 3-monthly follow-up assessments, patients should follow up with their physician for local standard-of-care treatment.

The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Experimental arms with insufficient clinical activity or unacceptable toxicity will not be expanded. Additional patients may be enrolled to ensure balance among treatment arms with respect to demographic and baseline characteristics, including potential predictive biomarkers, in order to enable further subgroup analyses. New experimental arms may be added during the study by amending the protocol.

Table 8 Treatment Regimens (MIBC Cohorts)

MIBC Cohort	Treatment [a]	Number of Patients: Preliminary Phase	Number of Patients: Expansion Phase	Appendix
Cohort 1 Cisplatin-ineligible PD-L1+	Atezo (comparator)	Variable [b, c]	Variable [b, d]	Appendix 8
	Atezo + Tira	Variable [c]	Variable [d]	Appendix 12
Cohort 2 Cisplatin-ineligible PD-L1−	Atezo (comparator)	Variable [b, c]	Variable [b, d]	Appendix 8
	Atezo + Tira	Variable [c]	Variable [d]	Appendix 12
Cohort 3 Cisplatin-eligible PD-L1 all-comers	Atezo + Cis + Gem (comparator)	30	25 [e]	Appendix 16
	Atezo + Tira + Cis + Gem	30	25 [e]	Appendix 17

Atezo = atezolizumab; Cis = cisplatin; Gem = gemcitabine; MIBC = muscle invasive bladder cancer; Tira = tiragolumab.

Note: This table is not applicable to France.

[a] The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Thus, all experimental arms may not be open for enrollment at the same time.

[b] The randomization ratio will depend on the number of experimental arms that are open for randomization (e.g., if an arm is added or randomization into an arm is suspended pending analysis of results from the preliminary phase). See Section 4.2 for more information.

[c] In the preliminary phase, approximately 90 patients will be enrolled in MIBC Cohorts 1 and 2 (cisplatin-ineligible cohorts) according to PD-L1 status. A minimum of 15 PD-L1+ patients will be enrolled in MIBC Cohort 1. If the minimum is not met by the time 90 patients have been enrolled, up to 10 additional patients may be included in total in the cisplatin-ineligible cohorts. If additional patients are enrolled in the preliminary phase, the total enrollment in the expansion phase will be reduced by a corresponding amount.

[d] If clinical activity is observed in an arm during the preliminary phase, additional patients will be enrolled in an expansion phase. Either MIBC Cohort 1 or 2 may be expanded individually, or both cohorts may be expanded. In case both cohorts are expanded, up to 100 additional patients will be enrolled in total in Cohorts 1 and 2. In case only one cohort is expanded, up to 50 patients will be enrolled in that cohort

[e] If clinical activity is observed in an arm during the preliminary phase, approximately 25 additional patients will be enrolled in each arm during the expansion phase.

3.1.3.1 Cisplatin-Ineligible MIBC Cohorts

Patients will be assigned to either MIBC Cohort 1 PD-L1+ or MIBC Cohort 2 PD-L1− following centralized PD-L1 testing of TURBT samples. Patients with PD-L1 IC2/3 will be assigned to MIBC Cohort 1 PD-L1+. Patients with a PD-L1 IC0/1 will be assigned to MIBC Cohort 2 PD-L1−.

Patients in the cisplatin-ineligible MIBC cohorts will be randomly assigned to a comparator arm (atezolizumab [Atezo]) or an experimental arm consisting of atezolizumab in combination with tiragolumab (Atezo+Tira) (Figure 2). Details on the treatment regimens for MIBC are provided in Appendix 8 and Appendix 12.

Approximately 90–190 patients will be enrolled in the cisplatin-ineligible MIBC Cohorts. Enrollment will take place in two phases: a preliminary phase, followed by an expansion phase. In the preliminary phase, approximately 90 patients will be enrolled, with a minimum of 15 patients enrolled in MIBC Cohort 1 PD-L1+. If the minimum is not met by the time that a total of 90 patients have been enrolled, up to 10 additional patients may be enrolled in the cisplatin-ineligible cohorts. If additional patients are enrolled in the preliminary phase, enrollment in the expansion phase will be reduced by a corresponding amount.

If clinical activity is observed during the preliminary phase, additional patients may be enrolled in an expansion phase. In the expansion phase, either MIBC Cohort 1 or 2 may be expanded individually, or both cohorts may be expanded. In case both cohorts are expanded, up to 100 additional patients will be enrolled in total in Cohorts 1 and 2. In case only one cohort is expanded, up to 50 patients will be enrolled in that cohort.

The randomization ratio will depend on the number of experimental arms that are available (e.g., if an arm is added or enrollment in an arm is suspended, pending analysis of results from the preliminary phase). Randomization will take into account arm-specific exclusion criteria. Patients will be ineligible for a specific arm if they meet any of the exclusion criteria outlined for that arm (see Section 4.1.4). Details on treatment assignment and randomization are provided in Section 4.2.

3.1.3.2 Cisplatin-Eligible MIBC Cohort

Patients in the cisplatin-eligible MIBC cohort will be randomly assigned to a comparator arm (atezolizumab in combination with cisplatin and gemcitabine [Atezo+Cis+Gem]) or an experimental arm consisting of atezolizumab in combination with tiragolumab, cisplatin, and gemcitabine (Atezo+Tira+Cis+Gem) (Figure 2).

Details on the treatment regimens for MIBC Cohort 3 are provided in Appendix 16 and Appendix 17.

Approximately 60−110 patients will be enrolled in the cisplatin-eligible MIBC Cohort. Enrollment will take place in two phases: a preliminary phase, followed by an expansion phase. During the preliminary phase, up to 30 patients will be enrolled in each arm. If clinical activity is observed in an arm during the preliminary phase, approximately 25 additional patients may be enrolled in each arm during the expansion phase.

The randomization ratio will depend on the number of arms that are available (e.g., if an arm is added or enrollment in an arm is suspended, pending analysis of results from the preliminary phase). Randomization will be stratified by PD-L1 status (IC0/1 versus IC2/3). Randomization will take into account arm-specific exclusion criteria. Patients will be ineligible for a specific arm if they meet any of the exclusion criteria outlined for that arm (see Section 4.1.4). Details on treatment assignment and randomization are provided in Section 4.2.

3.1.4 Safety Evaluation Phase

3.1.4.1 mUC Cohort

Because of the potential for overlapping toxicities, randomization will be suspended after enrollment of a minimum of 6 patients to allow for a safety evaluation in the Atezo+EV, Atezo+Magro, Atezo+TCZ, and Atezo+SG arms. The safety evaluation will be performed after a minimum of 6 patients have completed one cycle of treatment. Patients who withdraw prior to completion of one cycle will not be replaced. If a combination is determined to be sufficiently safe, randomization will be resumed in that arm.

3.1.4.2 MIBC Cohort

Because of the potential for overlapping toxicities of dual immune CPIs with chemotherapy, randomization will be suspended after enrollment of 6 patients to allow for a safety evaluation in the Atezo+Tira+Cis+Gem arm. The safety evaluation will be performed after 6 patients have completed one cycle of treatment. Patients who withdraw prior to completion of one cycle will not be replaced. If Atezo+Tira+Cis+Gem is determined to be sufficiently safe, randomization will be resumed in that arm. *This section is not applicable to France.*

3.1.5 Assessments and Monitoring

All patients will be closely monitored for adverse events throughout the study, and adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). The severity of CRS will also be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) CRS Consensus Grading Scale (see Section 5.3.3, Table 13).

Patients in the mUC cohort will undergo tumor assessments every 9 weeks (starting on Day 1 of Cycle 1) for the first 54 weeks and then every 12 weeks thereafter (see Section 4.5.6 and Appendix 8 through Appendix 15 for details). Patients in the MIBC cohorts will undergo tumor assessments at baseline, within 4 weeks prior to resuming systemic therapy following surgery, and then every 12 weeks (±2 weeks) while on treatment and for 24 months after the last dose of study treatment (see Section 4.5.7 and Appendix 8, Appendix 12, Appendix 16, and Appendix 17 for details). Response will be assessed by the investigator using RECIST v1.1 (see Appendix 1). If clinical activity is demonstrated in an experimental arm, the Sponsor may request that tumor assessment scans for that arm and the corresponding comparator/control arm be submitted for evaluation by a central reading facility.

Baseline tumor tissue samples will be collected from all patients. In the mUC cohort, this will be preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted. Tumor tissue will also be collected from patients who discontinue Stage 1 because of unacceptable toxicity or loss of clinical benefit, as determined by the investigator (if deemed clinically feasible by the investigator). In the MIBC cohorts, tumor tissue will

be collected during the patient's diagnostic TURBT and at cystectomy. These samples, as well as blood samples collected during the study, will be utilized for biomarker research (see rationale for biomarker assessments in Section 3.3.11 and details on tissue sample collection in Section 4.5.8).

To characterize the pharmacokinetic (PK) properties and/or immunogenicity of atezolizumab and other therapeutic agents, blood samples will be obtained at various timepoints before and during study treatment administration.

On the basis of a review of real-time safety data and available PK data, treatment regimens may be modified by the Sponsor as deemed appropriate.

The schedule of activities for each treatment arm is presented in Appendix 8 through Appendix 17.

3.1.6 Internal Monitoring Committee and Scientific Oversight Committee

An Internal Monitoring Committee (IMC) will monitor patient safety throughout the study. The IMC will include representatives from clinical science, safety science, and biostatistics. In addition to the ongoing assessment of the incidence, nature, and severity of adverse events, serious adverse events, deaths, and laboratory abnormalities performed by the investigator and the Medical Monitor, the IMC will review all necessary cumulative data at regular intervals during the study. At the time of each review, the IMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, a treatment regimen should be modified, the protocol should be amended, or enrollment should be held pending further safety evaluations). Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities will be detailed in an IMC Charter.

A Scientific Oversight Committee (SOC) will act as a consultative body to the Sponsor, providing external expert opinions on the safety data collected during the study. This committee will consist of an external group of at least three oncology experts in CIT who will advise the Sponsor on the interpretation of study data. For this purpose, the SOC will evaluate aggregate safety data on a periodic basis, approximately every 6 months from the time the first patient is enrolled in the study. Members will follow a charter that outlines their roles and responsibilities. Data being evaluated by the SOC will include demographic, adverse event, serious adverse event, and relevant laboratory data. The SOC may review efficacy data if safety concerns necessitate benefit–risk assessments. The Sponsor will retain all decision-making authority for this study.

3.1.7 *France-Specific Stipulation*

Information on the MIBC cohorts is not applicable to France.

The following sections and appendices which only contain details about the MIBC cohorts do not apply to France:

- *Section 2.2*
- *Section 3.1.3 and associated subsections*
- *Section 3.1.4.2*
- *Sections 3.3.8–3.3.10*
- *Sections 3.3.12–3.3.14*
- *Section 4.1.3*
- *Section 4.1.4 and associated subsections*
- *Section 4.5.2*
- *Section 4.5.7*
- *Section 6.4.4–6.4.6*
- *Section 6.9.2*
- *Appendix 16*
- *Appendix 17*

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient completes the last visit in both stages, including survival follow-up visits conducted by telephone or on-site visit.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 5–7 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population and Atezo Control Arm for the Metastatic Urothelial Carcinoma Cohort

This study will enroll patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen.

Atezolizumab (Tecentriq®) is approved for the treatment of UC in patients who have progressed during or following a platinum-containing regimen, non–small-cell lung cancer, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, melanoma, and alveolar soft part sarcoma. The approval for second-line treatment of UC patients who have progressed following a prior platinum-containing regimen was based on data from Cohort 2 of the ongoing Phase II study GO29293 (IMvigor210), which was followed by a full approval in the same indication in Europe based on results from both IMvigor210 and a Phase III study GO29294 (IMvigor211). In IMvigor210

Cohort 2, as of 12 July 2017, 310 patients had been enrolled, and an ORR of 16% (95% CI: 13, 21) with a complete response (CR) rate of 7%, and a median duration of response (DOR) was 24.8 months (95% CI: 13.8, 30.4) was observed. Safety evaluation found that 8% of patients had an adverse event that led to treatment withdrawal, and 16% of patients had a treatment-related Grade 3 or 4 adverse event, with the most common events being fatigue, diarrhea, and pruritus. Immune-mediated events occurred in 12% of patients overall, with 7% of patients having a Grade 3 or 4 immune-mediated event (Grade 3 or 4 rash [1%], ALT increased [2%], blood bilirubin increased [2%], and rhabdomyolysis [1%]). In IMvigor211, as of 13 March 2017, a median OS of 8.6 months, an ORR of 13.4% (10.5, 16.9), and a median DOR of 21.7 months was observed in the intent-to-treat (ITT) population.

Despite the promise of single-agent checkpoint inhibition, only a relatively small percentage of patients experience benefit, highlighting the need for immunotherapy combinations. The multiple combination partners in this study are expected to stimulate the immune system through a variety of mechanisms (see Appendix 8 through Appendix 17 for more details) with the aim of extending the benefit of atezolizumab to a larger population of inoperable locally advanced and metastatic UC.

3.3.2 Rationale for Stage 2

The advent of immunotherapy provided the first real advancement in mUC in 30 years. Despite this advancement, substantially more work needs to be done to extend the benefit to larger proportions of patients. Key to our ability to advance immunotherapy will be gaining a better understanding of the underlying tumor immune environment and how the sequencing of treatments will affect response.

The Stage 2 portion of this study allows some patients to proceed with subsequent CIT combinations after disease progression to advance the scientific understanding of immune-escape mechanisms in patients who fail to respond or progress on CIT regimens. Critical to patients' ability to enroll in Stage 2 is their ability to undergo a biopsy to allow for evaluation of the immune environment and any changes that may have happened during Stage 1 treatment. Participation in Stage 2 allows patients and providers access to treatment options with the potential for a durable response and improved toxicity profile not available through traditional chemotherapy. Stage 2 treatment would preclude treatment with other potentially more standard options; thus, patients will be informed during the Stage 2 consent process that by enrolling in Stage 2 they are foregoing therapy that may have a survival benefit.

3.3.3 Rationale for Atezo+EV and Atezo+SG Arms in Stage 2 for the Metastatic Urothelial Carcinoma Cohort

Patients may be given the opportunity to receive Stage 2 treatment with Atezo+EV or Atezo+SG after loss of clinical benefit.

The combination of Atezo+EV was chosen for Stage 2 because of the strong treatment responses documented in patients receiving single-agent enfortumab vedotin who had received prior CPI treatment. Specifically, in a Phase I trial of enfortumab vedotin, 8 of 17 (47%; 95% CI: 23, 72.2) patients with metastatic bladder cancer treated at the recommended Phase II enfortumab vedotin dose obtained a PR (Petrylak et al. 2017). These findings suggest that enfortumab vedotin may provide benefit in the post-CPI space. The addition of atezolizumab to enfortumab vedotin has the potential to improve response durability. Additionally, microtubule-disrupting therapy has the potential to induce immunogenic cell death and initiate an anti-tumor immune response.

The combination of Atezo+SG was chosen for Stage 2 because of the strong treatment responses observed in patients with mUC receiving single-agent sacituzumab govitecan who had progressed on platinum-based therapy and CPI therapy. Specifically, in the Phase II TROPHY-U-01 study, sacituzumab govitecan demonstrated an ORR of 29% in 35 patients including an ORR of 25.0% in patients with liver metastases (Tagawa et al. 2019). These findings suggest sacituzumab govitecan may provide benefit in the post-CPI space. The combination of atezolizumab with sacituzumab govitecan in patients who have progressed following chemotherapy and immunotherapy may provide synergy, by enabling atezolizumab to potentiate an anti-tumor immune response derived from the inflammation mediated by sacituzumab govitecan's anti-tumor activity.

3.3.4 Rationale for Immunotherapy-Based Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, CR, partial response (PR), and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response has been termed pseudoprogression (Hales et al. 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed immune cells and no viable cancer cells. Because of the potential for a response after pseudoprogression, this study will allow patients randomly allocated to immunotherapy-based treatment arms to continue combination treatment after apparent radiographic progression per RECIST v1.1, provided the benefit–risk ratio is judged to be favorable by the investigator (see criteria in Section 3.1.1). Patients should be discontinued for unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1.1 for details).

3.3.5 Rationale for Perioperative Treatment in Muscle Invasive Bladder Cancer

The therapeutic contribution of maintenance therapy following neoadjuvant therapy and surgery is unknown. This study is designed to assess treatment efficacy and to perform extensive biomarker analyses on sequential patient tissues.

IMVigor010 is a Phase III, randomized study that randomly assigned patients with MIBC to receive atezolizumab versus observation as an adjuvant therapy following surgical resection and lymph node dissection. Although the study did not meet its primary endpoint of showing a disease-free survival benefit with atezolizumab adjuvant therapy in the ITT population, a subgroup analysis of T3 and T4 patients, as well as nonclinical data (Liu et al. 2016, Pai et al. 2019, Hussain et al. 2020), suggest that immunotherapy may require that patients have residual or active disease for checkpoint immunotherapy to be effective.

3.3.6 Evidence for Immunotherapy in Patients with Muscle Invasive Bladder Cancer who are Ineligible for Cisplatin-Based Chemotherapy

Approximately 50% of patients with MIBC are ineligible to receive cisplatin-based neoadjuvant chemotherapy, and there are currently no perioperative systemic treatments recommended for these patients; cystectomy with bilateral pelvic lymph node dissection is the standard of care. Furthermore, less than half of patients with MIBC who are eligible for neoadjuvant chemotherapy will receive it due to personal preference or other co-morbidities. Therefore, new therapies are needed to improve outcomes for patients with MIBC.

PD-1/PD-L1 checkpoint immunotherapy is approved for all patients who have progressed on chemotherapy for mUC and for patients with 1L mUC who are either ineligible for platinum-based chemotherapy or are ineligible for cisplatin-based chemotherapy if their tumor is PD-L1+. The largest studies investigating the safety and efficacy of PD-1/PD-L1 checkpoint neoadjuvant immunotherapy in patients with MIBC were the ABACUS and PURE-01 studies (Powles et al. 2019, Necchi et al. 2018).

ABACUS was a single arm, Phase 2 study of 95 patients with T2-T4aN0M0 MIBC who were ineligible for or declined cisplatin-based chemotherapy. Patients were treated with 2 cycles of atezolizumab 1200 mg IV every 3 weeks prior to cystectomy.
PD-L1 positivity was seen in 35 of 88 (39.8%) patients in ABACUS and was associated with a numerically higher pCR rate (PD-L1+ disease: 13/35 [37.1%]; PD-L1− disease: 12/49 [24.5%]; $p = 0.21$). Pre-existing immunity is known to be a positive prognostic marker in patients treated with checkpoint immunotherapy, and in ABACUS, 17 of 42 (40.5%) patients with above median CD8 T-cell infiltration achieved a pCR, as compared to 8 of 41 (19.5%) patients with below median CD8 T-cell infiltration ($p = 0.04$). PD-L1+ disease and CD8 T-cell infiltration was associated with durable responses, with 75% and 85% 12-month OS, respectively.

PURE-01 was a single arm, Phase 2 study of 50 MIBC patients with T3 or less, N0 staging who were eligible to receive cisplatin-based chemotherapy. Patients were treated with 3 cycles of pembrolizumab 200 mg every 3 weeks before undergoing a radical cystectomy. A total of 35 of 50 (54.3%) patients with Combined Positive Score (CPS) $>$ 10% had a pCR, as compared to 15 of 50 (13.3%) of patients with CPS $<$ 10%.

3.3.7 Evidence for Immunotherapy in Patients with Cisplatin-Eligible Muscle Invasive Bladder Cancer

The addition of PD-L1 and PD-1 CPIs to standard platinum-based chemotherapy demonstrated encouraging anti-tumor activity and acceptable safety in early Phase I and II studies (Giaccone et al. 2015; Langer et al. 2016; Rizvi et al. 2016).

Several single-arm studies have evaluated combinations of CPIs with chemotherapy in the neoadjuvant setting for patients with MIBC (Gupta et al. 2020, Funt et al. 2021). In the BLASST-1 trial, 41 patients with MIBC received gemcitabine plus cisplatin plus nivolumab for 4 cycles before radical cystectomy with 27 out of 41 (65.8%) patients experiencing a pathological downstaging less than pT1 at the time of cystectomy (Gupta et al. 2020). In a separate study evaluating the combination of gemcitabine plus cisplatin plus atezolizumab in patients with MIBC, 27 out of 39 patients showed a pathologic response less than pT2, with 17 out of 39 (44%) patients showing pCR. Notably, 90% of patients had PD-L1− tumor, of which 4 out of 4 patients with PD-L1+ tumors, achieved a tumor downstaging less than pT2; 11 out of 11 patients who did not respond had PD-L1− tumors, and 23 out of 27 (85%) patients who responded had PD-L1− tumors. These results contrast with those of the ABACUS study, where patients with PD-L1− disease had fewer pCR than patients with PD-L1+ disease (24.5% vs. 37.1%; Powles et al. 2021). This also contrasts with the results from the PURE-01 study where patients with PD-L1+ disease also showed a higher pCR rate than patients with PD-L1− disease (54.3% vs 13.3%; Necchi et al. 2018). Further investigations are needed to better assess the impact of adding PD-L1 and PD-1 CPIs to cisplatin-based chemotherapy in patients with MIBC, in particular in patients with PD-L1− disease.

The results presented above suggest that the addition of PD-L1 and PD-1 CPIs to chemotherapy could also confer a durable benefit to patients who experience a pathological downstaging (Funt et al. 2021). The duration of recurrence-free survival in patients who experienced an incomplete pathological downstaging following neoadjuvant treatment with gemcitabine plus cisplatin plus atezolizumab will require longer follow up.

The IMvigor130 study is an ongoing Phase III study comparing atezolizumab monotherapy with platinum-based chemotherapy and the combination of atezolizumab plus platinum-based chemotherapy, in patients with untreated locally advanced or metastatic UC. Patients received either cisplatin or carboplatin in combination with gemcitabine as their chemotherapy. Exploratory analyses suggest that patients treated with gemcitabine plus cisplatin plus atezolizumab showed an improved OS when compared to patients treated with gemcitabine plus carboplatin plus atezolizumab, or

gemcitabine plus cisplatin plus placebo or gemcitabine plus carboplatin plus placebo (Table 9).

Table 9 Efficacy Outcomes in Patients Treated with Atezolizumab Plus Chemotherapy in IMvigor 130

IMvigor130: treatment subgroups	IC0/1		IC2/3		HR (95% CI)
	n	Median OS (months)	n	Median OS (months)	
Arm A (atezo + cis/gem)	102	19.5	35	Not reached	0.46 (0.25, 0.83)
Arm A (atezo + carbo/gem)	241	13.9	73	16.6	0.85 (0.61, 1.17)
Arm C (placebo + cis/gem)	102	12.8	34	27.9	0.51 (0.30, 0.86)
Arm C (placebo + carbo/gem)	207	13.0	57	14.0	1.00 (0.71, 1.42)

Atezo = atezolizumab; carbo = carboplatin; cis = cisplatin; gem = gemcitabine; HR = hazard ratio; IC0/1 = presence of programmed death-ligand 1 (PD-L1)–expressing immune cells on < 5% of the tumor area; IC2/3 = presence of PD-L1–expressing immune cells on ≥ 5% of the tumor area; OS = overall survival.

Note: PD-L1 expression on tumor-infiltrating immune cells assessed from archival pretreatment tumor samples (VENTANA SP142 assay).

In the IMvigor130 study, single-cell RNA sequencing was performed on peripheral blood mononuclear cells (PBMCs) obtained at Day 1 of Cycle 1 and Day 1 of Cycle 3 from 70 patients receiving atezolizumab plus platinum (cisplatin or carboplatin) and gemcitabine (Arm A) or placebo plus platinum and gemcitabine (Arm C) in order to assess for differences in the immune profiles of patients treated with cisplatin versus carboplatin. When comparing patients treated with cisplatin versus carboplatin, on-treatment enrichment of hallmark TNF-α signaling via NF-κB and inflammatory response gene sets was observed across all immune cell clusters and the trends were even more pronounced in patients treated with the combination of cisplatin plus gemcitabine plus atezolizumab. Among the top-ranked genes enriched in PBMCs in patients treated with cisplatin versus carboplatin following chemotherapy, such as NINJ1, which mediates plasma membrane rupture during lytic cell death, releasing damage-associated molecular patterns such as HMGB1, a key player driving immunogenicity in cell death (Apetoh et al. 2007; Galsky et al. 2021).

The results from the IMvigor130 study, as well as ongoing studies evaluating immunotherapy with and without chemotherapy in MIBC, suggest that cisplatin/gemcitabine induces immunogenic cell death and enhances anti-tumor immunity when combined with atezolizumab, even in patients with PD-L1– disease.

3.3.8 Rationale for Pathological Complete Response as a Primary Endpoint for the Muscle Invasive Bladder Cancer Cohorts

Pathological complete response (pCR), as well as pathological downstaging (an exploratory endpoint), has been validated as a surrogate marker of activity in this

setting due to its association with durable remission free survival (Rosenblatt et al. 2012; Bhindi et al. 2017).

Increased baseline CD8 T-cell infiltration and PD-L1+ disease have been shown to increase the probability of a pCR with immune therapy in the neoadjuvant setting (Powles et al. 2019).

This section is not applicable to France.

3.3.9 Rationale for Using Atezolizumab as the Comparator in the Cisplatin-Ineligible Muscle Invasive Bladder Cancer Cohorts

No standard of care exists for providing systemic therapy before or after surgical resection for patients with MIBC who decline or are ineligible for cisplatin-based neoadjuvant chemotherapy.

The Sponsor has chosen atezolizumab as a comparator treatment because the ABACUS and PURE-01 studies have shown that PD-1/PD-L1 checkpoint immunotherapy is active and safe in patients with MIBC, with response rates comparable to those historically observed with cisplatin-based chemotherapy. Based on the ABACUS and PURE-01 data, it is possible that compared to mUC, MIBC is typically more inflamed, and therefore more likely to benefit from PD-1/PD-L1 checkpoint immunotherapy, because PD-L1 expression was observed in only 25% and 28.5% of patients treated for mUC in the IMVigor211 and KN-045 studies, respectively.

Randomized studies evaluating immunotherapy combinations will allow us to identify safe and effective treatments for patients with MIBC who are ineligible for cisplatin-based chemotherapy, while also significantly increasing our understanding of cancer biology and improving our ability to iterate when designing new trials and treatments for all patients with MIBC. This study may also include possible future arms and cohorts using immunotherapy combinations that have demonstrated adequate clinical safety.

This section is not applicable to France.

3.3.10 Rationale for Separate PD-L1+ and PD-L1- Cohorts for the Cisplatin-Ineligible Muscle Invasive Bladder Cancer Cohorts

Atezolizumab has been shown to improve clinical outcomes for PD-L1+ and PD-L1− patients in multiple indications, with PD-L1+ patients often deriving the greatest benefit (Atezolizumab Summary of Product Characteristics). PD-1/PD-L1 blockade is approved by the FDA for second line mUC and for patients with PD-L1+ mUC who are not eligible to receive cisplatin-based chemotherapy, as well as for patients who are ineligible to receive platinum-based chemotherapy regardless of PD-L1 status.
For patients with MIBC, the pCR benefit of atezolizumab in the ABACUS study (Szabados et al. 2022) was numerically greater in PD-L1+ patients (37.1%; n = 13/35)

versus PD-L1− patients (24.5%; n=12/49), although this trend did not reach statistical significance (p=0.22). Notably, pCR rates for patients treated with neoadjuvant atezolizumab were higher than the reported pCR rate for patients who did not receive neoadjuvant treatment prior to cystectomy (15%, Grossman et al. 2003). Thus, both PD-L1+ and PD-L1− patients may benefit from atezolizumab or immunotherapy combinations. The design of this study will allow for evaluation of the efficacy of atezolizumab and other immunotherapy combinations in these patient subsets. *This section is not applicable to France.*

3.3.11 Rationale for Biomarker Assessments for the Metastatic Urothelial Carcinoma Cohort

Blood samples for biomarker assessments will be collected at baseline and during the study. Changes in biomarkers in blood may provide evidence of biologic activity of the specific treatment combinations. Correlations between surrogate biomarkers in blood (such as tumor burden markers, cytokines, chemokines, immune cell subpopulations, gene expression, and circulating tumor DNA [ctDNA]) and drug dose and efficacy and safety endpoints may allow for the development of a blood-based biomarker to help define future treatments and predict which patients are more likely to benefit from specific treatment combinations.

Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. Tumor tissue (if deemed clinically feasible by the investigator) will also be collected for patients who discontinue Stage 1 because of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), to enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of study treatments. Tumor samples will be evaluated for biomarkers such as tumor-infiltrating immune cells, PD-L1, CD8, and expression of targets specific to each drug combination. Evaluation of the tumor microenvironment in response to treatment within each arm, including changes in the number and functional status of tumor-infiltrating immune cells, could provide validation of the postulated mechanism of action and confirmation that an appropriate dose and exposure for the specific treatment combination have been achieved.

Tumor tissue and blood samples may be analyzed through use of next-generation sequencing (NGS) methods such as whole exome sequencing (WES) to identify somatic mutations that are 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, or can increase the knowledge and understanding of disease biology.

3.3.12 Rationale for Biomarkers Assessments for the Muscle Invasive Bladder Cancer Cohorts

Sequential cancer tissue, blood, urine, and fecal samples may be collected from patients participating in this study, allowing for several translational objectives to be explored.

This trial requires pre- and post-treatment tissue be collected for the analysis of biomarker pharmacodynamics and potential associations with primary and secondary endpoints; both can be collected as part of the routine care of the patients.
The pre-treatment sample requirement can be satisfied by the diagnostic tissue collected at TURBT or as part of routine care in all patients. Post-treatment tissue samples will be collected at surgery and will not create additional risks for patients because the samples will be collected after tumor tissues have been removed from the patient.

Blood and urine samples will be collected at baseline and during the study to evaluate changes in surrogate biomarkers, such as ctDNA. Changes in biomarkers such as cytokines associated with T-cell activation and lymphocyte subpopulations may provide evidence of biologic activity of atezolizumab and immunotherapy combinations in humans. Correlations between these biomarkers and safety and efficacy endpoints will be explored to identify blood-based biomarkers that might predict which patients are more likely to benefit from treatment.

This section is not applicable to France.

3.3.13 Rationale for Investigations into the Impact of Perioperative Therapy on ctDNA for the Muscle Invasive Bladder Cancer Cohorts

Change in ctDNA concentrations over time has potential for being used to detect disease recurrence (Moding et al. 2020). ctDNA shed from cancer cells into the peripheral blood can be collected non-invasively and tested for the presence of tumor-specific mutations. Several characteristics of UC make it a strong candidate for prognostication of disease recurrence utilizing ctDNA testing:

- UC carries a high somatic mutation rate; therefore, very small numbers of genes or targeted regions can be highly informative to predict disease characteristics (Todenhöfer et al. 2018).
- 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).
- Analyses of paired tumors in UC identified few subclones, bolstering the prognostic potential of longitudinal ctDNA testing after definitive therapy (Lamy et al. 2016; Nodentoft et al. 2014).
- An analysis was performed using the Natera Signatera ctDNA assay on samples taken longitudinally from 68 patients with MIBC who received neoadjuvant chemotherapy and underwent cystectomy. This analysis found that patients whose samples 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 of 21 months) (Christiensen et al. 2019).

These data present a biomarker selected sub-population of MIBC patients with a high unmet need for urgent treatment options. However, there are currently no data on 1) the

impact of neoadjuvant immunotherapy on ctDNA pre- and post-cystectomy in patients with urothelial cancer; 2) if maintenance immunotherapy can help prevent the recurrence of urothelial cancer following cystectomy in patients treated with neoadjuvant immunotherapy; 3) if maintenance immunotherapy would decrease the risk of disease recurrence if patients treated with neoadjuvant immunotherapy had measurable ctDNA following cystectomy.

As part of this study, we will measure ctDNA retrospectively at 4 timepoints: 1) before Day 1 of Cycle 1; 2) before cystectomy; 3) 4–6 weeks post-cystectomy; and 4) 3 months post-cystectomy. We will investigate any association between ctDNA results at these time points with event-free survival (EFS) and OS. These results will inform the design of future studies on the impact of neoadjuvant therapy, as well as the value of maintenance therapy, in patients receiving checkpoint immunotherapy. We will evaluate ctDNA at these time points in other arms of the study pending the outcomes of these investigations and clinical activity observed in other arms.

This design, and the use of ctDNA, will allow the Sponsor to evaluate 1) the impact of neoadjuvant therapy on ctDNA and pathologic response; 2) the impact of surgery on residual ctDNA following neoadjuvant immunotherapy; and 3) whether maintenance immunotherapy reduces the risk of ctDNA and disease recurrence in patients with MIBC following surgery.

This section is not applicable to France.

3.3.14 Rationale for Optional Stool Sample Collection for the Muscle Invasive Bladder Cancer Cohorts

Immunotherapy targeting the PD-L1/PD-1 axis has shown activity in UC, but not all patients respond to treatment, suggesting that host factors, including genetics and the tumor microenvironment, may play a role in determining response to therapy. The gut microbiome has been shown to be a key determinant in immune regulation in cancer, in part by influencing T-cell driven anti-tumor responses (Routy et al. 2018). Furthermore, antibiotic treatment is associated with poor survival outcomes with anti-PD-1 therapy in non–small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and UC (Elkrief et al. 2019). Additionally, the risk of colitis with CITs may be predicted based on a patient's pretreatment microbiome (Dubin et al. 2016; Chaput et al. 2017). Thus, heterogeneity in microbiome composition across patients may be a key driver of safety events in addition to efficacy.

This study will examine whether a patient's microbiome can determine response to a CIT combination, and conversely, whether a CIT combination can alter the microbiome to such an extent that on-treatment changes to the microbiome could be early predictors of immune mediated adverse events. Analyzing the microbiome in patients with MIBC may also provide the opportunity to evaluate the relationship between the microbiome and the risk of recurrence following cystectomy.

This section is not applicable to France.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 145–345 patients with locally advanced or metastatic UC after failure with platinum-containing chemotherapy will be enrolled in this study. Approximately 150–300 patients with MIBC will be enrolled this study *(patients in France will not be eligible to enroll in the MIBC cohorts)*.

4.1.1 Inclusion Criteria for the Metastatic Urothelial Carcinoma Cohort

Patients must meet all of the criteria outlined in Sections 4.1.1.1 and 4.1.1.2 to qualify for Stage 1 of the mUC Cohort. Patients must meet all of the criteria outlined in Sections 4.1.1.2 and 4.1.1.3 to qualify for Stage 2.

4.1.1.1 Inclusion Criteria for Stage 1 in the mUC Cohort

Patients must meet all of the following criteria to qualify for Stage 1:

- Age ≥ 18 years at the time of signing Informed Consent Form
- Life expectancy ≥ 3 months, as determined by the investigator
- Histologically documented, locally advanced (T4b, any N; or any T, N2–N3) or metastatic UC (M1, Stage IV) (also termed TCC or urothelial cell carcinoma of the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra)

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

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

- Availability of a representative tumor specimen that is suitable for determination of PD-L1 and/or additional biomarker status by means of central testing

  Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted.

  A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or 10–16 slides (16 slides preferred) containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report.

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

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

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

- Disease progression during or following treatment with no more than one platinum-containing regimen (e.g., GC, MVAC, CarboGem) for inoperable, locally advanced or metastatic UC or disease recurrence

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

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

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

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

Refer to Section 4.5.8 for additional information on tumor specimens collected at screening.

4.1.1.2 Inclusion Criteria for Stage 1 and Stage 2 in the mUC Cohort

Patients must meet all of the following criteria to qualify for Stage 1 or Stage 2:

- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- ECOG PS of 0 or 1 (see Appendix 3)
- Measurable disease (at least one target lesion) according to RECIST v1.1

  Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.

- 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/μL) without granulocyte colony-stimulating factor (G-CSF) support
  - WBC count $\geq 2.5 \times 10^9$/L (2500/μL)
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9.0 g/dL)

    Patients may be transfused; however, transfusions are not allowed within 2 weeks of screening laboratory tests for eligibility.

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

    For patients assigned to Atezo+Magro arm, hemoglobin ≥ 95 g/L (9.5 g/dL)
  - AST, ALT, and alkaline phosphatase (ALP) $\leq 2.5 \times$upper limit of normal (ULN) with the following exceptions:

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

    Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
  - Bilirubin $\leq 1.5 \times$ULN, with the following exception:

    Patients with known Gilbert disease: bilirubin level $\leq 3 \times$ ULN
  - Albumin ≥ 25 g/L (2.5 g/dL)
  - Creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault formula)
  - For patients not receiving therapeutic anticoagulation:

    PTT or aPTT $\leq 1.5 \times$ ULN

    PT or INR $\leq 1.5 \times$ ULN
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen during the 14 days prior to initiation of study treatment
- Negative HIV test at screening

  Patients without a prior positive HIV test result will undergo an HIV test at screening, unless not permitted per local regulations.
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by quantitative hepatitis B virus (HBV) DNA < 500 IU/mL at screening

  The HBV DNA test will be performed only for patients who have a positive total HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating eggs as outlined for each specific treatment arm in Appendix 8 through Appendix 15
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as outlined for each specific treatment arm in Appendix 8 through Appendix 15

4.1.1.3 Inclusion Criteria for Stage 2 in the mUC Cohort

Patients must meet all of the following criteria to qualify for Stage 2:

- Patients in the atezolizumab control arm: ability to initiate Stage 2 treatment within 3 months after loss of clinical benefit as determined by the investigator while receiving control treatment (see Section 3.1.1 for details)
- Patients in an experimental arm during Stage 1: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity not related to atezolizumab or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) while receiving Stage 1 treatment
- Availability of a tumor specimen from a biopsy performed upon discontinuation of Stage 1

4.1.2 Exclusion Criteria for the Metastatic Urothelial Carcinoma Cohort

Patients will be excluded from enrollment during Stage 1 and Stage 2 if they meet any of the applicable criteria outlined in subsequent sections, as summarized by treatment arm in Table 10. Event grades in the exclusion criteria are based on NCI CTCAE v4.0.

Table 10 Arm-Specific Exclusion Criteria in the mUC Cohort

Stage	Treatment Arm	Applicable Exclusion Criteria
1	Atezo (control)	Sections 4.1.2.1 and 4.1.2.2
	Atezo+EV	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.3
	Atezo+Nira	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.4
	Atezo+Magro	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.5
	Atezo+SG	Sections 4.1.2.1 and 4.1.2.2
	Atezo+TCZ	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.6
	Atezo+Tira	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.7
	Atezo+RO7122290	Sections 4.1.2.1 and 4.1.2.2
2	Atezo+EV	Sections 4.1.2.2 and 4.1.2.3
	Atezo+SG	Section 4.1.2.2

Atezo = atezolizumab; EV = enfortumab vedotin; Magro = magrolimab; Nira = niraparib; SG = sacituzumab govitecan; TCZ = tocilizumab; Tira = tiragolumab.

4.1.2.1 Exclusion Criteria for Stage 1 in the mUC Cohort

Patients who meet any of the following criteria will be excluded from Stage 1:

- Prior treatment with a T-cell co-stimulating therapy or a CPI including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Prior treatment with any of the protocol-specified study treatments including treatment with poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, nectin-4 targeting agents, signal regulatory protein α–targeting agents, TIGIT-targeting agents, Trop-2 targeting agents, FAP-directed therapies, 4-1BB (CD137)-directed therapies, or topoisomerase 1 inhibitors
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Any approved anti-cancer therapy, including chemotherapy or hormonal therapy, within 3 weeks prior to initiation of study treatment; **the following exceptions are allowed:**
  - Palliative radiotherapy for bone metastases or soft tissue lesions should be completed $>$14 days prior to baseline imaging.
  - Hormone-replacement therapy or oral contraceptives
- Eligibility only for the control arm

4.1.2.2 Exclusion Criteria for Stage 1 and Stage 2 in the mUC Cohort

Patients who meet any of the following criteria will be excluded from Stage 1 and from Stage 2:

- Prior allogeneic stem cell or solid organ transplantation
- Treatment with systemic immunostimulatory agents (including, but not limited to, IFN and IL-2) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor–α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressant medication during study treatment, with the following exceptions:

  Patients who received acute, low-dose, systemic immunosuppressant medications, or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for 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 last dose of atezolizumab

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

  Use of an indwelling catheter (e.g., PleurX®) is allowed.

- Uncontrolled tumor-related pain

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

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

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

- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL or corrected serum calcium $>$ ULN)

- Symptomatic, untreated, or actively progressing CNS metastases

  Asymptomatic patients with treated CNS lesions are eligible, provided that all of the following criteria are met:

  – Measurable disease, per RECIST v1.1, must be present outside the CNS.

  – The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.

  – The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment.

  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anti-convulsant therapy at a stable dose is permitted.

- History of leptomeningeal disease

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 4 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study.

Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

- Rash must cover <10% of body surface area.
- Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
- There is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.

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

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

- History of malignancy other than UC within 2 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer

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

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

- Active tuberculosis (TB) (i.e., has signs and symptoms of TB)
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

- Significant cardiovascular disease such as New York Heart Association (NYHA) cardiac disease (Class III or greater), myocardial infarction or cerebrovascular accident within 3 months prior to randomization, unstable arrhythmia, or unstable angina
- Uncontrolled hypertension (defined as systolic blood pressure $>$ 140 mmHg and/or diastolic blood pressure $>$ 95 mmHg)

  Anti-hypertensive therapy to achieve these parameters is allowed.
- Grade $\geq$3 hemorrhage or bleeding event within 28 days prior to initiation of study treatment
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study

  Placement of central venous access catheter (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.
- Adverse events from prior anti-cancer therapy that have not improved to Grade $\leq$1 or better, with the exception of alopecia of any grade and Grade $\leq$2 peripheral neuropathy
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, impair the ability of the patient to participate in the study, or may render the patient at high risk from treatment complications
- History of severe allergic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or recombinant human antibodies
- Known intolerance or hypersensitivity to any of the study drugs of their excipients (including histidine, trehalose dihydrate, and polysorbate 20)
- Known intolerance to any of the drugs required for premedication (acetaminophen, ranitidine, diphenhydramine, and methylprednisolone)
- Patients entering Stage 2: inability to tolerate atezolizumab during Stage 1
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Patients entering Stage 2: immunotherapy-related adverse events that have not resolved to Grade 1 or better or to baseline at the time of consent with the following exception

  Patients with ongoing endocrine events that are adequately managed with supplemental therapy are eligible.

4.1.2.3 Additional Exclusion Criteria for Atezo+EV Arm during Stage 1 and Stage 2 in the mUC Cohort

Patients who meet any of the following criteria will be excluded from the Atezo+EV arm during Stage 1 and Stage 2:

- Ongoing sensory or motor neuropathy Grade ≥ 2
- Active keratitis or corneal ulcerations
- Uncontrolled diabetes, defined as hemoglobin A_{1c} (HbA_{1c}) $\geq 8\%$ or 7 to $< 8\%$ with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained
- AST or ALT $\geq 3.0 \times$ ULN
- Evidence of active keratitis or corneal ulcerations during the Stage 1 ophthalmologic examination prior to Day 1 of Cycle 1 may be re-randomized to a different arm provided that screening assessments are within the screening window; Medical Monitor is available for consultation as needed.
- Evidence of active keratitis or corneal ulcerations during the Stage 2 ophthalmologic examination prior to Day 1 of Cycle 1 may be re-assigned to the Atezo+SG arm provided that screening assessments are within the screening window; Medical Monitor is available for consultation as needed.

4.1.2.4 Additional Exclusion Criteria for Atezo+Nira Arm during Stage 1 in the mUC Cohort

Patients who meet any of the following criteria will be excluded from the Atezo+Nira arm during Stage 1:

- Inability to swallow medication or a malabsorption condition that would alter the absorption of orally administered medications
- Patients with uncontrolled ventricular arrhythmia, uncontrolled major seizure disorder, unstable spinal cord compression, or superior vena cava syndrome

4.1.2.5 Additional Exclusion Criteria for Atezo+Magro Arm during Stage 1 in the mUC Cohort

Patients who meet any of the following criteria will be excluded from the Atezo+Magro arm during Stage 1:

- RBC transfusion dependence, defined as requiring more than 2 units of RBCs transfused during the 4-week period prior to screening
- History of hemolytic anemia or Evans syndrome in the last 3 months

4.1.2.6 Additional Exclusion Criteria for Atezo+TCZ Arm during Stage 1 in the mUC Cohort

Patients who meet any of the following criteria will be excluded from the Atezo+TCZ arm during Stage 1:

- Preexisting central nervous system demyelinating or seizure disorders

- History of diverticulitis, diverticulosis requiring antibiotic treatment, or other symptomatic lower gastrointestinal (GI) conditions that might predispose to perforations
- Current liver disease unrelated to the underlying cancer diagnosis, as determined by the investigator
- Active current infection or history of recurrent bacterial, viral, fungal, mycobacterial or other infections, including, but not limited to, TB and atypical mycobacterial disease, hepatitis B and C, and herpes zoster, but excluding fungal infections of nail beds
- Active TB requiring treatment within 3 years prior to baseline

  Negative TB test must be obtained prior to enrollment. Screening TB testing will be performed only if the study is currently enrolling patients in the Atezo+TCZ arm.
- Untreated latent TB
- Primary or secondary immunodeficiency (history of or currently active)
- ANC $< 2 \times 10^9$/L

4.1.2.7 Additional Exclusion Criteria for Atezo+Tira Arm during Stage 1 in the mUC Cohort

Patients who meet any of the following criteria will be excluded from the Atezo+Tira arm during Stage 1:

- Active Epstein-Barr virus (EBV) infection or known or suspected chronic active EBV infection at screening

  Patients with a positive EBV viral capsid antigen (VCA) IgM test at screening are excluded from this arm. An EBV polymerase chain reaction (PCR) test should be performed as clinically indicated to screen for active infection or suspected chronic active infection. Patients with a positive EBV PCR test are excluded from this arm.

4.1.2.8 Additional Exclusion Criteria for Atezo+RO7122290 Arm during Stage 1 in the mUC Cohort

Patients who meet any of the following criteria will be excluded from the Atezo+RO7122290 arm during Stage 1:

- Clinically significant cardiovascular or cerebrovascular disease within 6 months prior to Day 1 of study drug administration will be excluded.

4.1.3 Inclusion Criteria for the Muscle Invasive Bladder Cancer Cohorts

Patients must meet all of the following criteria to qualify for the MIBC cohorts:

- Age $\geq$ 18 years at the time of signing Informed Consent Form
- Signed Informed Consent Form

- Ability to comply with the protocol, in the investigator's judgment
- ECOG PS of 0 or 1
- Fit and planned-for cystectomy (according to local guidelines)
- Histologically documented MIBC (pT2-4), also termed TCC or urothelial cell carcinoma of the urinary bladder

  Residual disease after TURBT (surgical opinion, cystoscopy/endoscopy or radiological presence).

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

  Refer to Section 4.5.8 for additional information on tumor specimens collected at screening.
- Availability of a TURBT specimen that is suitable for determination of PD-L1 and additional biomarker status by means of central testing

  An FFPE TURBT specimen in a block (strongly preferred) or at least 20 unstained, freshly cut, serially sectioned slides must be submitted along with an associated pathology report. If a specimen from a prior TURBT is submitted, tissue must be collected at most 12 weeks prior to study treatment initiation.

  Tumor tissue of bladder or upper tract should be of good quality based on total and viable tumor content and must contain a muscle invasive component (i.e., T2 or greater) of the tumor as verified by local pathology review.

  Patients having additional tissue samples from procedures performed at different times in the course of their MIBC (e.g., a specimen from a prior TURBT) will be requested (but not required) to also submit these samples for central testing.
- N0 or M0 disease assessed by CT or magnetic resonance imaging (MRI) scan (within 4 weeks of study treatment initiation)
- 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/μL) without G-CSF support
  - WBC count $\geq 2.5 \times 10^9$/L (2500/μL)
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9.0 g/dL)

    Patients may be transfused; however, transfusions are not allowed within 2 weeks of screening laboratory tests for eligibility.

    Patients with a solitary kidney or chronic kidney disease with low erythropoietin production may use erythropoietin-stimulating agents.
  - AST, ALT, and ALP $\leq 2.5 \times$ ULN

- Bilirubin $\leq 1.5 \times$ULN, with the following exception:

  Patients with known Gilbert disease: bilirubin level $\leq 3 \times$ ULN
- Albumin ≥ 25 g/L (2.5 g/dL)
- Creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault formula)
- For patients not receiving therapeutic anticoagulation:

  PTT or aPTT $\leq 1.5 \times$ ULN

  PT or INR $\leq 1.5 \times$ ULN

- Negative HIV test at screening, with the following exception: patients with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count $\geq 200/\mu$L, and have an undetectable viral load.
- Negative total HBcAb test at screening, or positive total HBcAb test followed by quantitative HBV DNA <500 IU/mL at screening

  The HBV DNA test will be performed only for patients who have a positive total HBcAb test.
- Negative HCV antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and, if applicable, agreement to refrain from donating eggs as outlined for each specific treatment arm in Appendix 8, Appendix 12, Appendix 16, and Appendix 17.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as outlined for each specific treatment arm in Appendix 8, Appendix 12, Appendix 16, and Appendix 17.

This section is not applicable to France.

4.1.4 Exclusion Criteria for the Muscle Invasive Bladder Cancer Cohorts

Patients who meet any of the criteria in Section 4.1.4.1 will be excluded from the MIBC cohorts. Patients will be excluded from enrollment in specific arms if they meet any of the applicable criteria outlined in subsequent sections, as summarized by treatment arm

in Table 11. Event grades in the exclusion criteria are based on NCI CTCAE v4.0. *This section and the below subsections are not applicable to France.*

Table 11 Arm-Specific Exclusion Criteria in the MIBC Cohorts

Treatment Arm	Applicable Exclusion Criteria
Atezo + Tira	Section 4.1.4.1; Section 4.1.4.2
Atezo + Tira + Cis + Gem	Section 4.1.4.1; Section 4.1.4.2; Section 4.1.4.3
Atezo + Cis + Gem	Section 4.1.4.1; Section 4.1.4.3

Atezo = atezolizumab; Cis = cisplatin; Gem = gemcitabine; Tira = tiragolumab.

4.1.4.1 Exclusion Criteria for All MIBC Cohorts

Patients who meet any of the following criteria will be excluded from the MIBC cohorts:

- Prior treatment with systemic immunostimulatory agents (including, but not limited to, agents targeting CTLA-4, interferon and IL-2 prior to the initiation of study treatment
- Eligible only for the comparator arm
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor–α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressant medication during study treatment, with the following exceptions:

  Patients who received acute, low-dose (equivalent to < 10mg prednisone), systemic immunosuppressant medications, or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for 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 last dose of atezolizumab
- Uncontrolled tumor-related pain

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

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 4 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  – Rash must cover <10% of body surface area.
  – Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
  – There is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
- History of malignancy other than UC within 2 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer

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

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

- Active TB (i.e., has signs and symptoms of TB)
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety

- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

- Significant cardiovascular disease such as NYHA cardiac disease (Class III or greater), myocardial infarction or cerebrovascular accident within 3 months prior to randomization, unstable arrhythmia, or unstable angina
- Uncontrolled hypertension (defined as systolic blood pressure $>$140 mmHg and/or diastolic blood pressure $>$95 mmHg)

  Anti-hypertensive therapy to achieve these parameters is allowed.

- Grade $\geq$3 hemorrhage or bleeding event within 28 days prior to initiation of study treatment
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure other than cystectomy or nephroureterectomy, during the study

  Placement of central venous access catheter (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.

- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, impair the ability of the patient to participate in the study, or may render the patient at high risk from treatment complications
- History of severe allergic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or recombinant human antibodies
- Known intolerance or hypersensitivity to any of the study drugs of their excipients (including histidine, trehalose dihydrate, and polysorbate 20)
- Known intolerance to any of the drugs required for premedication (acetaminophen, ranitidine, diphenhydramine, and methylprednisolone)
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study

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

4.1.4.2 Additional Exclusion Criteria for Atezo+Tira and Atezo+Tira+Cis+Gem Arms in the MIBC Cohorts

Patients who meet any of the following criteria will be excluded from the Atezo+Tira and Atezo+Tira+Cis+Gem arms:

- Active EBV infection or known or suspected chronic active EBV infection at screening

  Patients with a positive EBV VCA IgM test at screening are excluded from this arm. An EBV PCR test should be performed as clinically indicated to screen for active infection or suspected chronic active infection. Patients with a positive EBV PCR test are excluded from this arm.

4.1.4.3 Additional Exclusion Criteria for the Cisplatin-Eligible MIBC Cohort

Patients who meet any of the following criteria will be excluded from the Atezo + Cis + Gem and Atezo + Tira + Cis + Gem arms:

- Patients who decline neoadjuvant cisplatin-based chemotherapy or in whom neoadjuvant cisplatin-based therapy is not appropriate based upon criteria published by Jiang et al. (2021)

  Impaired renal function (GFR < 50 mL/min); GFR should be assessed by calculation from serum/plasma creatinine (Cockcroft-Gault formula as below):

$$\text{CrCl} = \frac{(140 - \text{age}) \times (\text{wt})}{72 \times \text{Scr}} \quad (\times 0.85 \text{ if female})$$

  Where: CrCl = creatinine clearance in mL/min
  age = patient's age in years
  wt = patient's weight in kg
  Scr = serum creatinine in mg/dL

  – NCI CTCAE v4.0 Grade ≥ 2 audiometric hearing loss of 25 decibels at two contiguous frequencies

  – NCI CTCAE v4.0 Grade ≥ 2 peripheral neuropathy (i.e., sensory alteration or paresthesia, including tingling)

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a randomized, open-label study. After initial written informed consent has been obtained, prescreen testing (if applicable; see Section 4.5.2) has been completed, all screening procedures and assessments have been completed, and eligibility has been established for a patient (including determination of tumor PD-L1 expression status by central testing for patients in the MIBC Cohorts), the study site will obtain the patient's identification number and Stage 1 treatment assignment from the interactive web-based response system (IxRS). Patients in the mUC Cohort who enroll in Stage 2 will be assigned to treatment by the investigator through use of the IxRS and will retain the same patient identification number that was assigned in Stage 1.

Randomization will take into account general exclusion criteria and arm-specific exclusion criteria as outlined in Sections 4.1.2 and 4.1.4. For example, the Atezo+Nira arm will be removed as an option for patients who are ineligible for that arm. If a patient is only eligible for the comparator/control arm or is ineligible for three or more experimental arms, that patient will not be enrolled in the study.

After approximately 6 patients have been randomized into the Atezo+EV, Atezo+Magro, Atezo+TCZ, and Atezo+SG arms, enrollment into those arms will be halted for 1 cycle (21 days for Atezo+EV and Atezo+SG; 28 days for Atezo+Magro, and Atezo+TCZ) in order to evaluate the safety of the treatment regimen. Randomization into other study arms may continue during this time. After the evaluation period has been completed, safety data from the 6 patients will be reviewed by the Sponsor in close consultation with the study investigators. Randomization into the Atezo+EV, Atezo+Magro, Atezo+TCZ, or Atezo+SG arms will be reinitiated upon successful completion of the safety evaluation period (see Appendix 9, Appendix 11, Appendix 13, and Appendix 14 for details).

Patients in the mUC Cohort who are eligible for more than one treatment arm in Stage 2 will be assigned a treatment arm by the Sponsor. However, patients who receive Atezo+SG in Stage 1 will not be eligible for Atezo+SG in Stage 2. Patients who receive Atezo+EV in Stage 1 will not be eligible for Atezo+EV in Stage 2.

Patients who do not receive at least one dose of each drug for their assigned treatment regimen will not be included in the efficacy analyses. Additional patients may be enrolled in Stage 1 to reach the target number of treated patients planned for analysis.

In the cisplatin-eligible MIBC Cohort (Cohort 3), patients will be randomly assigned to a comparator arm or a treatment arm in a 1:1 ratio and will be stratified by PD-L1 expression status (IC0/1 vs. IC2/3).

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

Details on the therapeutic agents for each treatment arm are provided in the respective appendix for that treatment arm, as outlined in Table 6 for Stage 1 and Table 7 for Stage 2.

4.3.1 Investigational Medicinal Product Accountability

The IMPs for this study are atezolizumab, enfortumab vedotin, niraparib, magrolimab, tiragolumab, sacituzumab govitecan, tocilizumab, RO7122290, cisplatin, and gemcitabine. All IMPs required for completion of this study will be provided by the Sponsor where required by local practices. The study site will acknowledge receipt of IMPs supplied by the Sponsor. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by 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 a Drug Inventory Log.

Required premedications will be supplied or reimbursed by the Sponsor as per local practices.

4.3.2 Post-Trial Access to Study Treatment

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

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

4.4 CONCOMITANT THERAPY AND PROHIBITED FOOD

Details on concomitant therapy, prohibited food, and additional restrictions for each treatment arm are provided in the respective appendix for that treatment arm (see Appendix 8 through Appendix 17).

4.5 STUDY ASSESSMENTS

A schedule of activities to be performed during the study is provided for each treatment arm in Appendix 8 through Appendix 17. All activities must 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 infusion; 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 prescreen testing [if applicable; see Section 4.5.2] and screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Written informed consent must also be obtained before performing screening evaluations and study-related procedures for Stage 2.

Screening evaluations for Stage 1 and Stage 2 for the mUC Cohort and for the MIBC Cohorts are to be performed within 28 days prior to randomization. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment (see the schedule of activities for each cohort in Appendix 7).

Patients who fail their first screening for study eligibility (Stage 1 or Stage 2) may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening.

Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within a specified time prior to the initiation of study treatment (see the schedule of activities for each arm in Appendix 8 through Appendix 17) may be used; such tests do not need to be repeated for screening or re-screening.

4.5.2 Prescreen Testing for the Muscle Invasive Bladder Cancer Cohorts

By signing the prescreening consent form, patients may specifically allow for the collection of a tumor tissue sample during the patient's diagnostic TURBT (for details on tumor sample collection and testing please see Section 4.5.8 and the laboratory manual). Written informed consent for participation in the study (on the main study Informed Consent Form) must be obtained before performing any study-specific screening tests or evaluations. *This section is not applicable to France.*

4.5.3 Medical History, Molecular Profile, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history, will be recorded at baseline. The patient's molecular profile for UC, if available, will be recorded at screening and whenever updated information becomes available during the study. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within a specified time prior to initiation of study treatment will be recorded (as outlined for each arm in Appendix 8 through Appendix 17). 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.

4.5.4 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, GI, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions electronic Case Report Form (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.

4.5.5 Vital Signs

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

Vital signs should be measured at specified timepoints, as outlined for each arm in the schedules of activities (see Appendix 8 through Appendix 17), and as clinically indicated.

4.5.6 Tumor and Response Evaluations for the Metastatic Urothelial Carcinoma Cohort

Patients in the mUC Cohort will undergo tumor assessments at baseline, every 9 weeks (±1 week) for the first 54 weeks following initiation of combination treatment, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1. However, patients who continue treatment after disease progression will continue to undergo tumor assessments every 9 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new, non–protocol-specified anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Tumor assessments performed prior to or at the time of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.

All measurable and evaluable lesions should be assessed and documented at screening (and in both Stage 1 and Stage 2). Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to randomization do not have to be repeated at screening.

Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or MRI scans (with IV contrast) of the chest, abdomen, and pelvis. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen and pelvis should be performed. A CT scan with contrast or MRI scan with contrast of the head must be done at screening to evaluate CNS metastases in all patients (MRI scan must be performed if contrast is contraindicated). Bone scans and

CT or MRI scans of the neck and head should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease per RECIST v1.1 may be used.

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

All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases treated with radiotherapy or surgery will not be considered measurable or evaluable but will be documented at screening as a site of metastatic disease. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head CT scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). Tumor assessments must be continued after disease progression per RECIST v1.1 for patients who receive treatment beyond progression. This includes continued measurement of target lesions, evaluation of non-target lesions (including monitoring for further worsening of any non-target lesions that have shown unequivocal progression), and evaluation of any newly identified lesions (including measurements, if lesions are measurable; see Appendix 1) at all subsequent assessments.

Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1) prior to treatment administration at each cycle. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Available results must be reviewed by the investigator prior to treatment administration.

4.5.7 Tumor and Response Evaluations for the Muscle Invasive Bladder Cancer Cohorts

Patients in the MIBC Cohorts will undergo tumor assessments at baseline, within 4 weeks prior to resuming systemic therapy following surgery and then every 12 weeks (±2 weeks) while on treatment and until 24 months (104 weeks) after the treatment *discontinuation visit,* regardless of dose delays, or until disease recurrence, whichever occurs first (see Section 3.1.3 for details). *This section is not applicable to France.*

Tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease recurrence. At the investigator's discretion, tumor assessments may be repeated at any time if disease recurrence is suspected.

Screening assessments must include CT urography (CT of the chest, abdomen, and pelvis with and without IV contrast, with excretory imaging) or magnetic resonance urography with IV contrast of the chest, abdomen, and pelvis. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen and pelvis should be performed. Bone scans and CT or MRI scans of the neck and head should also be performed if clinically indicated. If a CT scan for tumor assessment is performed in a PET-CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Assessment of 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 et al. 2019).

As a general guideline for recurrence, if a suspected lesion is equivocal, for example because of its small size, continued study treatment (if applicable) and follow-up evaluation will clarify whether it represents true recurrence. If repeat scans confirm the presence of new lesions or intervening growth, then recurrence should be declared using the date of the initial scan. When a confirmatory biopsy of disease recurrence is not available, or a biopsy is not deemed safe or feasible by the investigator, recurrence on surveillance imaging will follow the guidelines defined by the Quantitative Imaging Biomarkers Alliance (Apolo et al. 2019), as detailed in Figure 3.

Figure 3 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 Society[27] and the American College of Radiology Incidental Findings Committee[28] 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 imagining.

CT = computed tomography; MRI = magnetic resonance imaging.

Source: Apolo et al. 2019.

Note: This figure is not applicable to France.

4.5.8 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, and other cells)
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (if considered standard of care in the region), *serum troponin (at baseline, if considered standard of care/required per local clinical practice, and as clinically indicated during the study),* glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST

  For patients enrolled in the United Kingdom, chemistry panel (serum or plasma) must include amylase and lipase where applicable (details provided in schedules of activities)
- Amylase, lipase, and uric acid will also be collected in select arms (see arm-specific schedule of activities for details).
- LDH
- Coagulation: INR, 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, unless not permitted per local regulations
- HBV serology: HBsAg, hepatitis B surface antibody, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- TB screening: Performed locally within 3 months prior to randomization when Atezo+TCZ arm is enrolling. Testing should be done per local guidance.
  If tuberculin (purified protein derivative) skin test is performed and returns positive result, a chest X-ray is required.
- C-reactive protein
- HbA_{1c}

- EBV serology (performed for specified arms only; details provided in schedules of activities):
  - EBV VCA IgM
  - EBV VCA IgG or EBNA IgG
  - EBV PCR (only if clinically indicated)
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum 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. During follow-up, pregnancy tests will be performed at 3 and 6 months.

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

- Serum sample for analysis of autoantibodies: anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody in all arms
- Plasma or serum samples for PK analysis (see Appendix 8 through Appendix 17)
- Plasma or serum samples for immunogenicity analysis (see Appendix 8 through Appendix 17)
- Plasma, serum, and peripheral blood mononuclear cell (PBMC) samples for exploratory research on biomarkers (see Appendix 8 through Appendix 17)
- MIBC Cohorts: blood samples for exploratory research on biomarkers (see Appendix 8, Appendix 12, Appendix 16 and Appendix 17)
- MIBC Cohorts: urine samples for exploratory research on biomarkers (see Appendix 8, Appendix 12, Appendix 16 and Appendix 17)
- mUC Cohort: tumor tissue sample collected at baseline (see Section 4.1.1.1) for exploratory research on biomarkers

  Baseline tumor tissue samples from the primary lesion or a metastatic lesion will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be used.

  A representative FFPE tumor specimen in a paraffin block (preferred) or 10–16 slides (16 slides preferred) containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report.

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. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. 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. If tumor tissue is from a TURBT specimen, it must contain a muscle-invasive component (i.e., T2 or greater) of the bladder tumor as verified by local pathology review.

Remaining archival tumor tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first.

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

- MIBC Cohorts: TURBT specimen collected at screening (see Section 4.1.3) for determination of PD-L1 and additional exploratory biomarker research

  If feasible at site, TURBT tissue will be divided and subsequently processed by two different methods as described in the laboratory manual: thorough biomarker assessments will require 1) fresh-frozen and 2) FFPE sample preparations from screening TURBT.

  The FFPE TURBT specimen should be submitted in a paraffin-fixed block (strongly preferred) or as a minimum of 20 unstained, freshly cut, serially sectioned slides along with an associated pathology report. If a specimen from a prior TURBT is submitted, tissue must be collected at most 12 weeks prior to study treatment initiation. Tumor tissue of the bladder or upper tract should be of good quality based on total and viable tumor content and must contain a muscle invasive component (i.e., T2 or greater) of the tumor as verified by local pathology review.

  Patients having additional tissue samples from procedures performed at different times in the course of their MIBC (e.g., a specimen from a prior TURBT) or with lymph node involvement identified at lymph node dissection will be requested (but not required) to also submit these samples for central testing.

  Remaining archival tumor tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first.

- MIBC Cohorts: After neoadjuvant treatment in the study, a cystectomy specimen from surgical resection (i.e., radical cystectomy) must be submitted along with an associated pathology report. For patients without a pCR, the specimen should contain tumor tissue of good quality based on total and viable tumor content. For patients with a pCR, a specimen should be submitted from the tumor bed.

  The cystectomy specimen will be divided and subsequently processed by two different methods as described in the laboratory manual: thorough biomarker assessments will require 1) fresh-frozen and 2) FFPE sample preparations from cystectomy.

  Remaining archival tumor tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first.

- MIBC Cohorts: tissue from lymph node dissection at time of cystectomy. Lymph nodes with evidence of tumor content and/or located proximal to the bladder are strongly preferred; lymph nodes without tumor content or unknown tumor content are also acceptable (see laboratory manual for details).
- Tumor tissue sample collected during Stage 1, for mUC Cohort: at the time of unacceptable toxicity, loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) (if deemed clinically feasible by the investigator); for MIBC Cohorts: at the time of disease recurrence, for exploratory research on biomarkers

  Biopsies should be performed within 40 days after determination of unacceptable toxicity, disease progression, or loss of clinical benefit, 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.

Exploratory biomarker research may include, but will not be limited to, analysis of genes or gene signatures associated with tumor immunobiology, PD-L1, cytokines associated with T-cell activation, T-cell receptor repertoire, or density, localization, and activation status of immune cells and their subsets. 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. DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. NGS methods may include whole genome sequencing (WGS) or WES of tissue and blood samples, but WGS or WES of blood samples will be performed only at participating sites (see Section 4.5.11).

Screening 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.

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 4.5.14), biologic samples will be destroyed no later than the time of completion of the final Clinical Study Report (CSR), with the following exceptions:

- Serum and plasma samples collected for PK analysis or immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final CSR has been completed.
- Plasma, serum, PBMC, blood, tumor tissue, urine, and stool samples collected for biomarker research will be destroyed no later than 5 years after the final CSR has been completed, with the exception of the samples that undergo WES, which will be stored until they are no longer needed or until they are exhausted. However, the storage period for the WES samples will be in accordance with the Institutional Review Board (IRB)/Ethics Committee (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 18 months after 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 will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of 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.

4.5.9 Ophthalmologic Examinations

Patients randomized to the Atezo+EV arm must undergo screening ophthalmologic examination within 14 days of Day 1 of Cycle 1 and as clinically indicated. Assessments should include the following: visual acuity, slit-lamp, tonometry, and dilated fundus examinations. Patients should be monitored and, if ocular symptoms and/or changes in vision are identified, considerations should be given to ophthalmology referral for further evaluation. Prior ophthalmologic exam done within 3 months of screening is acceptable provided symptoms are not new since the exam. Follow-up eye examinations should be performed per standard of care or if clinically indicated (e.g., subject develops new or worsening ocular symptoms). End of treatment (EOT) slit-lamp examinations are

required for patients who experience corneal adverse events during the study. EOT slit-lamp examinations must be performed ≥4 weeks from last dose.

4.5.10 Electrocardiograms

An ECG will be performed at screening, as clinically indicated, and as outlined for each arm in the schedules of activities (see Appendix 7 through Appendix 17). ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. It is recommended that patients be in a supine position for at least 10 minutes prior to ECG recording.

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.

4.5.11 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are 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. Research may include exploration of germline variants. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 4.5.11) will not be applicable at that site.

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 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.

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

Blood samples collected for WGS or WES are to 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).

Data generated from blood samples collected for WGS or WES will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a patient wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.12 Optional Tumor Biopsies in the Metastatic Urothelial Carcinoma Cohort

Consenting patients may undergo optional tumor biopsies 4 weeks (±7 days) after treatment initiation and may undergo additional on-treatment biopsies at any other time at the investigator's discretion (if deemed clinically feasible by the investigator). Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies.

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 Optional Biopsy Sample Informed Consent eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.8. Refer to Section 4.5.14 for details on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.13 Optional Stool Samples

Patients will be given the option of consenting to provide stool samples. Samples will be collected at baseline and before surgery. Patients who consent to providing optional stool samples will receive the collection device prior to baseline and on or before the Day 1 visit in the cycle before surgery.

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

The Informed Consent Form will contain a separate section that addresses optional stool samples. A separate, specific signature will be required to document a patient's agreement to provide optional stool samples.

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 Optional Stool Sample Informed Consent eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.8. Refer to Section 4.5.8 for details on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.14 Optional Samples for Research Biosample Repository

4.5.14.1 Overview of the Research Biosample Repository

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

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

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

4.5.14.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR 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 4.5.14) will not be applicable at that site.

4.5.14.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to CIT or diseases:

- RBR blood sample collected any time during the study
- Leftover blood, serum, plasma, PBMC, tumor tissue, urine, and stool samples (with the exception of leftover tissue from archival FFPE blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides) collected during Stage 1 or Stage 2 of the study, including leftover tissue samples from additional tumor biopsies or medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via WGS, NGS, or other genomic analysis methods.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

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

4.5.14.4 Confidentiality

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

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate

authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR specimens, 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 specimens 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.

4.5.14.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.14.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. However, if RBR specimens 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 specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, 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 specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from this study.

4.5.14.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment 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 or Sponsor determines it is in the best interest of the patient
- Use of another non–protocol-specified anti-cancer therapy
- Pregnancy
- For patients in the mUC Cohort: Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details)
- For patients in the MIBC Cohorts: disease recurrence as defined by the investigator (see Section 4.5.7 for more details), after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease)

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

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease or loss of clinical benefit may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit (for the mUC Cohort), or disease recurrence (for the MIBC Cohorts) will continue to undergo tumor response assessments as outlined in the schedule of activities provided for each arm in Appendix 8 through Appendix 17.

After treatment discontinuation, 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 until death (for the mUC Cohort) and for 2 years after treatment discontinuation (for the MIBC Cohorts) (unless the patient withdraws consent or the Sponsor terminates the study). If a 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. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

4.6.2 Patient Discontinuation from 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 withdrawal from the study may include, but are not limited to, the following:

- Withdrawal of consent
- Study termination or site closure
- 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 information on patients who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

A safety plan for each treatment arm, including a summary of risks and management guidelines for patients who experience specific adverse events, is provided in the respective appendix for that treatment arm in Appendix 8 through Appendix 17.

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

Severe COVID-19 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 COVID-19, 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 COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

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, X-ray) 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; 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 each treatment arm are listed in the respective appendix for that treatment arm (see Appendix 8 through Appendix 17).

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Events Reporting Period

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

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

After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special

interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity. Table 12 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 12 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 (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

The ASTCT CRS Consensus Grading Scale (see Table 13) (Lee et al. 2019) should be used in addition to NCI CTCAE when reporting severity of CRS (see Section 5.3.5.1 for details on CRS reporting).

Table 13 American Society for Transplantation and Cellular Therapy (ASTCT) Cytokine Release Syndrome Consensus Grading

Grade	Symptom(s)
1	• Fever [a], with or without constitutional symptoms • No hypotension • No hypoxia
2	• Fever [a] combined with at least one of the following: – Hypotension not requiring vasopressors – Hypoxia requiring low-flow oxygen [b] by nasal cannula or blow-by
3	• Fever [a] combined with at least one of the following: – Hypotension requiring one vasopressor, with or without vasopressin – Hypoxia requiring high-flow oxygen [b] by nasal cannula, face mask, non-rebreather mask, or Venturi mask
4	• Fever [a] combined with at least one of the following: – Hypotension requiring multiple vasopressors (excluding vasopressin) – Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)
5	• Death due to CRS for which the cause is not the principal factor leading to this outcome

BiPAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome.

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

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

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 14):

- 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 14 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	An adverse event will be considered related, unless it fulfills the criteria specified below. 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

There may be significant overlap in signs and symptoms of infusion-related reactions (IRRs) and CRS. While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, hemophagocytic lymphohistiocytosis (HLH), tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

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 on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction" or “cytokine

release syndrome"). Avoid ambiguous terms such as "systemic reaction." Cases of late-onset CRS should be reported as "cytokine release syndrome" on the Adverse Event eCRF. Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF or Cytokine Release Syndrome eCRF, as appropriate.

If a patient experiences both a local and systemic reaction to single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with associated signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF or Cytokine Release Syndrome eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 6.

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2)

and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of mUC should be recorded on the Death Attributed to Progressive 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).

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 Lack of Efficacy or Worsening of Urothelial Carcinoma

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any

uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., 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 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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

5.4.2.1 Events That Occur prior to Study Treatment Initiation

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

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the 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 serious adverse events that occur after the reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

Reporting requirements for pregnancies are described for each treatment arm in the respective appendix for that treatment arm (see Appendix 8 through Appendix 17).

5.4.4 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (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
- Intentional overdose: intentional 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.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

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, enfortumab vedotin, niraparib, magrolimab, tiragolumab, sacituzumab govitecan, tocilizumab, RO7122290, cisplatin, and gemcitabine 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.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with atezolizumab, enfortumab vedotin, niraparib, magrolimab, tiragolumab, sacituzumab govitecan, tocilizumab, RO7122290, cisplatin, and gemcitabine, 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.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.

- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

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.

5.5 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, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 135 days after the last 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, 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 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 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.

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

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

Drug	Document
Atezolizumab	Atezolizumab Investigator's Brochure
Enfortumab Vedotin	Enfortumab Vedotin Investigator's Brochure
Niraparib	Niraparib Investigator's Brochure
Magrolimab	Magrolimab Investigator's Brochure
Tiragolumab	Tiragolumab Investigator’s Brochure
Sacituzumab Govitecan	Sacituzumab Govitecan Investigator’s Brochure
Tocilizumab	Tocilizumab Investigator's Brochure
RO7122290	RO7122290 Investigator’s Brochure
Cisplatin	Cisplatin U.K. SmPC
Gemcitabine	Gemcitabine U.K. SmPC

SmPC = Summary of Product Characteristics.

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The final study analysis will be based on patient data collected through study discontinuation. If not otherwise specified, efficacy analyses will be based on the efficacy-evaluable population, defined as all patients who receive at least one dose of each drug for their assigned treatment regimen, and the safety analyses will be based

on the safety-evaluable population, defined as all patients who receive any amount of study treatment.

The analysis results will be summarized by the treatment that patients actually receive, as well as by stage (Stage 1 or Stage 2), if applicable. Data will be described and summarized as warranted by sample size. Continuous variables will be summarized through use of means, standard deviations, medians, and minimum and maximum values. Categorical variables will be summarized through use of counts and percentages. Listings will be used in lieu of tables in the event of small sample sizes.

In the mUC Cohort, new baseline values will be established for the Stage 2 efficacy and safety analyses. For evaluation of tumor response, new baseline tumor assessments will be established as described in Section 4.5.6. For other endpoints (e.g., change from baseline in vital signs or laboratory test results), the last non-missing value prior to the patient's first dose during Stage 2 will serve as the new baseline.

6.1 DETERMINATION OF SAMPLE SIZE

This study is not designed to make explicit power and type I error considerations for a hypothesis test. Instead, this study is designed to obtain preliminary efficacy, safety, and PK data on immunotherapy-based treatment combinations when administered to patients with MIBC and to patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen.

In the mUC Cohort, approximately 145–345 patients will be randomly allocated to the control and experimental arms during the study (see Table 6).

In the MIBC Cohorts, approximately 150–300 patients will be randomly allocated to the comparator and experimental arms during the study (see Table 8).

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment will be summarized by region, country, and investigator by treatment arm within the two stages. Patient disposition will be summarized by treatment arm within each stage. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm within each stage.

For safety-evaluable patients, study drug administration data will be tabulated or listed by treatment arm within each stage and any dose modifications will be flagged. Means and standard deviations will be used to summarize the total dose and dose intensity for each study drug. Reasons for discontinuation of study drugs will also be tabulated.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity, weight, malignancy duration, metastatic disease site, and baseline ECOG PS) will be summarized overall and by treatment arm within each stage.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint for the Metastatic Urothelial Carcinoma Cohort

The primary efficacy endpoint is objective response rate during Stage 1, as determined by the investigator according to RECIST v 1.1 and defined in Section 2 (see Table 3). Patients with missing or no response assessments will be classified as non-responders.

ORR, defined as the proportion of patients with a CR or PR, will be calculated for each arm, along with 95% CIs (Clopper-Pearson exact method). The difference in ORR between the experimental arms and the control arm will also be calculated, along with 95% CIs, using the Wald method with continuity correction.

6.4.2 Secondary Efficacy Endpoints for the Metastatic Urothelial Carcinoma Cohort

The secondary efficacy endpoints are progression-free survival (PFS), OS, OS at specific timepoints (e.g., 12 months), DOR, and disease control during Stage 1, as defined in Section 2 (see Table 3). PFS, DOR, and disease control are determined by the investigator according to RECIST v1.1.

DOR will be derived for efficacy-evaluable patients with a CR or PR.

For patients who do not have documented disease progression or death in a study stage, PFS and DOR will be censored at the day of the last tumor assessment.

Patients who are still alive at the time of OS analysis will be censored at the last date they were known to be alive.

The Kaplan-Meier method will be used to estimate the median for PFS, OS, and DOR, with 95% CIs constructed through use of the Brookmeyer and Crowley method. OS rate at specific timepoints will also be estimated through use of the Kaplan-Meier method, with 95% CIs calculated on the basis of the Greenwood estimate for the variance.

Disease control rate, defined as the proportion of patients with stable disease for ≥18 weeks, a PR, or a CR, will be calculated for each treatment arm, with 95% CIs estimated through use of the Clopper-Pearson exact method.

6.4.3 Exploratory Efficacy Endpoints for the Metastatic Urothelial Carcinoma Cohort

The exploratory efficacy endpoints are objective response, PFS, DOR, and disease control during Stage 2, as determined by the investigator according to RECIST v1.1 (see Table 4).

ORR, PFS, DOR, and disease control will be analyzed through use of the same methods described in Sections 6.4.1 and 6.4.2. DOR will be derived for efficacy-evaluable patients with a CR or PR.

6.4.4 Primary Efficacy Endpoint for the Muscle Invasive Bladder Cancer Cohorts

The primary efficacy endpoint for the MIBC Cohorts is pCR, defined as the proportion of patients with an absence of residual invasive cancer of the complete resected specimen. pCR rate will be calculated for each arm, along with 95% CIs. The difference in pCR between the experimental arms and the comparator arm will also be calculated, along with 95% CIs, using the Wald method with continuity correction.

Patients with missing or no response assessments will be classified as non-responders.

Patients will be considered not evaluable for the primary endpoint if they prematurely terminate neoadjuvant treatment due to withdrawal of consent or unrelated adverse events. Patients will not be considered evaluable for the primary or secondary endpoints if they refuse to undergo cystectomy against medical advice, or if they stop neoadjuvant therapy prematurely as a result of an Urgent Safety Measure Dear Investigator Letter (USM-DIL). Additional patients may be enrolled to ensure the desired sample size of the efficacy population.

This section is not applicable to France.

6.4.5 Secondary Efficacy Endpoints for the Muscle Invasive Bladder Cancer Cohorts

The secondary efficacy endpoints for the MIBC Cohorts are landmark recurrence-free survival (RFS), landmark EFS, and landmark OS, each at specific timepoints (e.g., 12, 18, 24 months). RFS, EFS, and OS are defined in Section 6.4.6.

Landmark RFS rates, landmark EFS rates, and landmark OS rates will be estimated for each study arm using the Kaplan-Meier method, with 95% CIs calculated through use of Greenwood's formula.

This section is not applicable to France.

6.4.6 Exploratory Efficacy Endpoints for the Muscle Invasive Bladder Cancer Cohorts

The exploratory efficacy endpoints are RFS, EFS, OS, and pathological downstaging rate.

RFS is defined as the time from Day 1 in the first cycle after surgery to the first documented recurrence of disease or death from any cause. For patients who do not have documented recurrence of disease or death, RFS will be censored at the day of the last tumor assessment post-surgery.

EFS is defined as the time from randomization to any of the following events (whichever occurs first): disease progression that precludes surgery, as assessed by the investigator (see Section 4.5.7); local or distant disease recurrence; or death from any cause. Patients who have not experienced such events will be censored at the time of their last post-tumor tumor assessment.

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

Pathological downstaging rate is defined as the proportion of patients that reach $\leq$pT2pN0 at the time of cystectomy.

The Kaplan-Meier method will be used to estimate the median RFS, EFS, and OS for each study arm. The Brookmeyer and Crowley method will be used to construct the 95% CI for the median RFS, EFS, and OS for each study arm.

This section is not applicable to France.

6.5 SAFETY ANALYSES

Verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v4.0, with severity of CRS graded according to the ASTCT CRS Consensus Grading Scale for CRS (see Table 13).

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs and ECGs, and exposure to study drugs. Exposure to combination treatment and length of safety follow-up will be summarized by treatment arm within each stage.

Treatment-emergent adverse events occurring after initiation of treatment will be summarized. For each patient, the maximum reported severity of each adverse event will be used in the summaries by severity grade. All treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of study treatment, Grade $\geq$3 adverse events, deaths, and causes of death will be listed and

summarized by mapped term, appropriate thesaurus level, and NCI CTCAE severity grade.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory test results will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs will be summarized.

6.6 PHARMACOKINETIC ANALYSES

Sparse samples will be collected for PK analyses of atezolizumab (patients who receive at least one dose of atezolizumab) and drugs given in combination with atezolizumab (patients who receive at least one dose of the drug). Serum or plasma concentrations of the various study drugs will be reported as individual values and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) by treatment arm and by cycle and day when appropriate and as data allow. Individual and median serum or plasma concentrations of the various study drugs will be plotted by treatment arm and cycle and day. PK data for combination drugs may be compared with available historical data from internal and published previous studies. Concentration data may be pooled with data from other studies using an established population PK model to derive PK parameters such as clearance, volume of distribution, and area under the curve.

The relationship between PK parameters and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

6.7 IMMUNOGENICITY ANALYSES

Immunogenicity will be assessed for atezolizumab and other study treatments as appropriate (refer to arm-specific appendices for details). The immunogenicity analyses will include all patients with at least one anti-drug antibody (ADA) assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

For atezolizumab, the numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline 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 postbaseline 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 postbaseline samples are negative, or if they are ADA positive at

baseline but do not have any postbaseline samples with a titer that is at least 0.60-titer unit greater than the titer of the baseline sample (treatment unaffected).

For other study treatments where ADA is tested, positivity will be determined according to standard methods established in previous studies of that drug.

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

6.8 BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in an effort to understand the association of these biomarkers with response to study drugs, taking into account efficacy, safety, PK, immunogenicity, and other biomarker endpoints.

6.9 INTERIM ANALYSES

6.9.1 Interim Analyses for the Metastatic Urothelial Carcinoma Cohort

It is anticipated that interim analyses will be conducted during the study, with the earliest interim analysis of the mUC Cohort taking place when at least one experimental arm has completed enrollment in the Stage 1 preliminary phase, and patients have been followed for a minimum of 9 weeks. Further interim analyses may be conducted as deemed appropriate by Sponsor. A posterior probability may be used to guide further enrollment based on the interim analysis of clinical activity in the experimental arm compared with the control arm. If the interim analysis suggests that the activity in an experimental arm is higher than that in the control arm, there may be further enrollment of 25 additional patients in the experimental arm (expansion phase). The final decision for expanding and ending this Phase Ib trial will be made considering the overall benefit–risk balance and totality of data, including time-to-event endpoints and safety data, as well as emerging external information.

An interim analysis will also be conducted after approximately 15 patients have been enrolled in a Stage 2 treatment arm and followed for a minimum of 9 weeks. If no clinical activity is observed in the Stage 2 treatment arm, further enrollment in that arm will be stopped.

If no clinical activity is observed in the Atezo + EV or Atezo + SG arm at the time of the interim analysis of patients enrolled during the preliminary phase of Stage 1 (n = 15), further enrollment in the Atezo + EV or Atezo + SG arm in Stage 1 will be stopped, while Stage 2 enrollment may also be paused for further evaluation.

The interim analyses will be performed and interpreted by Sponsor study team personnel.

6.9.2 Interim Analyses for the Muscle Invasive Bladder Cancer Cohort

It is anticipated that interim analyses will be conducted during the study when patients have completed their post-surgery pCR assessment. Further interim analyses may be conducted as deemed appropriate by Sponsor. A posterior probability may be used to guide further enrollment based on the interim analysis of clinical activity in the experimental arm compared with the comparator arm. If the interim analysis suggests that the activity in an experimental arm is higher than that in the comparator arm, there may be further enrollment of additional patients as specified in Section 3.1.3. The final decision for expanding and ending this Phase Ib trial will be made considering the overall benefit–risk balance and totality of data, including time-to-event endpoints and safety data, as well as emerging external information.

The interim analyses will be performed and interpreted by Sponsor study team personnel.

This section is not applicable to France.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification 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, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

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

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

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

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

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

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

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (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 9.6).

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

8.4 CONFIDENTIALITY

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

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

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

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

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 Roche policy on study data publication (see Section 9.5).

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 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 clinical study reports and other summary reports will be provided upon request.

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 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring. 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 4.5.8. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be employed to monitor and evaluate patient safety throughout the study. An SOC will provide external expert opinions on the safety data collected during the study.

9.5 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, both at scientific congresses, in clinical trial registries of the U.S. National Institutes of Health and the European Medicines Agency, 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. In addition, redacted Clinical Study Reports 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 provided upon request (see Section 8.4 for more details). For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following web site:

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

The results of this study may be published or presented at scientific congresses. For all clinical 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.

9.6 PROTOCOL AMENDMENTS

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

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

10. REFERENCES

American Cancer Society. Cancer facts & figures 2017 [resource on the Internet]. 2017 [cited 15 August 2017]. Available from: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html.

Apolo AB, Milowsky MI, Kim L. Eligibility and radiologic assessment in adjuvant clinical trials in bladder cancer. JAMA Oncology 2019;5:1790–8.

Bajorin DF, Dodd PM, Mazumdar M, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 1999;17:3173–81.

Bellmunt J, Choueiri TK, Fougeray R, et al. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. J Clin Oncol 2010;28:1850–5.

Bhindi B, Frank I, Mason, R, et al. Oncologic outcomes for patients with residual cancer at cystectomy following neoadjuvant chemotherapy: a pathologic stage-matched analysis. Eur Urol 2017;72:660–4.

Chalasani V, Chin JL, Izawa JI. Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. Can Urol Assoc 2009;3:S193–8.

Challita-Eid PM, Satpayev D, Yang P, et al. Enfortumab vedotin antibody-drug conjugates targeting nectin-4 is a highly potent therapeutic agent in multiple preclinical cancer models. Cancer Res 2016;76(10):3003–13.

Chaput N, Lepage P, Soularue E, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. Ann Oncol 2017;28:1368–79.

Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013;39:1–10.

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.

De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC Study 30986. J Clin Oncol 2012;30:191–9.

Dubin K, Callahan M, Ren B, et al. Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. Nat Commun 2016;7:10391.

Elkrief A, Derosa L, Kromer G, et al. The negative impact of antibiotics on outcomes in cancer patients treated with immunotherapy: a new independent prognostic factor?. Ann Oncol 2019;30:1572–9.

[EAU] European Association of Urology. EAU Guidelines [resource on the Internet]. 2013 [cited 22 September 2017]. Available from: https://uroweb.org/guidelines/.

Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11 [resource on the Internet]. Lyon, France: International Agency for Research on Cancer; 2013 [cited 15 August 2017]. Available from: http://globocan.iarc.fr.

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

Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. Lancet Oncol 2011;12:211–4.

Galsky MD, Guan X, Banchereau R, et al. Cisplatin (cis)-related immunomodulation and efficacy with atezolizumab (atezo) + cis- vs carboplatin (carbo)-based chemotherapy (chemo) in metastatic urothelial cancer (mUC) [abstract]. European Society for Medical Oncology (ESMO) Congress 2021.

Grossman BH, 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.

Hales RK, Banchereau J, Ribas A, et al. Assessing oncologic benefit in clinical trials of immunotherapy agents. Ann Oncol 2010;21:1944–51.

Howlader N, Morton LM, Feuer EJ, et al. Contributions of subtypes of non-hodgkin lymphoma to mortality trends. Cancer Epidemiol Biomarkers Prev 2016;25:174–9.

Hussain M, 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(15 Suppl):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.

Jiang DM, Gupta S, Kitchlu A, et al. Defining cisplatin eligibility in patients with muscle-invasive bladder cancer. Nat Rev Urol 2021;18:104–114.

Jiao S, Xia W, Yamaguchi H, et al. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin Canc Res 2017;23:3711–20.

Katz H, Wassie E, Alsharedi M. Checkpoint inhibitors: the new treatment paradigm for urothelial bladder cancer. Med Oncol 2017;34:170.

Kaufman DS, Shipley WU, Feldman AS. Bladder cancer. Lancet 2009;374:239–49.

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.

Liu J, Blake J, Yong M, et al. Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease. Cancer Discov 2016;6:1382–99.

Loehrer PJ Sr, Einhorn LH, Elson PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol 1992;10:1066–73.

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

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.

Moding E, Liu Y, Nabet B, et al. Circulating tumor DNA dynamics predict benefit from consolidation immunotherapy in locally advanced non-small-cell lung cancer. Nat Cancer 2020;1:176–83.

[NCCN] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: bladder cancer [resource on the Internet]. 2017 [cited 15 August 2017]. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx.

[NCCN] National Comprehensive Cancer Network. Recommendations of the NCCN COVID-19 Advisory Committee. Cancer and COVID-19 vaccination [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.

Necchi A, Anichini A, Raggi D, et al. Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): an open-label, single-arm, phase II study. Int J Clin Oncol 2018;36:3353–60.

Pai C, Huang J, Lu X, et al. Clonal deletion of tumor-specific T cells by interferon-γ confers therapeutic resistance to combination immune checkpoint blockade. Immunity 2019;50:477–92.

Petrylak DP, Perez RP, Zhang J, et al. A phase 1 study of enfortumab vedotin (ASG-22CE; ASG-22ME): updated analysis of patients with metastatic urothelial cancer. J Clin Oncol 2017;35(15 Suppl):106.

Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2018;391(10122):748–757.

Powles T, Kockx M, Rodriguez-Vida A, et al. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. Nat Med 2019;25:1706–14.

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

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.

Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 2018;359:91–7.

[SEER] Surveillance, Epidemiology, and End Results Program. Cancer stat facts: bladder cancer [resource on the Internet]. 2020 [cited 22 September 2020]. Available from: https://seer.cancer.gov/statfacts/html/urinb.html.

[SITC] Society for Immunotherapy of Cancer. SITC Statement on SARS-CoV-2 vaccination and cancer immunotherapy [resource on the Internet]. 2020 [updated 23 December 2020; cited 26 May 2021]. Available from: https://www.sitcancer.org/aboutsitc/press-releases/2020/sitc-statement-sars-cov-2-vaccination-cancer-immunotherapy.

Sonpavde G, Galsky MD, Latini D, et al. Cisplatin-ineligible and chemotherapy-ineligible patients should be the focus of new drug development in patients with advanced bladder cancer. Clin Genitourin Cancer 2014;12:71–3.

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, Yagoda A, Scher HI, et al. Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. J Urol 1985;133:403–7.

Sternberg CN, Yagoda A, Scher HI, et al. Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. Cancer 1989;64:2448–58.

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.

Tagawa ST, Faltas BM, Lam ET, et al. Sacituzumab govitecan (IMMU-132) in patients with previously treated metastatic urothelial cancer (mUC): Results from a phase I/II study. J Clin Oncol 2019;37(7 Suppl):3199–212.

Tecentriq® (atezolizumab) Summary of Product Characteristics, Genentech.

Thompson RH, Boorjian SA, Kim SP, et al. Eligibility for neoadjuvant/adjuvant cisplatin-based chemotherapy among radical cystectomy patients. BJU Int 2014;113:E17–21.

Thomsen MBH, Nordentoft I, Lamy P, et al. Comprehensive multiregional analysis of molecular heterogeneity in bladder cancer. Sci Rep 2017;7:11702.

Todenhöfer T, Struss WJ, Seiler R, et al. Liquid biopsy-analysis of circulating tumor DNA (ctDNA) in bladder cancer. Bladder Cancer 2018;4:1929.

Tseng D, Voklmer J-P, Willingham SB, et al. Anti-CD47 antibody-mediated phagocytosis of cancer by macrophages primes an effective antitumor T-cell response. Proc Natl Acad Sci 2013;110:11103–8.

Vale CL. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 2005;48:202–5.

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.

Wykes MN, Lewin SR. Immune checkpoint blockade in infectious diseases. Nat Rev Immunol 2018;18:91–104.

Yanagita T, Murata Y, Tanaka D, et al. Anti-SIRPα antibodies as a potential new tool for cancer immunotherapy. JCI Insight 2017;2:e89140.

Appendix 1
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval ≤ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

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

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, because CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

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

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

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

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

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes because they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well, and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is < 5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non-lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to < 10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis < 10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedules of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

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

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

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

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table A1-1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table A1-1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

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

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

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as having "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table A1-1.

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

REFERENCE

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Appendix 2
Placeholder for Future Use

The Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST) appendix has been removed as the Sponsor no longer plans to perform these analyses. Appendix 2 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 3
ECOG Performance Status Scale

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

ECOG = Eastern Cooperative Oncology Group.

Appendix 4
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 and/or tiragolumab for patients who have previously experienced a severe or life-threatening skin adverse reaction and pericardial disorders while receiving another immunostimulatory anti-cancer 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
- Dysautonomia
- Epidermolysis bullosa acquisita
- Gestational pemphigoid
- Giant cell arteritis
- Goodpasture syndrome
- 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
- Granulomatosis with polyangiitis

Appendix 5
Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

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

Appendix 6
Risks Associated with Atezolizumab and Guidelines for Management of Atezolizumab-Specific Adverse Events

Note: Because of the expected pharmacologic activity of tiragolumab, the adverse event management guidelines described in this appendix, including those for continuing, withholding, resuming, and discontinuing atezolizumab, as outlined below, are applicable to tiragolumab as well as atezolizumab where noted.

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

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

Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections in this appendix or the treatment arm-specific appendices.

- In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.
- Consider withholding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5−1 mg/kg/day of prednisone or equivalent) may be administered.
- For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.

- Withhold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1–2 mg/kg/day oral prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.
- In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.
- The investigator should consider the benefit–risk balance for a given patient prior to further administration of atezolizumab. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over $\geq$1 month to the equivalent of $\leq$10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for $>$12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for $>$12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for $>$12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Coronavirus disease 2019 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table A6-1.

Table A6-1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab. – Consider resuming on radiographic evidence of improvement.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL with or without transbronchial biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c, d] • For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.

BAL = bronchoscopic alveolar lavage.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

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

Table A6-1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

Event	Management
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c, d] • Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment • Bronchoscopy or BAL with or without transbronchial biopsy is recommended. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

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

HEPATIC EVENTS

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table A6-2.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table A6-2 Management Guidelines for Hepatic Events

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

LFT = liver function tests.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table A6-3.

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

Table A6-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

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

GI = gastrointestinal.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

Table A6-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table A6-4.

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

Table A6-4 Management Guidelines for Endocrine Events

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

MRI = magnetic resonance imaging.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

Table A6-4 Management Guidelines for Endocrine Events (cont.)

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

MRI = magnetic resonance imaging.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

Table A6-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement as clinically needed. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.

MRI = magnetic resonance imaging.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

Table A6-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement as clinically needed.

MRI = magnetic resonance imaging.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table A6-5.

Table A6-5 Management Guidelines for Ocular Events

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

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

IMMUNE-MEDIATED CARDIAC EVENTS

In high-risk patients (including those with abnormal baseline cardiac troponin levels, when available), transthoracic echocardiogram (TTE) monitoring should be considered, as clinically indicated, and based on local testing practice. Management guidelines for cardiac events are provided in Table A6-6.

IMMUNE-MEDIATED MYOCARDITIS

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

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, a TTE for evaluation of left ventricular ejection fraction and global longituidinal strain (GLS), and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-6.

IMMUNE-MEDIATED PERICARDIAL DISORDERS

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

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

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer (e.g., metastatic disease), cancer treatment (e.g., chest radiotherapy), cardiac injury (e.g., injury due to myocardial infarction or iatrogenesis), and autoimmune disorders, and should be managed accordingly.

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

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-6. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table A6-6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2–4 or Immune-mediated pericardial disorders, Grades 2–4	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider anti-arrhythmic drugs, temporary pacemaker, ECMO, VAD or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1 g/day IV methylprednisolone for 3–5 days and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 24 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

INFUSION-RELATED REACTIONS AND CYTOKINE RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, anti-pyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction

(Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for the medical management of IRRs and CRS are provided in Table A6-7.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-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's judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

Table A6-7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome

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

Table A6-7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

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

Table A6-7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

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

Note: The management guidelines have been adapted from the NCCN guidelines for the management of CAR T-cell–related toxicities (Version 2.2019). Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

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

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretic 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.

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

PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table A6-8.

Table A6-8 Management Guidelines for Pancreatic Events, Including Pancreatitis

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

GI = gastrointestinal.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

Table A6-8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

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

GI = gastrointestinal.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

DERMATOLOGIC EVENTS

The majority of cases of rash reported with the use of atezolizumab were mild in severity and self-limiting, with or without pruritus. Although rare, cases of severe cutaneous adverse reactions such as Steven's-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have also been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table A6-9.

Table A6-9 Management Guidelines for Dermatologic Events

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

SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Myasthenia may be associated with myositis (see section on immune-mediated myositis) and patients should be managed accordingly. Management guidelines for neurologic disorders are provided in Table A6-10, with specific guidelines for myelitis provided in Table A6-11.

Table A6-10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • For general immune-mediated neuropathy: – If event resolves to Grade 1 or better, resume atezolizumab. [b] – If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] • For facial paresis: – Initial observation OR initiate prednisone 1–2 mg/kg/day (if progressing from mild). Initiate treatment with gabapentin, pregabalin, or duloxetine, for pain. – If event resolves fully, resume atezolizumab. [b] – If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines and proceed as per Guillain-Barré syndrome management.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone. • Consider IVIG or plasmapheresis in patients with rapid progression with bulbar and/or respiratory symptoms. • In life threatening cases, consider IV methylprednisolone 1g/day for 3–5 days and consider other immunosuppressants.

Table A6-10 Management Guidelines for Neurologic Disorders (cont.)

IVIG = intravenous immunoglobulin.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

Table A6-11 Management Guidelines for Immune-Mediated Myelitis

Event	Management
Immune-mediated myelitis, Grade 1	• Continue atezolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Investigate etiology and refer patient to neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Initiate non-opiod treatment (e.g., pregabalin, gabapentin, duloxetine) for pain. • Hospitalize patient. – Initiate treatment with corticosteroids equivalent to 1 g/day IV methylprednisolone. – If event does not improve or there is worsening of symptoms within 3 days, consider IVIG or plasmapheresis and manage as per institutional guidelines. • Refer patient to neurologist.

IVIG = intravenous immunoglobulin.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-12.

Table A6-12 Management Guidelines for Immune-Mediated Meningoencephalitis

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

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

RENAL EVENTS

Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including pre-renal and post-renal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-13.

Table A6-13 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function closely, including creatinine and urine protein, until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase (CK)/creatine phosphokinase (CPK) increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Patients may initially present with low grade

nondescript symptoms including mild pain and weakness; thus, there should be a low threshold for suspicion of myositis. Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis (see Table A6-6 and section on immune-mediated myocarditis) and myasthenia gravis (bulbar symptoms such as dysphagia, dysarthria, dysphonia, and dyspnea) (see Table A6-10 and section on neurologic disorders).

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-14.

Table A6-14 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact the Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

Table A6-14 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact the Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Consider IVIG or plasmapheresis • If event does not improve within 24–48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. • For recurrent events, treat as a Grade 4 event. Permanently discontinue atezolizumab and contact the Medical Monitor.

IVIG=intravenous immunoglobulin

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

Table A6-14 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Consider IVIG or plasmapheresis • If event does not improve within 24–48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

IVIG=intravenous immunoglobulin

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

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

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

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH).

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

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

- Fever $\geq 38.5°C$
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected HLH should be treated according to the guidelines in Table A6-15.

Table A6-15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis

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

HLH = hemophagocytic lymphohistiocytosis.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

REFERENCES

Adashek ML, Feldman M. Cytokine release syndrome resulting from anti–programmed death-1 antibody: raising awareness among community oncologist. J Oncol Practice 2019;15:502–4.

La Rosée P. Treatment of hemophagocytic lymphohistiocytosis in adults. Hematology Am Soc Hematol Educ Protram 2015;1:190–6.

La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465–77.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625–38.

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355–62.

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.

Rotz SJ, Leino D, Szabo S, et al. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. Pediatr Blood Cancer 2017;64:e26642.

Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908–14.

Appendix 7
Study Details Specific to Screening

Table A7-1 Schedule of Activities for Stage 1 Screening (mUC Cohort, All Arms)

Assessment/Procedure	Stage 1 Screening [a] Days –28 to –1
Informed consent [b]	x
Demographic data	x
Medical history and baseline conditions	x
Molecular profile of urothelial carcinoma (if available)	x
Vital signs [c]	x
Weight	x
Height	x
Complete physical examination [d]	x
ECOG Performance Status	x
ECG [e]	x
Hematology [f]	x [g]
Chemistry [h]	x [g]
Hemoglobin A_{1c} [i]	x [g]
Coagulation (PT/INR and aPTT)	x [g]
TSH, free T3 (or total T3), and free T4 [j]	x [g]
Viral Serology [k]	x [g]
C-reactive protein	x [g]
LDH	x [g]
Pregnancy test [l]	x [g]
Urinalysis [m]	x [g]
TB testing [n]	x
Serum autoantibody sample [o]	x
Tumor biopsy [p]	x
Tumor response assessments (including chest, abdomen, pelvis, and head) [q]	x
Concomitant medications [r]	x
Adverse events [s]	x

Table A7-1 Schedule of Activities for Stage 1 Screening (mUC Cohort, All Arms) (cont.)

ADA = anti-drug antibody; CT = computed tomography; Discon = discontinuation; EBNA = Epstein-Barr nuclear antigen; EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EV = enfortumab vedotin; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; TB = tuberculosis; TCZ = tocilizumab; Treat = treatment; TSH = thyroid-stimulating hormone; VCA = viral capsid antigen.

[a] Patients who fail their first screening for study eligibility (Stage 1) may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the initiation of study treatment may be used; such tests do not need to be repeated for screening or re-screening.

[b] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[c] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, 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. 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 the infusion and at 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 the infusion and at 30 (±10) minutes after the infusion.

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

[e] ECG recordings will be obtained during screening. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[f] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[g] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[h] Chemistry panel (serum or plasma) includes 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, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. For U.K. patients, amylase and lipase must be included in screening chemistry panel.

[i] Hemoglobin A1c will be drawn during Screening only if the Atezo+EV arm is open for enrollment.

[j] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1.

Table A7-1 Schedule of Activities for Stage 1 Screening (mUC Cohort, All Arms) (cont.)

[k] At screening, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, HBsAb, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection. Patients will also be tested for the following, but only if a tiragolumab-containing arm is open for enrollment: 1) EBV VCA IgM, 2) EBV VCA IgG, and 3) EBV PCR (the latter only if clinically indicated).

[l] All women of childbearing potential will have a serum pregnancy test at screening. Urine or serum 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. During follow-up, pregnancy tests will be performed at 3 and 6 months.

[m] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[n] Negative TB test must be obtained prior to enrollment. Screening TB testing will be performed only if the study is currently enrolling patients in the Atezo+TCZ arm.

[o] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[p] Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted. Refer to Section 4.5.8 in the protocol body for tissue sample requirements.

[q] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to randomization do not have to be repeated at screening. Screening assessments must include CT scans or MRI scans of the chest, abdomen, and pelvis. A CT scan with contrast or MRI scan with contrast of the head must be done at screening to evaluate CNS metastasis in all patients. Refer to Section 4.5.6 in the protocol body for further details on tumor assessments.

[r] Includes 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 study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[s] 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 related to study treatment or trial-related procedures until a final outcome can be reported.

Table A7-2 Schedule of Activities for Stage 2 Screening (mUC Cohort)

Assessment/Procedure	Stage 2 Screening [a]
Informed consent	x [b]
Vital signs [c]	x
Weight	x
Complete physical examination [d]	x
ECOG Performance Status	x
ECG [e]	x
Hematology [f]	x [g]
Chemistry [h]	x [g]
Hemoglobin A_{1c} [i]	x [g]
Coagulation (INR, aPTT)	x [g]
TSH, free T3 (or total T3 [j]), free T4	x [g]
Viral serology [k]	x [g]
C-reactive protein	x [g]
LDH	x [g]
Pregnancy test [l]	x [g]
Urinalysis [m]	x [g]
Serum autoantibody sample [n]	x
Tumor response assessments (including chest, abdomen, pelvis, and head) [o]	x [o, p]
Concomitant medications [r]	x
Adverse events [s]	x

CT = computed tomography; DL_{CO} = diffusion capacity of the lung for carbon monoxide; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EV = enfortumab vedotin; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HAV = hepatitis A virus; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HEV = hepatitis E virus; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition (scan); RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

[a] The visit at which response assessment shows progressive disease may be used as the Stage 2 screening visit. Patients who fail their first screening for study eligibility may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the consent form prior to re-screening.

[b] Written informed consent must be obtained before performing screening evaluations for Stage 2 except as noted in footnote "p" below.

[c] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[d] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

Table A7-2 Schedule of Activities for Stage 2 Screening (mUC Cohort) (cont.)

[e] ECG recordings will be obtained during screening. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[f] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[g] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[h] Chemistry panel (serum or plasma) includes 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, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. For U.K. patients, amylase and lipase must be included in screening chemistry panel.

[i] Hemoglobin A1c will be drawn during screening only if the Atezo+EV arm is open for enrollment.

[j] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1.

[k] At screening, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, HBsAb, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

[l] All women of childbearing potential will have a urine or serum pregnancy test at screening. Urine or serum 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. During follow-up, pregnancy tests will be performed at 3 and 6 months.

[m] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted

[n] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[o] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to randomization do not have to be repeated at screening. Screening assessments must include CT scans or MRI scans of the chest, abdomen, and pelvis. A CT scan with contrast or MRI scan with contrast of the head must be done at screening to evaluate CNS metastasis in all patients. Refer to Section 4.5.6 in the protocol body for further details on tumor assessments.

[p] Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.

[r] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 7 days prior to initiation of study treatment.

Table A7-2 Schedule of Activities for Stage 2 Screening (mUC Cohort) (cont.)

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

Table A7-3 Schedule of Activities for Screening (MIBC Cohorts, All Arms)

Assessment/Procedure	Stage 1 Screening [a] Days –28 to –1
Informed consent [b]	x
Demographic data	x
Medical history and baseline conditions	x
Molecular profile of urothelial carcinoma (if available)	x
Vital signs [c]	x
Weight	x
Height	x
Complete physical examination [d]	x
ECOG Performance Status	x
ECG [e]	x
Hematology [f]	x [g]
Chemistry [h]	x [g]
Coagulation (PT/INR and aPTT)	x [g]
TSH, free T3 (or total T3), and free T4 [i]	x [g]
Viral serology [j]	x [g]
C-reactive protein	x [g]
LDH	x [g]
Pregnancy test [k]	x [g]
Urinalysis [l]	x [g]
Cardiac and muscle enzymes tests (tropoinin I or T and CPK)	x [g]
TB testing [m]	x
Serum autoantibody sample [n]	x
Stool sample (optional) [o]	x
Tumor biopsy [p]	x
Tumor response assessments (including chest, abdomen, pelvis, and head) [q]	x
PD-L1 (SP142) tumor status [r]	x
Concomitant medications [s]	x
Adverse events [t]	x

Table A7-3 Schedule of Activities for Screening (MIBC Cohorts, All Arms) (cont.)

ADA = anti-drug antibody; CT = computed tomography; Discon = discontinuation; EBNA = Epstein-Barr nuclear antigen; EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; TB = tuberculosis; TCZ = tocilizumab; Treat = treatment; TSH = thyroid-stimulating hormone; VCA = viral capsid antigen.

Note: This table is not applicable to France.

[a] Patients who fail their first screening for study eligibility (Stage 1) may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the initiation of study treatment may be used; such tests do not need to be repeated for screening or re-screening.

[b] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[c] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, 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. 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 the infusion and at 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 the infusion and at 30 (±10) minutes after the infusion.

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

[e] ECG recordings will be obtained during screening. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[f] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[g] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[h] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. For U.K. patients, amylase and lipase must be included in screening chemistry panel.

[i] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1.

Table A7-3 Schedule of Activities for Screening (MIBC Cohorts, All Arms) (cont.)

[j] At screening, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, HBsAb, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection. Patients will also be tested for the following, but only if a tiragolumab-containing arm is open for enrollment: 1) EBV VCA IgM, 2) EBV VCA IgG, and 3) EBV PCR (the latter only if clinically indicated).

[k] All women of childbearing potential will have a serum pregnancy test at screening. Urine or serum 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. During follow-up, pregnancy tests will be performed at 3 and 6 months.

[l] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[m] Negative TB test must be obtained prior to enrollment for patients with symptoms of active TB infection.

[n] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[o] Not applicable for a patient that has not consented to providing optional stool samples. Screening stool samples should be provided by the patient before first treatment in the study.

[p] Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted. Refer to Section 4.5.8 in the protocol body for tissue sample requirements.

[q] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to the initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans or MRI scans of the chest, abdomen, and pelvis. A CT scan with contrast or MRI scan with contrast of the head may be done at screening to evaluate CNS metastasis in all patients, if clinically indicated. Refer to Section 4.5.7 in the protocol body for further details on tumor assessments.

[r] Samples for PD-L1 tumor status should be sent for central laboratory testing unless the patient has provided a tumor sample for PD-L1 testing during prescreening.

[s] Includes 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 study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[t] 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 related to study treatment or trial-related procedures until a final outcome can be reported.

Appendix 8
Study Details Specific to Atezo Arm (Comparator/Control)

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A8–1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (Atezo) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that targets programmed death-ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed death-1 (PD-1) and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. 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 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 cancer patients 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 (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, hypophysitis, myocarditis, and myasthenia gravis, have been observed (see Appendix 6). To date, these events have been manageable with treatment.

Atezolizumab (Tecentriq®) is approved for the treatment of urothelial carcinoma (UC), non–small cell lung cancer (NSCLC), 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.

A8–2 RATIONALE FOR ATEZO ARM

A8–2.1 THE PD-L1 PATHWAY

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).

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.

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 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).

CIT agents, particularly immune checkpoint inhibitors, have made a significant impact on the treatment of patients with UC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A8–2.2 BENEFIT-RISK ASSESSMENT

Atezolizumab is currently approved for the treatment of UC in patients who have progressed during or following a platinum-containing regimen and will, therefore, be the comparator/control arm for this study. For patients with locally advanced or metastatic UC (mUC) in the post-platinum setting, preferred treatment regimens include single-agent checkpoint inhibitors (NCCN 2017).

Immunotherapy in mUC has shown significant promise. Results from the pivotal multicenter Phase II study GO29293 (IMvigor210) and Phase III study GO29294 (IMvigor211) showed that durable responses were achieved in second-line post-platinum patients with mUC who received atezolizumab monotherapy (Rosenberg et al. 2016; Powles et al. 2018). In IMvigor210 Cohort 2, the objective response rate (ORR) in all patients was 15%, responses were seen in all PD-L1 immunochemistry subgroups, and the median survival in all patients was 7.9 months. Importantly, atezolizumab was well tolerated, with a low rate of treatment-related Grade 3 or 4 adverse events and discontinuations due to adverse events (Rosenberg et al. 2016). In IMvigor211, as of 13 March 2017, a median overall survival of 8.6 months, an ORR of 13.4% (10.5, 16.9), and a median duration of response (DOR) of 21.7 months was observed in the intent-to-treat (ITT) population. Atezolizumab continued to be well tolerated with a lower rate of treatment-related Grade 3 or 4 adverse events and fewer discontinuations due to adverse events than chemotherapy.

Based on the totality of evidence described above, atezolizumab is considered to be an appropriate treatment option for patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen.

The current standard of care for muscle invasive bladder cancer (MIBC) is radical cystectomy and it is unfortunately rarely curative. Platinum-based neoadjuvant chemotherapy is associated with an improvement in OS, but is only suitable for a minority of patients. Therefore, new neoadjuvant therapeutic options are required. Atezolizumab has shown significant activity in patients with advanced mUC, and there is evidence that PD-1/PD-L1 checkpoint blockade can generate pathologic complete responses (pCR) and durable responses in patients with UC (Powles et al. 2019, Necchi et al. 2018).

The potential risks for patients with MIBC will be related to the adverse events associated with study treatments. In most countries, patients wait an average of 4–8 weeks between establishing the diagnosis of urothelial cancer and surgery. Participation in this trial that includes preoperative treatment is not expected to result in relevant delays of surgery for participants. Furthermore, atezolizumab did not have an impact on operability or increases the risks associated with surgery in the ABACUS study (Powles et al. 2019). For more information on the benefit-risk assessment, please refer to Section 1.4.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.5.

A8–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO ARM

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage (Tecentriq® U.S. Package Insert; Tecentriq Summary of Product Characteristics). Anti-tumor activity has been observed across doses ranging from 1 to 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 pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A8–4 MATERIALS AND METHODS SPECIFIC TO ATEZO ARM

A8–4.1 TREATMENT IN ATEZO ARM

A8–4.1.1 Formulation, Packaging, and Handling

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

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

A8–4.1.2 Dosage, Administration, and Compliance

Treatment in the Atezo arm will be administered as outlined in Table A8-1.

For the mUC Cohort, patients in the atezolizumab control arm will receive treatment until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 in the protocol body for details). Treatment must be initiated no later than 7 days after treatment assignment.

For the MIBC Cohorts 1 and 2, patients will undergo surgery after Cycle 3; treatment in Cycle 4 should be reinitiated 4–6 weeks after surgery, but can be reinitiated up to 12 weeks after surgery if surgical complications arise (see Table A8-1). Patients will continue treatment until Cycle 17. It is recommended that treatment be initiated as soon as possible and no later than 7 days after randomization.

Table A8-1 Treatment Regimen for Atezo Arm

Cycle Length	Dose, Route, and Regimen
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle

Atezo = atezolizumab.
Note: For MIBC Cohorts 1 and 2, patients will receive treatment for a total of 17 cycles. Treatment in Cycles 1–3 will be administered prior to surgery. Treatment in Cycle 4 should be reinitiated 4–6 weeks after surgery, but can be reinitiated up to 12 weeks after surgery if surgical complications arise.

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

Administration of atezolizumab 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A8-2.

Table A8-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during the infusion and 30 (±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, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (± 10) minutes after the infusion.

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

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A8-5.1.2. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.4.4. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab are available to date.

A8–4.1.3 Stage 2 Treatment

Patients in the mUC Cohort who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1 in the protocol body) may be given the option of receiving a different treatment combination during Stage 2, as outlined in Table A8-3, provided they meet eligibility criteria (see Section 4.1 in the protocol body). Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A8-3 Stage 2 Treatment Regimens Available for the Atezo Arm

Study Treatment	Appendix
Atezo+EV	Appendix 9
Atezo+SG	Appendix 13

Atezo=atezolizumab; EV=enfortumab vedotin; SG=sacituzumab govitecan.

Refer to Appendix 13 for details specific to the Atezo+SG arm and Appendix 9 for the Atezo+EV arm.

A8–4.2 CONCOMITANT THERAPY FOR ATEZO ARM

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 study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A8–4.2.1 Cautionary Therapy for Atezo Arm

A8–4.2.1.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor-α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α 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 6 for details).

A8–4.2.1.2 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 A8–4.2.2) may be used during the study at the discretion of the investigator.

A8–4.2.2 Prohibited Therapy for Atezo Arm

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, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2 [mUC Cohort] and Section 4.1.4 [MIBC Cohorts] in the protocol body), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances outlined in Section A8–4.2.3.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin 2) are prohibited within 4 weeks or 5 half-lives of the drug, 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.

A8–4.2.3 Permitted Therapy for Atezo Arm

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

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section A8–4.3)
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin at a stable dose)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards

- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section A8–4.2.2)
- 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
- Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  After 2 cycles of treatment, palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy.
- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator. See Appendix 6 for further information.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections A8–4.2.1 and A8–4.2.2) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-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 5).

A8–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO ARM

Contraception requirements for women in the atezolizumab arm are outlined below:

- Women of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use contraception methods, 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 last dose of study treatment.

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

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

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

A8–5 ASSESSMENT OF SAFETY FOR ATEZO ARM

A8–5.1 SAFETY PLAN FOR ATEZO ARM

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 Sections A8–5.1.1 and A8–5.1.2). Guidelines for management of patients who experience specific adverse events are provided in Appendix 6.

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. Adverse events will be reported as described in Sections 5.2–5.6 in the protocol body.

A8–5.1.1 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, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any

organ system and lead to hemophagocytic lymphohistiocytosis (HLH). See Appendix 6 and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A8–5.1.2 Management of Patients Who Experience Adverse Events in Atezolizumab Arm

A8–5.1.2.1 Dose Modifications

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

A8–5.1.2.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Appendix 6). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for >12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for >12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator.
The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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.

Refer to Section A8–4.1.2 for information on dose interruptions for reasons other than toxicity (e.g., surgical procedures).

A8–5.1.2.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 6. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

A8–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO ARM (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 in the protocol body for reporting instructions). Adverse events of special interest for the atezolizumab arm 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 in the protocol body)
- 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.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ upper limit of normal
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, HLH, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, and optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

A8–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO ARM

A8–5.3.1 Pregnancies in Female Patients

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

A8–5.3.2 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 in the protocol body).

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.

A8–5.3.3 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 in the protocol body).

A8–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO ARM

Table A8-4 Schedule of Activities for Atezo Arm (mUC Cohort)

Assessment/Procedure	Stage 1 Screening [a] Days –28 to –1	Treatment Cycles (21-Day Cycles) Cycle 1 [b] Day 1	 Cycles ≥2 Day 1 (±3 D)	Stage 2 Screen [c] (see Appendix 7) or Treat Discon [d]	Follow-Up Q3M (± 7 D)
Informed consent	See Appendix 7.			x [e, f]	
Molecular profile of urothelial carcinoma (if available)		Whenever updated information becomes available			
Vital signs [g]		x	x	x	
Weight [h]		x	x	x	
Complete physical examination [i]				x	
Limited physical examination [j, h]		x	x		
ECOG Performance Status [h]		x	x	x	
ECG [k, h]		Perform as clinically indicated.		x [f]	
Hematology [l]		x [m]	x [m]	x [n]	
Chemistry [o]		x [m]	x [m]	x [n]	
Coagulation (PT/INR and aPTT)				x [f, n]	
TSH, free T3 (or total T3), and free T4 [p]		x [m, n]		x [n]	
HIV, HBV, and HCV testing				x [f, n]	
C-reactive protein		x		x [f, n]	
LDH				x [f, n]	
Pregnancy test [q]		x	x	x [n]	x [q]
Urinalysis [r]		x	x	x [f, n]	
Serum autoantibody sample [s]		Perform if a patient experiences a suspected immune-related adverse event			
PK samples		Refer to Table A8-5.			
ADA samples		Refer to Table A8-5.			

Table A8-4 Schedule of Activities for Atezo Arm (mUC Cohort) (cont.)

Assessment/Procedure	Stage 1 Screening [a] Days –28 to –1	Treatment Cycles (21-Day Cycles) Cycle 1 [b] Day 1	Treatment Cycles (21-Day Cycles) Cycles ≥2 Day 1 (±3 D)	Stage 2 Screen [c] (see Appendix 7) or Treat Discon [d]	Follow-Up Q3M (± 7 D)
Biomarker samples	See Appendix 7.	Refer to Table A8-5.			
Blood sample for RBR (optional) [t]		x			
Tumor biopsy		x [u]			
Tumor biopsy (optional)		x [v]			
Tumor response assessments		x [w, x, y]			
Concomitant medications [z]		x	x	x	
Adverse events [aa]		x	x	x	x
Atezolizumab administration [bb, cc]		x	x		
Survival follow-up and anti-cancer treatment					x [dd]

ADA = anti-drug antibody; CT = computed tomography; D = day; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q3M = every 3 months; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; TB = tuberculosis; Treat = treatment; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Patients who fail their first screening for study eligibility (Stage 1) may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the initiation of study treatment may be used; such tests do not need to be repeated for screening or re-screening.

[b] Treatment must be initiated no later than 7 days after treatment assignment.

[c] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 in protocol body for details) or unacceptable toxicity may be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.2 in protocol body) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

Table A8-4 Schedule of Activities for Atezo Arm (mUC Cohort) (cont.)

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 or patients who have discontinued Stage 2 treatment will then undergo follow-up assessments.

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[f] Assessments to be performed only for patients undergoing Stage 2 screening.

[g] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, 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. 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 the infusion and at 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 the infusion and at 30 (±10) minutes after the infusion.

[h] Assessment may be performed within 24 hours prior to dosing during the treatment period.

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

[j] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] ECG recordings will be obtained during screening. It is recommended that patients 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, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[m] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

[n] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[o] Chemistry panel (serum or plasma) includes 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, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. For U.K. patients, amylase and lipase must be included on Day 1 of each treatment cycle.

Table A8-4 Schedule of Activities for Atezo Arm (mUC Cohort) (cont.)

[p] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[q] All women of childbearing potential will have a serum pregnancy test at screening. Urine or serum 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. During follow-up, pregnancy tests will be performed at 3 and 6 months. If a pregnancy test was performed within 96 hours prior to Day 1 of Cycle 1, it does not have to be repeated.

[r] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[s] Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[t] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[u] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 in protocol body for tissue sample requirements.

[v] Consenting patients may undergo optional tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[w] Patients will undergo tumor assessments at baseline, every 9 weeks (±1 week) for the first 54 weeks following treatment initiation, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays until loss of clinical benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new, non–protocol-specified anti-cancer therapy.

[x] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[y] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

[z] Includes 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 study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[aa] 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.

Table A8-4 Schedule of Activities for Atezo Arm (mUC Cohort) (cont.)

[bb] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[cc] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 in protocol body for details).

[dd] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a 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. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table A8-5 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo Control Arm (mUC Cohort)

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, and PBMC)
	30 (± 10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, and PBMC)
Day 1 of Cycles 4, 8, 12, 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum in Cycles 4 and 8)
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)

ADA = anti-drug antibody; Atezo = atezolizumab; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Table A8-6 Schedule of Activities for Atezo Arm (MIBC Cohorts)

Assessment/Procedure	Screening [a]	Treatment Cycles (21-Day Cycles)/Surgery				Treat Discon [e]	Follow-Up Q3M (± 7 D) [f]
		Cycle 1 [b]	Cycles 2–3	Surgery [c]	Cycles 4–17 [d]		
	Days –28 to –1	Day 1-	Day 1 (±3 D)		Day 1 (±3 D)		
Molecular profile of urothelial carcinoma (if available)	See Appendix 7.	Whenever updated information becomes available					
Vital signs [g]		x	x		x	x	
Weight [h]		x	x		x	x	
Complete physical examination [i]						x	
Limited physical examination [j, h]		x	x		x		
ECOG Performance Status [h]		x	x		x	x	
ECG [k, h]		Perform as clinically indicated.					
Hematology [l]		x [m]	x [m]		x [m]	x	
Chemistry [n]		x [m]	x [m]		x [m]	x	
TSH, free T3 (or total T3), and free T4 [o]		x [m]				x	
C-reactive protein		x	x		x	x	
Pregnancy test [p]		x	x		x	x	x [p]
Urinalysis [q]		x	x		x		
Serum autoantibody sample [r]		Perform if a patient experiences a suspected immune-related adverse event					
PK samples		Refer to Table A8-7.					
ADA samples		Refer to Table A8-7.					
Biomarker samples		Refer to Table A8-7.					

Table A8-6 Schedule of Activities for Atezo Arm (MIBC Cohorts) (cont.)

Assessment/Procedure	Screening [a]	Treatment Cycles (21-Day Cycles)/Surgery				Treat Discon [e]	Follow-Up Q3M (± 7 D) [f]
		Cycle 1 [b]	Cycles 2–3	Surgery [c]	Cycles 4–17 [d]		
	Days –28 to –1	Day 1-	Day 1 (±3 D)		Day 1 (±3 D)		
Blood sample for RBR (optional) [s]	See Appendix 7.	x					
Stool sample (optional) [t]		x [t]					
Tumor biopsy		x [u]			x [u]		
Tumor response assessments					x [v, w]		
Concomitant medications [x]		x	x		x	x	
Adverse events [y]		x	x		x	x	x
Atezolizumab administration [z, aa]		x	x		x		
Cystectomy				x [bb]			
Lymph node dissection				x [bb]			
Survival follow-up and anti-cancer treatment							x [cc]

ADA = anti-drug antibody; CT = computed tomography; D = days; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MIBC = muscle invasive bladder cancer; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q3M = every 3 months; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; Treat = treatment; TSH = thyroid-stimulating hormone.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

This table is not applicable to France.

[a] Patients who fail their first screening for study eligibility may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. Results of standard-of-care tests or

Table A8-6 Schedule of Activities for Atezo Arm (MIBC Cohorts) (cont.)

examinations performed prior to obtaining informed consent and within 28 days prior to the initiation of study treatment may be used; such tests do not need to be repeated for screening or re-screening.

[b] Treatment must be initiated no later than 7 days after treatment assignment.

[c] A minimum of 7 days between time of last infusion and surgery is required.

[d] Treatment in Cycle 4 should be reinitiated 4–6 weeks after surgery, but can be reinitiated up to 12 weeks after surgery if surgical complications arise.

[e] Patients will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients.

[f] Patients should return for follow-up visits every 3 months until 24 months after the treatment discontinuation visit. Patients may then continue with standard-of-care treatment with their doctor.

[g] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, 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. 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 the infusion and at 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 the infusion and at 30 (±10) minutes after the infusion.

[h] Assessment may be performed within 24 hours prior to dosing during the treatment period.

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

[j] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] It is recommended that patients 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, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[m] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

[n] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. For U.K. patients, amylase and lipase must be included on Day 1 of each treatment cycle.

Table A8-6 Schedule of Activities for Atezo Arm (MIBC Cohorts) (cont.)

[o] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[p] All women of childbearing potential will have a serum pregnancy test at screening. Urine or serum 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. During follow-up, pregnancy tests will be performed at 3 and 6 months. If a pregnancy test was performed within 96 hours prior to Day 1 of Cycle 1, it does not have to be repeated.

[q] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[r] Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[s] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[t] Stool samples will be collected before surgery for cystectomy and lymph node dissection, preferably after Day 1 of Cycle 3. Patients who consent to providing optional stool samples will receive the collection device on or before Day 1 of Cycle 3.

[u] During the study (i.e., up to 24 months after the treatment discontinuation visit), patients will undergo tumor biopsy sample collection at the time of disease recurrence as determined by the investigator (see Section 4.5.7 in the protocol body for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or disease recurrence, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 in protocol body for tissue sample requirements.

[v] Patients will undergo tumor assessments at baseline, within 4 weeks prior to resuming systemic therapy following surgery, and then every 12 weeks (±2 weeks) while on treatment and until 24 months (104 weeks) after the treatment discontinuation visit, regardless of dose delays, or until disease recurrence, whichever occurs first (see Section 3.1.3 in the protocol body for details). Tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease recurrence.

[w] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[x] Includes 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 study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[y] 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.

Table A8-6 Schedule of Activities for Atezo Arm (MIBC Cohorts) (cont.)

[z] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[aa] Treatment will continue until unacceptable toxicity or disease recurrence (as defined in Section 4.5.7) or until completion of 14 cycles post-surgery, whichever comes first.

[bb] A specimen from surgical resection (i.e., radical cystectomy) along with an associated pathology report and tissue from lymph node dissection must be submitted. See Section 4.5.8 in protocol body for tissue sample requirements.

[cc] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months for 24 months after the treatment discontinuation visit (unless the patient withdraws consent or the Sponsor terminates the study). If a 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. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table A8-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo Comparator Arm (MIBC Cohorts)

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (blood, PBMC, plasma, serum, and urine)
	30 (± 10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (PBMC, plasma, and serum)
Day 1 of Cycle 3	Prior to study treatment	• Biomarker (blood and urine)
Surgery for cystectomy	Prior to surgery	• Biomarker (blood, PBMC, and urine)
Day 1 of Cycles 4, 8, 12, 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum in Cycles 4 and 8) • Biomarker (blood and urine, Cycle 4)
Day 1 of Cycle 6 (~3 months post-cystectomy)	At visit	• Biomarker (blood and urine)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)

ADA = anti-drug antibody; Atezo = atezolizumab; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Notes: On the basis of emerging safety 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. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

This table is not applicable to France.

A8–7 REFERENCES

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.

Butte MJ, Keir ME, Phamduy TB, et al. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

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.

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.

De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC Study 30986. J Clin Oncol 2012;30:191–9.

Fehrenbacher L, Spira A, Ballinger M, et al. 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.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.

[NCCN] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: bladder cancer [resource on the Internet]. 2017 [cited 15 August 2017]. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx.

Necchi A, Anichini A, Raggi D, et al. Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): an open-label, single-arm, phase II study. Int J Clin Oncol 2018;36:3353–60.

Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2018;391:748–57.

Powles T, Kockx M, Rodriguez-Vida A, et al. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. Nat Med 2019;25:1706–14.

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.

Tecentriq® (atezolizumab) Summary of Product Characteristics, Genentech.

Tecentriq® (atezolizumab) U.S. Package Insert, Genentech.

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.

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 9
Study Details Specific to Atezo+EV Arm (Stages 1 and 2)

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A9–1 BACKGROUND ON ATEZO+EV ARM

A9–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (Tecentriq®) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that targets programmed death-ligand 1 (PD-L1). It inhibits the interaction between PD-L1 and its receptors, programmed death-1 (PD-1) and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. 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 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 cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, hypophysitis, myocarditis, and myasthenia gravis, have been observed (see Appendix 6). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma (UC), non–small cell lung cancer (NSCLC), 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.

A9–1.2 BACKGROUND ON ENFORTUMAB VEDOTIN

Enfortumab vedotin is an antibody–drug conjugate (ADC) composed of a fully human $IgG1_K$ antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable linker (Challita-Eid et al. 2016). Enfortumab vedotin is thought to induce cytotoxicity by binding to nectin-4 protein on the surface of cells, leading to internalization and causing proteolytic cleavage of the linker and intracellular release of MMAE that subsequently disrupts tubulin polymerization and leads to mitotic arrest.

As of the 2 October 2017 data cutoff date, there had been three clinical trials that had assessed the safety and tolerability of enfortumab vedotin. The first completed study (AGS-22M6E-11-1) evaluated the safety and pharmacokinetics of enfortumab vedotin given as monotherapy every 3 weeks (Q3W) in patients with malignant solid tumors that

expressed Nectin-4. The second study, ASG-22CE-13-2 (EV-101), is ongoing and is evaluating the safety and pharmacokinetics of escalating doses of enfortumab vedotin given as monotherapy on Days 1, 8, and 15 of each 28-day cycle in patients with metastatic UC (mUC) and other malignant solid tumors that express nectin-4.

In Study AGS-22M6E-11-1, 9 patients were treated with enfortumab vedotin at doses of 0.6 to 1.2 mg/kg. Eight patients (88.9%) treated with enfortumab vedotin experienced at least one treatment-emergent adverse event (TEAE); no patients experienced a serious TEAE or dose-limiting toxicity (DLT). TEAEs occurring in more than 2 patients were fatigue (4 [44.4%] patients), alopecia, constipation, and decreased appetite (3 [33.3%] patients). The Sponsor closed this study without enrolling planned dose expansion cohorts on the basis of the pharmacokinetic profile, which favored a weekly dosing schedule.

As of 25 October 2018, 201 patients had received at least one dose of enfortumab vedotin in Study ASG-22CE-13-2 (EV-101). Of the 201 patients, 155 were patients with mUC. ASG-22CE-13-2 tested escalating dose levels of 0.5, 0.75, 1, and 1.25 mg/kg, with expansion cohorts at 0.75-, 1-, and 1.25-mg/kg dose levels. A maximum tolerated dose was not reached in this study, and the recommended Phase II dose of 1.25 mg/kg given on Days 1, 8, and 15 of a 28-day cycle was established (see Section A9–3.2 for additional details). As of the cutoff date, 112 patients with mUC received 1.25 mg/kg, the objective response rate (ORR) was 42.9% (48 of 112 patients), including 5 patients (4.5%) with complete response and 43 patients (38.4%) with partial response.

Study SGN22E-002 (EV-103) is a Phase Ib study evaluating safety/tolerability and anti-tumor activity of the combination of enfortumab vedotin given on Day 1 and Day 8 of each 21-day cycle and pembrolizumab and/or chemotherapy in patients with locally advanced or mUC. As of the data cutoff of 3 January 2019, 42 patients have been treated with escalating dose levels of 1 (n = 3) and 1.25 mg/kg (n = 39) enfortumab vedotin in combination with pembrolizumab. No efficacy data has been shared, only that 39 of 42 (93%) patients have experienced at least 1 TEAE. The most common TEAEs occurring in ≥ 20% of patients were fatigue (52%), decreased appetite and diarrhea (36% each), nausea (31%), alopecia and peripheral sensory neuropathy (29% each), weight decreased (26%), constipation, pruritus and rash maculo-papular (24% each), and anemia and dyspnea (21% each). Overall, 37 (88%) patients experienced at least 1 TEAE considered to be enfortumab vedotin-related, the most common (≥ 20% of patients) being fatigue (18 [43%] patients), alopecia, decreased appetite and diarrhea (12 [29%] patients each), peripheral sensory neuropathy (11 [26%] patients), and nausea (9 [21%] patients). Twenty-five (60%) patients experienced Grade ≥ 3 TEAEs, the most common being hyperglycemia (6 [14%] patients), acute kidney injury, anemia, fatigue, and lipase increased (4 [10%] patients each). Lipase increase was considered enfortumab vedotin-related in 3 (7%) patients, fatigue and hyperglycemia in 3 (7%) patients, and acute kidney injury in 2 (5%) patients. Thirteen (31%) patients

experienced at least 1 serious TEAE (42 serious TEAE events were reported). Five patients had serious TEAEs that were enfortumab vedotin-related; the majority of these serious TEAEs were reported in 1 patient who also experienced extravasation. One TEAE lead to death, an event of multiple organ dysfunction syndrome. Thirty-two of forty-two (73%) patients remained on treatment, 10 of 42 (27%) patients have discontinued treatment due to progression.

Overall, the safety data and early efficacy data support further investigation of enfortumab vedotin in the treatment of mUC.

A9–2 RATIONALE FOR ATEZO+EV ARM

A9–2.1 THE PD-L1 PATHWAY

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).

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-resenting 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.

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 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).

CIT agents, particularly immune checkpoint inhibitors (CPIs), have made a significant impact on the treatment of patients with UC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A9–2.2 ANTIBODY-DRUG CONJUGATES AND NECTIN-4

ADCs consist of novel, highly active cytotoxics linked to monoclonal antibodies against cancer-specific targets with the aim of targeting drug delivery. The antibody moiety typically targets molecules expressed or prevalent on the surface of cancer cells; therefore, delivering maximum anti-cancer effects with minimal toxicity. ADCs have the potential to improve the therapeutic index of cytotoxic agents and minimize exposure to normal tissue.

Nectins are thought to mediate $Ca2^{+}$-independent cell–cell adhesion via both hemophilic and heterophilic trans-interactions at adherens junctions where they can recruit cadherins and modulate cytoskeleton rearrangements (Rikitake and Takai 2008). Nectin-4 is a Type I transmembrane protein that has been found to be highly expressed in a number of epithelial cancers, including urothelial, lung, ovarian, breast, and pancreatic cancer. In normal tissue, nectin-4 expression is moderate to weak and mainly found in the epithelium of the bladder, skin, salivary gland ducts, gastrointestinal tract, and breast ducts. The expression pattern and levels of nectin-4 on tumors suggest that it would be an attractive target for ADC therapy in several solid tumors.

A9–2.3 BENEFIT-RISK ASSESSMENT

Immunotherapy in mUC has shown significant promise. Results from the pivotal multicenter Phase II study GO29293 (IMvigor210) and Phase III study GO29294 (IMvigor211) showed that durable responses were achieved in second-line post-platinum patients with mUC who received atezolizumab monotherapy (Rosenberg et al. 2016; Powles et al. 2018). In IMvigor210 Cohort 2, the ORR in all patients was 15%, and responses were seen in all PD-L1 immunochemistry subgroups and the median survival in all patients was 7.9 months. Importantly, atezolizumab was well tolerated, with a low rate of treatment-related Grade 3 or 4 adverse events and discontinuations due to adverse events (Rosenberg et al. 2016). In IMvigor211, as of 13 March 2017, a median overall survival of 8.6 months, an ORR of 13.4% (10.5, 16.9), and a median duration of response (DOR) of 21.7 months was observed in the intent-to-treat (ITT) population. Atezolizumab continued to be well tolerated with a lower rate of treatment-related Grade 3 or 4 adverse events and fewer discontinuations due to adverse events than chemotherapy.

As of 25 October 2018, 201 patients had received at least one dose of enfortumab vedotin in Study ASG-22CE-13-2 (EV-101). Of the 201 patients, 155 were patients with mUC. ASG-22CE-13-2 tested escalating dose levels of 0.5, 0.75, 1, and 1.25 mg/kg, with expansion cohorts at 0.75-, 1-, and 1.25-mg/kg dose levels. A maximum tolerated dose was not reached in this study, and the recommended Phase II dose of 1.25 mg/kg given on Days 1, 8, and 15 of a 28-day cycle was established (see Section A9–3.2 for additional details). As of the cutoff date, 112 patients with mUC received 1.25 mg/kg,

the ORR was 42.9% (48 of 112 patients), including 5 patients (4.5%) with complete response and 43 patients (38.4%) with partial response.

There is currently no data available for the combination of atezolizumab and enfortumab vedotin in UC; however, nonclinical data show that an MMAE ADC, but not the unconjugated antibody, increases tumor immunogenicity by induction of immunogenic cell death, antigen presentation, and tumor immune infiltration (Gardai et al. 2015). These results suggest that the effects are due to MMAE, the cytotoxic component of enfortumab vedotin. Brentuximab vedotin, a CD30-directed ADC conjugated to MMAE, was safely combined with nivolumab in relapsed/refractory Hodgkin lymphoma, the combination demonstrated increased anti-tumor activity above what would be expected with the additive effects of each agent alone (Herrera et al. 2018). In this study, 61% of patients experienced a complete response, with an 82% overall response rate. The combination was well tolerated, 10% of patients experienced serious treatment-related adverse events, 8% of patients required steroids for immune-mediated adverse events, and no patients discontinued treatment because of immune-mediated adverse events. The frequency and severity of adverse events were similar to those observed with each agent administered individually. It is therefore reasonable to expect that patients may experience prolonged progression-free and overall survival from the combination of enfortumab vedotin and atezolizumab in locally advanced and mUC, as patients with Hodgkin's lymphoma did with brentuximab vedotin and nivolumab, since both enfortumab vedotin and atezolizumab have also shown single-agent efficacy and have the potential for immune synergy.

In summary, the safety profile of atezolizumab in combination with enfortumab vedotin is not yet defined. Overlapping toxicities include gastrointestinal (GI), rash, neuropathy, anemia, infusion-related reactions (IRRs), hyperglycemia/diabetes mellitus, and ocular adverse effects. Aggressive safety monitoring will be put into place for these events.

Considering the high therapeutic need for tolerable and effective treatment in second-line treatment of patients, the compelling clinical data for both atezolizumab and enfortumab vedotin, as well as the anticipated safety profile of the combination, the benefit–risk assessment favors moving forward with the evaluation of the combination in locally advanced or metastatic UC patients who have failed prior platinum-containing chemotherapy.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.5.

A9–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+EV ARM

A9–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert; Tecentriq Summary of Product Characteristics). Anti-tumor activity has been observed across doses ranging from 1 to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached, and no DLTs 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 pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A9–3.2 RATIONALE FOR ENFORTUMAB VEDOTIN DOSE AND SCHEDULE

Enfortumab vedotin will be administered at a dose of 1.25 mg/kg IV on Days 1 and 8 of each 21-day cycle. The dose of enfortumab vedotin was established in Study ASG-22CE-13-2. That study tested escalating dose levels of 0.5, 0.75, 1, and 1.25 mg/kg, with expansion cohorts at 0.75-, 1-, and 1.25-mg/kg dose levels. A maximum tolerated dose was not reached in this study. Preliminary data as of the cutoff date (2 October 2017) show 168/172 (97.7%) patients have experienced at least one TEAE, with 64 (37.2%) patients reporting serious TEAEs as of the data cutoff. Many patients (n = 148 [86.0%]) experienced a TEAE considered possibly or probably related to enfortumab vedotin. The most common related TEAEs (≥ 20% of patients overall) were fatigue (71 [41.3%] patients), nausea (60 [34.9%] patients), alopecia (59 [34.3%] patients), dysgeusia (52 [30.2%] patients), decreased appetite (47 [27.3%] patients), diarrhea (44 [25.6%] patients), and pruritus (40 [23.3%] patients).

Of the 14 patients in the 1-mg/kg dose cohort, 2 (14.3%) patients experienced treatment-related DLTs (proctalgia and blood uric acid increased). There were no DLTs at other dose levels tested.

Nine (4.9%) patients have died because of a serious TEAE as of the data cutoff; in 2 patients, TEAEs leading to death were assessed as at least partially related to study drug (urinary tract obstruction in 1 patient with mUC and respiratory failure in 1 patient with mUC and pneumonia, both in the 1.25-mg/kg dose cohort). The non-related fatal events were acute renal failure (1 patient in the 0.75-mg/kg dose cohort), pneumonia (1 patient in the 1-mg/kg cohort), acute respiratory failure (1 patient in the 1-mg/kg dose cohort), cardiac arrest (1 patient in the 1-mg/kg dose cohort), malignant bowel obstruction (1 patient in the 1.25-mg/kg dose cohort), perforation of the small intestine and sepsis (1 patient in the 1.25-mg/kg dose cohort), and worsening of general health condition (1 patient in the 1.25-mg/kg dose cohort).

After the data cutoff date (2 October 2017), 2 additional deaths were reported that were considered at least possibly related to study drug. One patient with mUC and diabetes who was treated with enfortumab vedotin (1.25 mg/kg) died of diabetic ketoacidosis and hyperglycemia. Both events were considered possibly related to study drug by the investigator. One patient with mUC who was treated with enfortumab vedotin (1.25 mg/kg) died of multi-organ failure, which was considered as possibly related to the study drug by the investigator.

On the basis of pharmacokinetic (PK) data from the Phase I study (ASG-22CE-13-2), the half-life of enfortumab vedotin is approximately 1–2 days. No notable intra-cycle accumulation (<30%) of ADC was observed with the dosing regimen (on Days 1, 8, and 15 of every 28-day cycle) at any dose level. Minimal intra-cycle accumulation (<50%) of MMAE was observed. At the same dose level, the average weekly total exposure of enfortumab vedotin following administration on Days 1 and 8 of each 21-day cycle is predicted to be similar to that observed for dosing on Days 1, 8, and 15 of a 28-day cycle. Additionally, responses were observed at all dose levels of enfortumab vedotin tested down to 0.5 mg/kg on Days 1, 8, and 15 of every 28-day cycle. Thus, it is anticipated that the dosing schedule in the current study will achieve ADC exposures over each 21-day cycle that may lead to a favorable balance of anti-tumor activity and safety similar to that observed in the Phase I study (ASG-22CE-13-2).

A9–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+EV ARM

A9–4.1 SAFETY EVALUATION FOR PATIENTS IN ATEZO+EV ARM

Because of the potential for overlapping rash and GI toxicities identified for atezolizumab and enfortumab vedotin, special caution will be taken with a planned safety evaluation (see Section 3.1.4 in the protocol body). Randomization to the atezolizumab plus enfortumab vedotin (Atezo+EV) arm will be paused after the enrollment of 6 patients until all of the patients in that arm have completed a safety evaluation of at least 1 cycle (21 days) of treatment. Patients who withdraw prior to 21 days will not be replaced, and the safety evaluation will be based on the available data at the time all remaining patients have a follow-up of 21 days. If the combination is deemed to be sufficiently safe, randomization will be resumed.

A9–4.2 TREATMENT IN ATEZO+EV ARM

A9–4.2.1 Formulation, Packaging, and Handling

A9–4.2.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

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

A9–4.2.1.2 Enfortumab Vedotin

The enfortumab vedotin drug product is supplied as a sterile, preservative-free, white to off-white, lyophilized powder in 10-mL glass vials yielding a total of 30 mg of investigational product.

For information on the formulation and handling of enfortumab vedotin, see the pharmacy manual and the Enfortumab Vedotin Investigator's Brochure.

A9–4.2.2 Dosage, Administration, and Compliance

Patients in the Atezo+EV arm will receive treatment as outlined in Table A9-1 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease; see Section 3.1.1 in the protocol body for details). Treatment must be initiated no later than 14 days after treatment assignment.

Table A9-1 Treatment Regimen for Atezo+EV Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Enfortumab vedotin 1.25 mg/kg IV on Days 1 and 8 • Atezolizumab 1200 mg IV on Day 1

Atezo+EV = atezolizumab plus enfortumab vedotin.

Note: Atezolizumab will be administered at least 60 minutes after the end of the enfortumab vedotin infusion.

A9–4.2.2.1 Enfortumab Vedotin Administration

Enfortumab vedotin will be administered at a dose of 1.25 mg/kg IV over 30 minutes on Days 1 and 8 of each 21-day cycle. At least 1 week must elapse between doses of enfortumab vedotin.

Enfortumab vedotin will be administered at milligram per kilogram doses based on the subject's actual body weight at baseline, and doses will not need to change unless the subject's weight changes by ≥ 10% from baseline weight or the dose adjustment criteria is met. Actual weight will be used except for patients weighing greater than 100 kg at baseline (i.e., Day 1 of Cycle 1) and/or any subsequent dosing; in such cases, the dose will be calculated based on a weight of 100 kg. The maximum dose permitted during this study is 125 mg.

Administration of enfortumab vedotin 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. All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards.

Patients should be observed for 60 minutes after the infusion before administering atezolizumab. During the course of study treatment, enfortumab vedotin should not be administered to patients whose creatinine clearance falls below 30 mL/min. Blood glucose should be checked prior to each dosing, and the enfortumab vedotin dose should be withheld for blood glucose >250 mL/dL. Dose reduction to either 1.0 mg/kg or 0.75 mg/kg will be allowed depending on the type and severity of toxicity (see Section A9–5.1.4.1). No further dose reductions will be allowed. If a patient's dose is reduced because of a toxicity that subsequently resolves, the patient may re-escalate one dose level each cycle up to the original dose at the discretion of the investigator. The Medical Monitor is available to advise as needed. The timing of efficacy or safety evaluations should not be affected by dose interruptions or reductions. The injection site should be monitored closely for redness, swelling, pain, and infection during and at any time after administration. In case of enfortumab vedotin extravasation, atezolizumab should be held at the investigator's discretion. The Medical Monitor is available to advise as needed. Guidelines for enfortumab vedotin treatment interruption or discontinuation because of toxicities are provided in Section A9–5.1.4. Enfortumab vedotin treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Vital signs are recommended to be measured within 60 minutes of the infusion, and during and after the infusion if clinically indicated.

A9–4.2.2.2 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. Atezolizumab should be administered 1 hour following the enfortumab vedotin infusion.

Administration of atezolizumab 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A9-2.

Table A9-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during the infusion and 30 (±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, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

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

Guidelines for medical management of IRRs for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Appendix 6. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

A9–4.2.3 Stage 2 Treatment

Patients who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1 in the protocol body) may be given the option to receive Atezo+SG during Stage 2, provided they meet eligibility criteria (see Section 4.1 in the protocol body; see Table A9-3). Patients who experience unacceptable toxicity not related to atezolizumab may also be eligible to receive treatment during Stage 2, provided they meet eligibility criteria. The Medical Monitor is available to advise as needed. Patients who enter Stage 2 will receive the same treatment and follow the

same assessment schedule as patients who were randomly allocated to the Atezo+SG arm during Stage 1 (see Appendix 13).

Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A9-3 Stage 2 Treatment Regimen Available for the Atezo+EV Arm

Study Treatment	Appendix
Atezo+SG	Appendix 13

Atezo = atezolizumab; EV = enfortumab vedotin; SG = sacituzumab govitecan.

Refer to Appendix 13 for details specific to the Atezo+SG arm.

A9–4.3 CONCOMITANT THERAPY FOR ATEZO+EV ARM

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 study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A9–4.3.1 Cautionary Therapy for Atezo+EV Arm

A9–4.3.1.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α 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 6 for details).

A9–4.3.1.2 Strong CYP3A4 or P-Glycoprotein Inhibitors

PK studies have shown that MMAE is a substrate but not a potent inhibitor of the transported permeability glycoprotein (P-gp). MMAE is also known to be a substrate of CYP3A. Given this, patients who receive strong CYP3A4 inhibitors or P-gp inhibitors or inducers should be closely monitored for adverse reactions.

A9–4.3.1.3 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 A9–4.3.2) may be used during the study at the discretion of the investigator.

A9–4.3.1.4 Non-Live Vaccines

Non-live vaccines are allowed during the course of the study. At this time there is insufficient experience with COVID-19 vaccines to support concrete recommendations concerning the use of COVID-19 vaccines in patients receiving enfortumab vedotin alone and/or in combination.

Per the recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all cancer patients receiving active therapy (including immune CPIs) with the understanding that there are limited safety and efficacy data in these patients (NCCN COVID-19 vaccination and cancer patients). Ultimately, for each patient, the decision to receive a non-live vaccine will be a benefit-risk discussion between the patient and the treating physician. This decision will depend on a number of factors, such as the type of non-live vaccine, the potential risk of infection, the underlying disease, and age of the patient.

Given the potential for adverse events related to vaccine administration, sites are strongly encouraged to administer vaccines on a non-study treatment dosing day, if possible. This will help minimize confusion on attribution of potential adverse events.

A9–4.3.2 Prohibited Therapy for Atezo+EV Arm

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, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2 in the protocol body), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances outlined in Section A9–4.3.3.

- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, 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.

A9–4.3.3 Permitted Therapy for Atezo+EV Arm

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

- Oral contraceptives with a failure rate of < 1% per year (see Section A9–4.4)
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin at a stable dose)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section A9–4.3.2)
- 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
- Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  After 2 cycles of treatment, palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy.
- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator. See Appendix 6 for further information.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections A9–4.3.1 and A9–4.3.2) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-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 5).

A9–4.4 CONTRACEPTION REQUIREMENTS FOR ATEZO+EV ARM

Contraception requirements for women and men in the Atezo+EV arm are outlined below:

- Women of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agree 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 last dose of atezolizumab and 6 months after the last dose of enfortumab vedotin. Women must also agree not to breastfeed and refrain from donating eggs during the treatment period and for 6 months after the last dose of enfortumab vedotin.

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

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

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

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agree to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for 6 months after the last dose of enfortumab vedotin. Men must refrain from donating sperm during this same period.

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of enfortumab vedotin to avoid exposing the embryo.

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

A9–5 ASSESSMENT OF SAFETY FOR ATEZO+EV ARM

A9–5.1 SAFETY PLAN FOR ATEZO+EV ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and monotherapy enfortumab vedotin in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A9–5.1.1, A9–5.1.2, and A9–5.1.3). Guidelines for the management of patients who experience specific adverse events are provided in Section A9–5.1.4.

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. Because of the potential for overlapping toxicities such as rash and GI toxicities identified for atezolizumab and enfortumab vedotin, special caution will be taken with a planned safety evaluation of the first 6 patients randomized to the Atezo+EV arm. Randomization to the Atezo+EV arm will be paused after the enrollment of 6 patients until all of the patients in that arm have completed a safety evaluation of 21 days. If the combination is sufficiently safe, the randomization will be resumed.

Administration of study treatment 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. Adverse events will be reported as described in Sections 5.2–5.6 in the protocol body.

A9–5.1.1 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, hypophysitis, adrenal insufficiency, Guillain-Barré

syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions (SCARs). In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 6 and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A9–5.1.2 Risks Associated with Enfortumab Vedotin

The important identified risks for enfortumab vedotin are skin reactions (SCAR and rash), hyperglycemia, and pneumonitis/interstitial lung disease (ILD). Other identified risks are extravasation events, peripheral neuropathy, diarrhea/nausea/vomiting, dry eye (ocular disorders), anemia, and neutropenia. The potential risks are corneal disorders and blurred vision (ocular disorders), IRRs (other than extravasation events), anti-drug antibodies (ADAs), embryofetal toxicity, and testicular and ovarian toxicity.

A9–5.1.2.1 Important Identified Risks

Skin Reactions (Rash and Severe Cutaneous Adverse Reactions)

The target of enfortumab vedotin, Nectin-4, is expressed in the skin; adverse events of skin reactions have been observed in clinical trials and in the post-marketing setting.

As noted, SCAR, including cases of Stevens-Johnson syndromes (SJS) and toxic epidermal necrolysis (TEN), have been reported in clinical trials and the post-marketing setting. Some SJS and TEN events have had fatal outcomes. In addition, serious cases of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) have been reported. SDRIFE has a stereotypical appearance of skin reaction around the gluteal and intertriginous areas (Häusermann et al. 2004). SDRIFE can also present with pustules, papules and blistering (Tan and Tan 2011) and does not involve the mucosa, distinguishing it from SJS, which requires two or more sites of mucosal involvement (Lerch et al. 2018).

Skin reactions are common and various types have been observed in patients treated with enfortumab vedotin. Rash, maculopapular rash, and rash erythematous are most frequently reported. The onset of skin reactions is typically within the first cycle of treatment, but may occur later.

Patients and caregivers should be advised to contact the investigator immediately for signs or symptoms of skin reactions and mucosal abnormalities, including mucositis. Patients should be monitored closely for these reactions starting in the first cycle and throughout treatment. Prompt clinical evaluation by pertinent specialists, including, but not limited to, dermatologists, should be considered. Examination of skin and any mucosal involvement should occur at the outset and following any progression or evolution of the reactions. SJS/TEN can be misdiagnosed; thus, histologic confirmation,

including consideration of multiple biopsies, is critical to early recognition, as diagnosis and intervention can improve prognosis (Chang et al. 2020).

Hyperglycemia

While hyperglycemia, including some serious and fatal events, has been observed in patients treated with enfortumab vedotin, a potential mechanism of enfortumab vedotin-induced hyperglycemia has not been established, despite a comprehensive literature review of the biology and potential risks of targeting Nectin-4, studies examining Nectin-4 expression and ADC tissue cross-reactivity, a thorough review of the in vivo toxicology studies, and data from in vitro assays examining the impact of ADC and free MMAE on human tissues relevant to glucose homeostasis. This suggests that hyperglycemia is unlikely to be a Nectin-4 biology-related effect due to the lack of involvement of Nectin-4 in glucose homeostasis.

Data suggest that hyperglycemia events were more common in patients with a prior medical history of hyperglycemia who were treated with enfortumab vedotin. Furthermore, hyperglycemia events were more common in patients with an elevated baseline HbA_{1c} or a higher baseline BMI.

The onset of hyperglycemia is typically within the first cycle of treatment.

Patients should be assessed for symptoms of hyperglycemia. Patients should be monitored for blood glucose levels and additional assessments should be performed if any symptoms of hyperglycemia are observed, including a thorough evaluation for infection. Patients with, or at risk for, diabetes mellitus or hyperglycemia should be closely monitored. In addition, if steroids are used to treat any other condition, blood glucose levels may require additional monitoring.

Pneumonitis/ILD

Pneumonitis/ILD has occurred in subjects that received enfortumab vedotin as monotherapy and in combination with pembrolizumab. Patients should be monitored for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams.

A9–5.1.2.2 Other Identified Risks

Extravasation Events

Enfortumab vedotin is administered intravenously and extravasation may occur. Extravasation of enfortumab vedotin may be associated with skin and soft tissue injury and a more severe localized reaction; therefore, precautions should be taken to prevent extravasation. For patients with adequate venous access, a secure and free-flowing peripheral venous catheter may be adequate for drug administration. For patients with difficult peripheral venous access or who are at risk for extravasation (i.e., limited vein selection, small or fragile veins, local neuropathies, or lymphedema), consideration

should be given to placement of a central venous port or catheter. The patient and the infusion site should be monitored closely throughout the infusion. In addition to monitoring for redness or swelling, observe for symptoms of burning, stinging or a sensation of coolness around the injection site. In case of enfortumab vedotin extravasation, the combination agent (atezolizumab) should be held until assessment of benefit–risk by the investigator (Medical Monitor is available to advise as needed). Events of extravasation should be managed per institutional guidelines.

Peripheral Neuropathy

The cytotoxic component of enfortumab vedotin, MMAE, is a microtubule-disrupting agent (Challita-Eid et al. 2016). Peripheral neuropathy is often associated with drugs that affect microtubules and is associated with other MMAE ADCs (Donaghy 2016). The onset of peripheral neuropathy in clinical trials of enfortumab vedotin monotherapy typically began after two cycles of treatment. With enfortumab vedotin in combination, based on exposure-safety analysis increased exposure to enfortumab vedotin is associated with increased probability of peripheral neuropathy Grade $\geq$ 2.

Diarrhea, Vomiting, and Nausea

Nectin-4 expression has been identified in the esophagus and the stomach (Study ES10-001) and weak staining was observed in the mucosal glands of other gastrointestinal (GI) tract organs including the small intestine, colon, and rectum. The GI toxicities of diarrhea, nausea, and vomiting are common events reported with the use of MMAE-ADCs, including enfortumab vedotin.

Patients should be monitored for GI events and managed according to Table A9-4 and local standard of care, including appropriate use of antiemetics. Investigators should inform patients to maintain adequate hydration and to notify site staff if they experience nausea, vomiting, or diarrhea.

Dry Eye (Ocular Disorders)

Dry eye may occur due to various etiologies that affect the tear-film quality, including meibomian gland or lacrimal gland dysfunction. Other risk factors include contact lens wear. Symptoms of dry eye and blurred vision are often coincidental and may be associated with corneal epithelial changes. Separately, keratitis or other corneal epithelial changes have been reported with several ADCs containing anti-tubulin cytotoxic moieties. MMAE ADCs however, are not typically associated with these events (Eaton et al. 2015). Dry eye events are frequently reported across the enfortumab vedotin program and are considered an identified risk.

Anemia

Among hematological changes, anemia is among the most frequently observed treatment-emergent adverse events reported in enfortumab vedotin clinical studies and

is an identified risk. Anemia is multifactorial and can often be confounded by the disease process and comorbidities.

Neutropenia

Similar to anemia, among hematological changes, neutropenia is among the most frequently observed treatment-emergent adverse event reported in enfortumab vedotin clinical studies and is an identified risk. Neutropenia is also multifactorial and can often be confounded by the disease process and comorbidities.

In addition to routine infection prevention precautions, patients with clinical signs and symptoms indicative of infection in the setting of neutropenia should be managed according to the standard of care. Patients should be monitored for fever, as well as changes in blood counts, and signs of neutropenia.

A9–5.1.2.3 Potential Risks

Anti-Drug Antibodies

There is potential for an immunogenic response with any antibody therapy. Across studies, none of the patients who were confirmed positive for ADA post-baseline experienced systemic IRRs.

Infusion-Related Reactions Other than Extravasation-Site Reactions

Because enfortumab vedotin is an ADC, there is a risk of a hypersensitivity reaction and/or systemic IRRs and other local IRRs with enfortumab vedotin administration. Patients should be closely monitored for IRRs to facilitate early identification and management. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. Supportive measures may include administering medications for IRRs. Patients who have experienced an IRR may be premedicated for subsequent infusions. Premedication may include pain medication (e.g., acetaminophen or equivalent), an antihistamine (e.g., diphenhydramine hydrochloride), and a corticosteroid administered approximately 30 to 60 minutes prior to each infusion or according to institutional standards. If anaphylaxis occurs, study treatment administration should be immediately and permanently discontinued.

Corneal Disorders and Blurred Vision

In addition to dry eye (identified risk), corneal disorders and blurred vision are potential risks. Eye examinations are to be performed and patients should be monitored as described in Section 4.5.9 and the schedule of activities.

Embryofetal Toxicity

There have been no reports of pregnancy in clinical studies with enfortumab vedotin. The effect of enfortumab vedotin on human embryofetal development are unknown. In an animal reproduction study, administration of enfortumab vedotin to pregnant rats during organogenesis at clinically relevant systemic exposures was associated with an

increased rate of embryofetal mortality, structural malformations and skeletal anomalies. Patients should be advised of the potential risk to the fetus.

Testicular and Ovarian Toxicity

Fertility studies with enfortumab vedotin or MMAE have not been conducted. However, in rats, repeated dosing with enfortumab vedotin resulted in histologic findings of testicular toxicity, spermatid/spermatocyte depletion, and hypospermia/abnormal spermatids. These findings were not reversed by the end of the recovery period. In multiple Good Laboratory Practice-compliant repeat-dose cynomolgus monkey studies with other MMAE-conjugated ADCs, ovarian changes were observed consisting of decreased number or absent secondary and tertiary ovarian follicles with correlative decreased ovarian weights. These studies were performed with ADCs targeting five discrete antigens and one non-targeted ADC, suggesting that these findings are antigen independent and driven by the mechanism of action of MMAE. In these studies, there was sparing of the primordial and primary follicles and evidence of reversibility during the period covered by the clinical protocol and label-driven contraception recommendations. These results have not been observed in nonclinical studies involving enfortumab vedotin.

These results suggest the potential for enfortumab vedotin to impair reproductive function and fertility.

A9–5.1.3 Risks Associated with Combination Use of Atezolizumab and Enfortumab Vedotin

The following adverse events are potential overlapping toxicities associated with combination use of Atezo+EV: GI toxicity, rash, SCAR, neuropathy, anemia, IRRs, hyperglycemia/diabetes mellitus, and ocular adverse events.

A9–5.1.4 Management of Patients Who Experience Adverse Events in Atezo+EV Arm

A9–5.1.4.1 Dose Modifications

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

Dose reduction for enfortumab vedotin-associated toxicity is allowed depending on the type and severity of toxicity. Patients should initially dose reduce to 1.0 mg/kg (dose level −1). If additional dose reduction is needed, an additional dose reduction to 0.75 mg/kg (dose level −2) may occur. Dose-modification recommendations for treatment-associated toxicity are presented in Table A9-4. If a patient's dose is reduced because of a toxicity that subsequently resolves, the patient may re-escalate one dose level each cycle up to the original dose at the discretion of the investigator. The Medical Monitor is available to advise as needed. The timing of efficacy or safety evaluations should not be affected by dose interruptions or reductions.

A9–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table A9-4). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for >12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for >12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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.

Enfortumab vedotin treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table A9-4). If enfortumab vedotin is withheld for ≥ 84 days after event onset, the investigator will decide whether the patient should discontinue enfortumab vedotin permanently. The Medical Monitor is available to advise as needed

If atezolizumab is discontinued, enfortumab vedotin can be continued until the patient has documented progressive disease if the patient is likely to derive clinical benefit as determined by the investigator. If enfortumab vedotin is discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section A9–4.2.2 for information on dose interruptions for reasons other than toxicity (e.g., surgical procedures).

A9–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 6 for atezolizumab-related adverse events. Table A9-4 includes generic guidance for how to manage enfortumab vedotin when atezolizumab-associated adverse events occur. Table A9-4 includes management guidelines for enfortumab vedotin-associated adverse events. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases. For cases in which management guidelines are not covered in Appendix 6, the Enfortumab Vedotin Investigator's Brochure, or the protocol, patients should be managed as deemed appropriate by the investigator according to best medical judgment.

Table A9-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+EV Arm

Event	Action to Be Taken
Dermatologic event	
Grade 1	• Continue atezolizumab and enfortumab vedotin. • Follow guidelines for atezolizumab in Appendix 6. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Grade 2	• Continue atezolizumab and enfortumab vedotin. • For worsening rash or skin reactions or skin reactions with concomitant fever, consider withholding enfortumab vedotin until toxicity is Grade ≤ 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by one level. • Follow guidelines for atezolizumab in Appendix 6. • Consider patient referral to dermatologist/specialist for diagnosis and specialized care. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Grade 3	• Withhold atezolizumab and enfortumab vedotin for up to 12 weeks after event onset. • Follow guidelines for atezolizumab in Appendix 6. • Refer patient to dermatologist/specialist for diagnosis and specialized care. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab and enfortumab vedotin. Consider dose reduction by 1 level for enfortumab vedotin. • If event does not resolve to Grade 1 or better while withholding atezolizumab and enfortumab vedotin, permanently discontinue atezolizumab and contact the Medical Monitor. For recurrent Grade 3 events, permanently discontinue enfortumab vedotin.
Grade 4	• Permanently discontinue atezolizumab and enfortumab vedotin and contact the Medical Monitor.
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue enfortumab vedotin.
Neuropathy	
Grade 1	• Continue atezolizumab and enfortumab vedotin. • Investigate etiology.

Table A9-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+EV Arm (cont.)

Event	Action to Be Taken
Neuropathy (cont).	
Grade 2	• Withhold atezolizumab and enfortumab vedotin for up to 12 weeks after event onset. • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab and enfortumab vedotin at the same treatment doses. • For the second occurrence of Grade 2 neuropathy, if the event resolves to Grade 1 or better, resume atezolizumab at the same dose and reduce the dose of enfortumab vedotin by one dose level. If event does not resolve to Grade 1 or better while withholding atezolizumab and enfortumab vedotin, permanently discontinue atezolizumab and contact the Medical Monitor.
Grade 3 or 4	• Permanently discontinue atezolizumab and enfortumab vedotin, and contact the Medical Monitor. • Initiate treatment as per institutional guidelines.
Corneal events	
Grade 1	• Continue atezolizumab and enfortumab vedotin. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Grade 2	• Withhold atezolizumab and enfortumab vedotin for up to 12 weeks after event onset. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab and enfortumab vedotin. • For the second occurrence of Grade 2 ocular events, if the event resolves to Grade 1 or better, resume atezolizumab at the same dose and reduce the dose of enfortumab vedotin by one dose level. • For the second occurrence of a Grade 2 ocular event, if the event resolves to Grade 1 or better, resume atezolizumab at the same dose and reduce the dose of enfortumab vedotin by one dose level. • If event does not resolve to Grade 1 or better while withholding atezolizumab and enfortumab vedotin, permanently discontinue atezolizumab and enfortumab vedotin and contact the Medical Monitor.

Atezo = atezolizumab; EV = enfortumab vedotin.

Table A9-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+EV Arm (cont.)

Event	Action to Be Taken
Corneal events (cont.)	
Grade 3 or 4	• Permanently discontinue atezolizumab and enfortumab vedotin, and contact the Medical Monitor. • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over >1 month.
Hyperglycemia	
Grade 1 or 2	• Continue atezolizumab and enfortumab vedotin. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Grade 3	• Withhold enfortumab vedotin and atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab and enfortumab vedotin once hyperglycemia/elevated blood glucose had improved to Grade ≤2 and patient is clinically and metabolically stable.
Grade 4	• Withhold enfortumab vedotin and atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab and enfortumab vedotin once hyperglycemia/elevated blood glucose had improved to Grade ≤2 and patient is clinically and metabolically stable.
New onset Type 1 diabetes mellitus	• Follow guidelines for atezolizumab in Appendix 6.
Enfortumab vedotin-related toxicities not described above	
Any grade anaphylaxis	• Permanently discontinue enfortumab vedotin. • Follow guidelines for atezolizumab in Appendix 6.
Hematologic event	
Grade 1	• Continue atezolizumab and enfortumab vedotin.
Grade 2	• Continue atezolizumab and enfortumab vedotin. • For Grade 2 thrombocytopenia, withhold enfortumab vedotin until toxicity is Grade 1 or better, resume treatment at the same dose level.
Grade 3	• Withhold enfortumab vedotin until toxicity is Grade 1 or better, resume treatment at the same dose level or consider dose reduction by one dose level. Transfusions or growth factors may be used as indicated per institutional guidelines. • Continue atezolizumab.

Atezo = atezolizumab; EV = enfortumab vedotin.

Table A9-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+EV Arm (cont.)

Event	Action to Be Taken
Enfortumab vedotin-related toxicities not described above (cont.)	
Hematologic event (cont.)	
Grade 4	• Withhold atezolizumab and enfortumab vedotin until toxicity is Grade 1 or better, reduce dose by one dose level of enfortumab vedotin and resume treatment, or discontinue at the discretion of the investigator. Transfusions or growth factors may be used as indicated per institutional guidelines. • For anemia, treatment discontinuation should be strongly considered. Withhold atezolizumab until toxicity is Grade ≤1, resume atezolizumab treatment, or discontinue at the discretion of the investigator.
Non-hematologic event	
Grade 1 or 2	• Continue atezolizumab and enfortumab vedotin.
Grade 3	• Withhold enfortumab vedotin until toxicity is Grade 1 or better, resume treatment at the same dose level or consider dose reduction by one dose level of enfortumab vedotin. • Patients with Grade 3 electrolyte abnormalities that are corrected with appropriate therapy may continue enfortumab vedotin treatment without interruption. • Continue atezolizumab.
Grade 4	• Withhold atezolizumab and enfortumab vedotin until toxicity is Grade 1 or better, reduce enfortumab vedotin dose by one dose level and resume treatment, or discontinue at the discretion of the investigator. • Patients with Grade 4 electrolyte abnormalities that are corrected with appropriate therapy may continue enfortumab vedotin treatment without interruption.
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue enfortumab vedotin.
Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Continue enfortumab vedotin.
Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Enfortumab vedotin may be continued at the discretion of the investigator per medical judgment.

Atezo = atezolizumab; EV = enfortumab vedotin.

A9–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO+EV ARM (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 in the protocol body for reporting instructions). Adverse events of special interest for atezolizumab 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 in the protocol body)
- 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.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10\times$ upper limit of normal
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, HLH, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, and optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade $\geq$ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., SJS, dermatitis bullous,TEN)
- Myelitis
- Facial paresis

A9–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+EV ARM

A9–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab and 6 months after the last dose of enfortumab vedotin. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study 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 when updated information on the course and outcome of the pregnancy becomes available.

A9–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of enfortumab vedotin. 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. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to enfortumab vedotin. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A9–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF,

and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 in the protocol body).

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.

A9–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male 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 in the protocol body).

A9–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+EV ARM

Table A9-5 Schedule of Activities for Atezo+EV (Stage 1 and Stage 2)

	Stage 1 Screening [a]	Pretreatment Testing	Treatment Cycles (21-day cycles)				Stage 2 Screen [c] (see Appendix 7) or Treat Discon [d]	Follow-Up Q3M (±7 D)
			Cycle 1 [b]		Cycles ≥2			
	Days −28 to −1	Prior to Cycle 1, Day 1	Day 1	Day 8 (+3 D)	Day 1 (±3 D)	Day 8 (+3 D)		
Informed consent	See Appendix 7.						x [e, f]	
Molecular profile of urothelial carcinoma (if available)			Whenever updated information becomes available					
Vital signs [g]			x	x	x	x	x	
Weight [h]			x		x		x	
Complete physical examination [i]							x	
Limited physical examination [j, h]			x	x	x	x		
ECOG Performance Status [h]			x		x		x	
ECG [k, h]			Perform as clinically indicated.				x [f]	
Ophthalmologic examination [l]		x	Perform as clinically indicated.				x [l]	
HbA_{1c}							x [f]	
Hematology [m]			x [n]	x	x [n]	x	x [o]	
Chemistry [p]			x [n]	x	x [n]	x	x [o]	
Coagulation (INR and aPTT)							x [f, o]	
TSH, free T3 (or total T3), free T4 [q]			x [n, o]				x [o]	
HIV, HBV, and HCV testing							x [f, o]	
C-reactive protein							x [f, o]	
LDH							x [f, o]	
Pregnancy test [r]			x		x		x [o]	x [r]
Urinalysis [s]			x		x		x [f, o]	
Serum autoantibody sample [t]			Perform if a patient experiences a suspected immune-mediated adverse event.					

Table A9-5 Schedule of Activities for Atezo+EV (Stage 1 and Stage 2) (cont.)

	Stage 1 Screening [a]	Pretreatment Testing	Treatment Cycles (21-day cycles)				Stage 2 Screen [c] (see Appendix 7) or Treat Discon [d]	Follow-Up Q3M (±7 D)
			Cycle 1 [b]		Cycles ≥2			
	Days −28 to −1	Prior to Cycle 1, Day 1	Day 1	Day 8 (+3 D)	Day 1 (±3 D)	Day 8 (+3 D)		
PK samples	See Appendix 7.		Refer to Table A9-6 and Table A9-7.					
ADA samples			Refer to Table A9-6 and Table A9-7.					
Biomarker samples			Refer to Table A9-6 and Table A9-7.					
Blood sample for RBR (optional) [u]			x					
Tumor biopsy			x [v]					
Tumor biopsy (optional)			x [w]					
Tumor response assessments			x [x, y, z]					
Concomitant medications [aa]			x	x	x	x	x	
Adverse events [bb]			x	x	x	x	x	x
EV administration [cc, dd]			x	x	x	x		
Atezolizumab administration [dd, ee]			x		x			
Survival follow-up and anti-cancer treatment								x [ff]

ADA = anti-drug antibody; Atezo = atezolizumab; CT = computed tomography; D = day; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EOT = end of treatment; EV = enfortumab vedotin; HbA_{1c} = hemoglobin A1c; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; PK = pharmacokinetic; Q3M = every 3 months; RBR = Research Biosample Repository; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; Treat = treatment; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Patients who fail their first screening for study eligibility (Stage 1) may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the initiation of study treatment may be used; such tests do not need to be repeated for screening or re-screening.

[b] Treatment must be initiated no later than 14 days after treatment assignment.

Table A9-5 Schedule of Activities for Atezo+EV (Stage 1 and Stage 2) (cont.)

[c] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 in protocol body for details) or unacceptable toxicity may be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.2 in protocol body) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 or patients who have discontinued Stage 2 treatment will then undergo follow-up assessments.

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[f] Assessments to be performed only for patients undergoing Stage 2 screening.

[g] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, 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. 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.

[h] Assessment may be performed within 24 hours prior to dosing during the treatment period.

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

[j] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] ECG recordings will be obtained during screening. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[l] Patients will have 14 days to complete the screening ophthalmologic examination which should occur following randomization to the Atezo+EV arm but prior to Day 1 of Cycle 1 and as clinically indicated. Assessments should include the following: visual acuity, slit-lamp, tonometry, and dilated fundus examinations. Patients should be monitored and, if ocular symptoms and/or changes in vision are identified, considerations should be given to ophthalmology referral for further evaluation. Prior ophthalmologic exam done within 3 months of screening is acceptable provided symptoms are not new since the exam. Follow-up ophthalmology assessments should be performed per standard of care or if clinically indicated (e.g., subject develops new or worsening ocular symptoms). EOT slit-lamp examinations are required for patients who

Table A9-5 Schedule of Activities for Atezo+EV (Stage 1 and Stage 2) (cont.)

experience corneal adverse events during the study. EOT slit-lamp examinations must be performed ≥ 4 weeks from last dose. Any patient who is found to have evidence of active keratitis or corneal ulcerations during the Stage 1 ophthalmologic examination prior to Day 1 of Cycle 1 may be re-randomized to a different arm provided that screening assessments are within the screening window; the Medical Monitor is available to consult as needed. Any patient who is found to have evidence of active keratitis or corneal ulcerations during the Stage 2 ophthalmologic examination prior to Day 1 of Cycle 1 may be re-assigned to the Atezo + SG arm provided that screening assessments are within the screening window; the Medical Monitor is available to consult as needed.

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[n] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

[o] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[p] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide (if considered standard of care in the region), *serum troponin (at baseline, if considered standard of care/required per local clinical practice, and as clinically indicated during the study),* glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, amylase, lipase, and uric acid.

[q] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[r] All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum 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. During follow-up, pregnancy tests will be performed at 3 and 6 months. If a pregnancy test was performed within 96 hours prior to Day 1 of Cycle 1, it does not have to be repeated.

[s] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[t] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[u] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[v] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details), if deemed clinically feasible by the investigator (Stage 1 only). Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 in protocol body for tissue sample requirements.

[w] Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

Table A9-5 Schedule of Activities for Atezo+EV (Stage 1 and Stage 2) (cont.)

[x] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Refer to Section 4.5.6 in protocol body for further details on tumor assessments.

[y] Patients will undergo tumor assessments at baseline, every 9 weeks (±1 week) for the first 54 weeks following treatment initiation, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until loss of clinical benefit as determined by the investigator (see Section 3.1.1 in protocol body for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new, non–protocol-specified anti-cancer therapy.

[z] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[aa] Includes 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 study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[bb] 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.

[cc] Patients will receive enfortumab vedotin on Days 1 and 8 of a 21-day cycle and will receive a dose of 1.25 mg/kg with each infusion.

[dd] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details).

[ee] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Atezolizumab should be administered 60 minutes after enfortumab vedotin infusion.

[ff] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a 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. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table A9-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+EV Arm: Stage 1 Preliminary Phase

Visit	Time	Sample
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, and PBMC)
	30 (±10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, and PBMC)
Day 1 of Cycles 4 and 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)

ADA = anti-drug antibody; Atezo+EV = atezolizumab plus enfortumab vedotin; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Table A9-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+EV Arm: Stage 1 Expansion Phase and Stage 2

Visit	Time	Sample
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • EV PK (serum) • EV PK (plasma) • EV ADA (serum) • Biomarker (plasma, serum, and PBMC)
	30 (± 10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
	End of enfortumab vedotin infusion	• EV PK (serum) • EV PK (plasma)
Day 8 of Cycle 1	Prior to study treatment	• EV PK (serum) • EV PK (plasma)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • EV PK (serum) • EV PK (plasma) • EV ADA (serum) • Biomarker (plasma, serum, and PBMC)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • EV PK (serum) • EV PK (plasma) • EV ADA (serum) • Biomarker (plasma and serum)

ADA = anti-drug antibody; Atezo = atezolizumab; EV = enfortumab vedotin; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Table A9-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+EV Arm: Stage 1 Expansion Phase and Stage 2 (cont.)

Visit	Time	Sample
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • EV PK (serum) • EV PK (plasma) • EV ADA (serum) • Biomarker (plasma and serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • EV PK (serum) • EV PK (plasma) • EV ADA (serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • EV PK (serum) • EV PK (plasma) • EV ADA (serum) • Biomarker (plasma and serum)

ADA = anti-drug antibody; Atezo = atezolizumab; EV = enfortumab vedotin; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

A9–7 REFERENCES

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.

Butte MJ, Keir ME, Phamduy TB, et al. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Challita-Eid PM, Satpayev D, Yang P, et al. Enfortumab vedotin antibody-drug conjugate targeting nectin-4 is a highly potent therapetutic agent in multiple preclinical cancer models. Cancer Res 2016;76:3003–13.

Chang WC, Abe R, Anderson P, et al. SJS/TEN 2019: From science to translation. J Dermatol Sci 2020; 98:2–12.

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.

De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC Study 30986. J Clin Oncol 2012;30:191–9.

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.

Diefenbach CS, Connors JM, Friedberg JW, et al. Hodgkin lymphoma: current status and clinical trial recommendations. J Natl Cancer Inst 2017;109:djw249.

Donaghy H. Effects of antibody, drug and linker on the preclinical and clinical toxicities of antibody-drug conjugates. MAbs. 2016;8:659–71.

Eaton JS, Miller PE, Mannis MJ, et al. Ocular adverse events associated with antibody-drug conjugates in human clinical trials. J Ocul Pharmacol Ther 2015;31:589–604.

Fehrenbacher L, Spira A, Ballinger M, et al. 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;387:1837–1846.

Gardai SJ, Epp A, Law C-L. Brentuximab vedotin-mediated immunogenic cell death. Cancer Res 2015;75(15 suppl): abstract 2469.

Häusermann P, Harr T, Bircher AJ. Baboon syndrome resulting from systemic drugs: is there strife between SDRIFE and allergic contact dermatitis syndrome? Contact Dermatitis. 2004;51:297-310.

Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin Lymphoma. Blood 2018:131;1183–94.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–723.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–422.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.

Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, et al. Current Perspectives on Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Clin Rev Allergy Immunol. 2018 ;54:147-176.

Petrylak DP, Perez RP, Zhang J, et al. A phase 1 study of enfortumab vedotin (ASG-22CE; ASG-22ME): updated analysis of patients with metastatic urothelial cancer. J Clin Oncol 2017;35(15 Suppl):106.

Rikitake Y, Takai Y. Interactions of the cell adhesion molecule nectin with transmembrane and peripheral membrane proteins for pleiotropic functions. Cell Mol Life Sci 2008;65:253–263.

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;387:1909–1920.

Tecentriq® (atezolizumab) Summary of Product Characteristics, Genentech.

Tecentriq® (atezolizumab) U.S. Package Insert, Genentech.

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.

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;187:1113–1119.

Appendix 10
Study Details Specific to Atezo+Nira Arm

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A10–1 BACKGROUND ON ATEZO+NIRA ARM

A10–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (Atezo) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that targets programmed death-ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed death-1 (PD-1) and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. 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 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 cancer patients 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 (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, hypophysitis, myocarditis, and myasthenia gravis, have been observed (see Appendix 6 for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab (Tecentriq®) is approved for the treatment of urothelial carcinoma (UC), non–small-cell lung cancer (NSCLC), 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.

A10–1.2 BACKGROUND ON NIRAPARIB

Niraparib (Nira) is an orally available, potent, highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)-1 and -2 inhibitor.

Niraparib has shown clinical activity in patients with ovarian cancer with a median duration of progression-free survival (PFS) that was significantly longer among those receiving niraparib than among those receiving placebo, regardless of the presence or absence of germline *BRCA* mutations or homologous recombination deficiency status and was generally well tolerated as monotherapy (Mirza et al. 2016).

Niraparib is being developed as a monotherapy agent for tumors with defects in the homologous recombination DNA repair pathway, as a sensitizing agent in combination

with cytotoxic agents and radiotherapy, and in combination with immune-oncology biologics.

Niraparib is approved in some countries for maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

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

A10–2 RATIONALE FOR ATEZO+NIRA ARM

A10–2.1 THE PD-L1 PATHWAY

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).

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.

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 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).

CIT agents, particularly immune checkpoint inhibitors, have made a significant impact on the treatment of patients with UC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A10–2.2 PARP INHIBITION

DNA is constantly under repair because of genotoxic stress, such as damaging byproducts of cellular metabolism, disruptions of chemical bonds, and environmental agents. This genotoxic stress or genomic instability is a characteristic of tumor cells (Lord and Ashworth 2012). Genomic instability can lead to single- and/or double-strand breaks in the DNA, and preservation of the genomic code requires multiple DNA repair pathways collectively called DNA damage response (DDR) pathways (Lord and Ashworth 2012). The DDR pathways are defined by the type of DNA lesion they process but include a similar set of processes: detection of DNA damage, the accumulation of DNA repair factors at the site of damage, and the physical repair of the lesion (Lord and Ashworth 2012). Single-strand breaks are repaired via base excision repair (BER). The majority of double-strand break repair is accomplished by two mechanisms: homologous recombination and non-homologous end joining (NHEJ). Homologous recombination is slower and more accurate because it uses the sister chromatid as a template during the S-phase/G2 phases of the cell cycle. NHEJ is faster but more prone to error because damaged ends are directly ligated. Many DNA repair processes involve PARP-1 and PARP-2, zinc-finger DNA-binding enzymes that sense DNA damage and convert it into intracellular signals to promote DNA repair. For example, PARP inhibitors block DNA repair by the BER pathway, and in normal cells, the homologous recombination repair pathway compensates for PARP-mediated inhibition of BER and maintains the fidelity of DNA repair. In cells with a deficiency in homologous recombination repair, such as those with *BRCA*1 and *BRCA*2 mutations, PARP inhibition leads to irreparable double-strand breaks, collapsed replication forks, and an increased use of the less faithful NHEJ pathway. These disruptions result in genomic instability and ultimately cell death. This complementarity of a cellular defect and drug-induced effect is referred to as synthetic lethality, and in this manner, treatment with PARP inhibitors represents an opportunity to selectively kill cancer cells with deficiencies in homologous recombination and other DNA repair mechanisms.

Clinical studies have shown that PARP inhibitors have anti-tumor activity in patients with certain types of cancer, including, but not limited to, those patients with defined *BRCA* mutations (Fong et al. 2009; Audeh et al. 2010; Gelmon et al. 2011; Kummar et al. 2012). *BRCA*1 and *BRCA*2 mutations are found in the majority of patients with inherited breast or ovarian cancer (Wooster et al. 1995; Turner and Ashworth 2011), and inactivation of *BRCA*1 and *BRCA*2 and other genes in the homologous recombination repair pathway by somatic mutations or gene silencing due to promoter hypermethylation occurs in a significant portion of sporadic tumors (Chen et al. 1999; Turner et al. 2004). In particular, germline *BRCA*1 or *BRCA*2 mutations are found in 10%–15% of all newly diagnosed epithelial ovarian carcinomas, and strongly reduced expression of *BRCA*1 has been observed in a significant portion of sporadic ovarian cancers (Chen et al. 1999; Kaelin 2005). Collectively, over half of newly diagnosed ovarian cancers have defects in the homologous recombination pathway and may be

sensitive to PARP inhibitors (Stefansson et al. 2009; Konstantinopoulos et al. 2010; Kang et al. 2012). Notwithstanding these results, the low frequency of germline *BRCA* mutations in other solid tumors appeared to initially limit the use of PARP. However, use of next-generation sequencing has led to the identification of novel somatic mutations in genes encoding for components involved in homologous recombination that can functionally imitate *BRCA* loss and synergize with PARP inhibitor treatment. This concept was termed "BRCAness," defined as a tumor with homologous recombination deficiency without a deficiency in *BRCA*1/2 (Turner et al. 2004). The list of genes that, when mutated, may be involved in homologous recombination deficiency continues to expand and currently include genes, such as *ATM, ATR, BAP1, CDK12, CHK1, CHK2, FANCA, FANCC, FANCD2, FANCF, PALB2, NBS1, WRN, RAD51c, RAD51d, MRE11A,* and *BLM* (McCabe et al. 2006; Gottipati et al. 2010; Ledermann et al. 2012; Tang et al. 2012; Booth et al. 2013; Min et al. 2013; Bajrami et al. 2014; Duan et al. 2014; Lajud et al. 2014; Michels et al. 2014; Yu et al. 2014; Lombardi et al. 2015; Mateo et al. 2015; Johnson et al. 2016; Pollard et al. 2016; Zhang et al. 2016; Engert et al. 2017; Rimar et al. 2017; Swisher et al. 2017).

Clinical data to support the concept of PARP inhibitors has been reported with niraparib as maintenance treatment for women with platinum-sensitive, recurrent ovarian cancer (Mirza et al. 2016). In this study, women with germline *BRCA1/2* mutations and those with homologous recombination deficiency had the largest benefit from treatment with niraparib, although women lacking these predictive features still benefited compared with placebo (overall PFS of 9.3 months vs. 3.9 months; $p<0.001$) (Mirza et al. 2016). These findings set the stage for expanding the development of PARP inhibitors in tumors that are genetically wild type for *BRCA1/2* but deficient in homologous recombination because of somatic or germline mutations in other genes linked to homologous recombination–mediated DNA repair.

Bladder cancer or UC has a low frequency of germline *BRCA1/2* mutations (Cavanaugh and Rogers 2015; Mersch et al. 2015; Rimar et al. 2017); however, Bentley et al. (2004) theorized that the high frequency of chromosomal instability in patients with bladder cancer may be the result of a deficiency in the repair of double-strand breaks and thus the homologous recombination pathway. The Cancer Genome Atlas (TCGA) analysis of bladder cancer supported this theory because truncating and missense mutations in genes associated with the BRCAness phenotype and genes known to confer PARP inhibitor sensitivity (*CHEK1/2, RAD51, BRCA1/2, ATM, ATR, MDC1*, and *FANCF*) were identified in 34% of tumors (Cancer Genome Atlas Research Network 2014). In addition, Plimack et al. (2015) found that response to neoadjuvant cisplatin chemotherapy was associated with mutations in general DNA repair genes ($p<0.001$), some of which are strongly associated with homologous recombination (*ATM* and *FANCC*). Of the patients who responded to neoadjuvant cisplatin, 13 of 15 (87%) patients were found to have deleterious mutations in genes associated with

DNA repair, whereas none of the non-responders contained these mutations. The presence of these mutations was also found to be associated with significantly improved PFS (p=0.0085) and overall survival (p=0.007). The rate of complete response was 41% in DDR-positive patients (Plimack et al. 2015). The incidence of these mutations in homologous recombination genes, as well as their association with platinum sensitivity, suggests PARP is a rational target for the treatment of UC.

A10–2.3 BENEFIT-RISK ASSESSMENT

Immunotherapy in metastatic UC (mUC) has shown significant promise. Results from the pivotal multicenter Phase II study GO29293 (IMvigor210) and Phase III study GO29294 (IMvigor211) showed that durable responses were achieved in second-line post-platinum patients with mUC who received atezolizumab monotherapy (Rosenberg et al. 2016; Powles et al. 2018). In IMvigor210 Cohort 2, the objective response rate (ORR) in all patients was 15%, and responses were seen in all PD-L1 immunochemistry subgroups and the median survival in all patients was 7.9 months. Importantly, atezolizumab was well tolerated, with a low rate of treatment-related Grade 3 or 4 adverse events and discontinuations due to adverse events (Rosenberg et al. 2016). In IMvigor211, as of 13 March 2017, a median overall survival of 8.6 months, an ORR of 13.4% (10.5, 16.9), and a median duration of response (DOR) of 21.7 months was observed in the intent-to-treat (ITT) population. Atezolizumab continued to be well tolerated with a lower rate of treatment-related Grade 3 or 4 adverse events and fewer discontinuations due to adverse events than chemotherapy.

Despite the promise of single-agent checkpoint inhibition, only a small percentage of patients with mUC will experience benefit, highlighting the need for combinations (Rosenberg et al. 2016). Emerging data from TCGA suggest that UC carries the third highest mutation rate of all studied cancers, including reasonable subsets of tumors with somatic mutations in genes implicated in the homologous recombination pathway in both early-stage and late-stage disease (Rimar et al. 2017), including a high number of loss of function mutations in DNA damage repair genes. These findings suggest a role of PARP inhibitors in the treatment of mUC. In addition to the primary mechanism of action for PARP inhibitors (i.e., irreparable double-strand breaks, collapsed replication forks, an increased use of the NHEJ pathway resulting in genomic instability, and ultimately cell death), a second equally important mechanism of PARP inhibitors has been shown (Murai et al. 2011) in which the PARP inhibitors trap the PARP enzymes at the site of DNA damage referred to as PARP trapping. This irreversibly bound PARP–DNA complex prevents DNA repair, transcription, and replication and is ultimately cytotoxic. These two mechanisms both contribute to the emerging data that combining PARP inhibitors with checkpoint inhibitors may be a useful therapeutic strategy even in the absence of germline BRAC1/2 mutations via generation of cytosolic DNA that activates T cells through the stimulator of interferon genes pathway (Erdal et al. 2017) with an increase of infiltrating lymphocytes. PARP inhibition may also induce upregulation of

PD-L1, thereby providing further rationale for combining checkpoint inhibitors with PARP inhibition (Jiao et al. 2017).

Initial evidence of the ability to combine niraparib with a checkpoint inhibitor comes from data generated in a multicenter, open-label, single-arm Phase I/II study (NCT02657889) evaluating the safety and efficacy of combination treatment with niraparib and pembrolizumab in patients with recurrent ovarian cancer or metastatic triple-negative breast cancer (TNBC). In the dose-escalation phase of the study, the recommended Phase II dose was established at 200 mg niraparib in combination with 200 mg pembrolizumab. In the Phase II portion of the study, 83 patients had been enrolled as of August 2017 and 36.1% reported treatment-related Grade ≥3 adverse events with the most common (occurring in ≥5% of patients) being anemia (8.4%), fatigue (6.0%), platelet count decreased (6.0%), and thrombocytopenia (6.0%). No new safety signals were reported and responses were observed even in patients with *BRCA* wild-type and PD-L1–negative tumors (Konstantinopoulos et al. 2017).

On the basis of these results, as well as the tolerable safety profiles of atezolizumab and niraparib, combination treatment with these two agents appears to have promising therapeutic potential in solid tumors such as mUC.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit-risk assessment, please refer to Section 1.5.

A10–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEO+NIRA ARM

A10–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W; 1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert; Tecentriq Summary of Product Characteristics). Anti-tumor activity has been observed across doses ranging from 1 to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached, and no dose-limiting toxicities (DLTs) 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 pharmacokinetic, efficacy, and safety data (see the Atezolizumab Investigator's Brochure for details).

A10–3.2 RATIONALE FOR NIRAPARIB DOSE AND SCHEDULE

Niraparib will be administered at a dose of 200 mg once daily (QD) by mouth.

The approved starting dose of niraparib is 300 mg QD in recurrent ovarian cancer. According to the European Summary of Product Characteristics, a starting dose of

200 mg QD may be considered in patients who weigh below 58 kg. The most commonly administered dose of niraparib over the course of the Phase III clinical trial (NCT01847274; NOVA) was 200 mg QD, following dose modification. Further exploratory analyses of that study indicated that individual dose modification maintained efficacy and reduced the rate of new adverse events.

The 200-mg dose was selected on the basis of pharmacokinetic and pharmacodynamic profiles, nonclinical results, and a Phase I dose-escalation study (Sandhu et al. 2013). Pharmacodynamic functional studies showed that PARP inhibition in peripheral blood mononuclear cells exceeded 50% at most doses greater than 80 mg/day (Sandhu et al. 2013).

The recommended Phase II dose of niraparib in combination with checkpoint inhibitors was established on the basis of a Phase I/II study evaluating the safety and efficacy of combination treatment with niraparib and pembrolizumab in patients with advanced or metastatic triple-negative breast cancer (Konstantinopoulos et al. 2017).
The recommended Phase II dose was determined to be 200 mg niraparib QD orally and pembrolizumab 200 mg IV on Day 1 of each 21-day cycle. The DLT was thrombocytopenia. On the basis of these data, niraparib 200 mg QD will be used in combination with atezolizumab.

A10–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+NIRA ARM

A10–4.1 TREATMENT IN ATEZO+NIRA ARM

A10–4.1.1 Formulation, Packaging, and Handling

A10–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

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

A10–4.1.1.2 Niraparib

Niraparib will be supplied by the Sponsor as 100-mg capsules packed in high-density polyethylene white bottles with a two-piece, pulp-backed, heat-induction-foil inner seal, tamper-evident cap.

For information on the formulation and handling of the niraparib capsules, see the pharmacy manual and the Niraparib Investigator's Brochure.

A10–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus niraparib (Atezo+Nira) arm will receive treatment as outlined in Table A10-1 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 in the protocol body for details). Treatment must be initiated no later than 7 days after treatment assignment.

Table A10-1 Treatment Regimen for Atezo+Nira Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 • Niraparib 200 mg by mouth once daily

Atezo + Nira = atezolizumab plus niraparib.

Any dose modification or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.4.4. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab are available. There is no specific treatment in the event of niraparib overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

A10–4.1.2.1 Atezolizumab Administration

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

Atezolizumab should be infused over 60 (±15) minutes on Day 1 of Cycle 1 and on Day 1 of Cycle 4.

Administration of atezolizumab 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A10-2.

Table A10-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during the infusion and 30 (±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, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

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

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A10–5.1.4). The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

A10–4.1.2.2 Niraparib Administration

Niraparib will be administered orally once a day, continuously throughout the 21-day cycle. Two capsules of 100 mg strength (200 mg/day) will be taken at each dose administration. Patients will be instructed to take their niraparib dose in the morning at approximately the same time each day. On Day 1 of Cycles 1 and 4, patients should take their tablets in clinic 30 minutes prior to the atezolizumab infusion. On Day 15 of Cycle 1 and Day 1 of Cycle 2, patients should take their tablets at the clinic, as directed by site personnel.

To assess patient compliance with self-administration of niraparib, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.

For those patients experiencing nausea and who are at Cycle 2 and beyond, bedtime administration may be a potential method for managing nausea. Niraparib may be taken with or without food or water. Patients must swallow and not chew the capsules. Niraparib will be dispensed to patients on Day 1 of every cycle (every 21 days) thereafter until the patient discontinues study treatment.

Niraparib dose may be escalated on or after Day 1 of Cycle 3 from 200 mg QD (2 capsules) to 300 mg QD (3 capsules) if platelets $\geq$100,000/μL, hemoglobin $\geq$9 g/dL, and neutrophils $\geq$1500/μL for all laboratory tests performed during the first 2 cycles at the investigator's discretion. The Medical Monitor is available to advise as needed.

Dose interruption will be allowed for no longer than 28 days. In addition, dose reduction will be allowed based on treatment side effects. Dose reductions to 100 mg QD (1 capsule) will be allowed. No further dose reductions will be allowed. The timing of efficacy or safety evaluations should not be affected by dose interruptions or reductions (see Section A10–5.1.2).

In the niraparib arm, prophylactic cytokine (granulocyte colony-stimulating factor [G-CSF]) should not be given in the first cycle of the study but may be administered in subsequent cycles.

A10–4.1.3 Stage 2 Treatment

Patients who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1 in the protocol body) may be given the option of receiving a different treatment combination during Stage 2, as outlined in Table A10-3, provided they meet eligibility criteria (see Section 4.1 in the protocol body). Patients who experience unacceptable toxicity related to niraparib may also be eligible to receive treatment during Stage 2, provided they meet eligibility criteria. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A10-3 Stage 2 Treatment Regimens Available for the Atezo+Nira Arm

Study Treatment	Appendix
Atezo+EV	Appendix 9
Atezo+SG	Appendix 13

Atezo = atezolizumab; EV = enfortumab vedotin; SG = sacituzumab govitecan; Nira = niraparib.

Refer to Appendix 13 for details specific to the Atezo+SG arm.

A10–4.2 CONCOMITANT THERAPY FOR ATEZO+NIRA ARM

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 study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A10–4.2.1 Cautionary Therapy for Atezo+Nira Arm

A10–4.2.1.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor-α(TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab and niraparib. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator. The Medical Monitor is available to advise as needed.

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 6 for details).

A10–4.2.1.2 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 A10–4.2.2) may be used during the study at the discretion of the investigator.

A10–4.2.1.3 Cytochrome P450 1A2 Substrates

Niraparib weakly induces cytochrome P450 (CYP) 1A2 in vitro and is an insensitive substrate for P-glycoprotein; therefore, investigators should be advised to use caution with drugs that are sensitive substrates for CYP1A2 with a narrow therapeutic range (e.g., theophylline and tizanidine).

Even though inhibition of CYP3A4 in the liver is not expected with niraparib treatment, the potential to inhibit CYP3A4 at the intestinal level has not been established at relevant niraparib concentrations. Therefore, caution is recommended when niraparib is combined with active substances, the metabolism of which is CYP3A4-dependent and, notably, those having a narrow therapeutic range (e.g., cyclosporine, tacrolimus, alfentanil, ergotamine, pimozide, quetiapine, and halofantrine).

A10–4.2.2 Prohibited Therapy for Atezo + Nira Arm

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, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2 in the protocol body), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances outlined in Section A10–4.2.3.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin 2) are prohibited within 4 weeks or 5 half-lives of the drug, 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.

A10–4.2.3 Permitted Therapy for Atezo + Nira Arm

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

- Oral contraceptives with a failure rate of $< 1\%$ per year (see Section A10–4.3)
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin at a stable dose)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards

- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section A10–4.2.2)
- 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
- Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  After 2 cycles of treatment, palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy.
- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator. See Appendix 6 for further information.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections A10–4.2.1 and A10–4.2.2) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-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 5).

A10–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO+NIRA ARM

Contraception requirements for women and men in the Atezo + Nira arm are outlined below:

- Women of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agree 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 last dose of atezolizumab and 6 months after the last dose of niraparib. Women must refrain from donating eggs during the treatment period and for 6 months after the last dose of niraparib.

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

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

  Hormonal contraception must be supplemented by a barrier method.

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

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods and agree to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 3 months after the last dose of niraparib. Men must refrain from donating sperm during this same period.

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 3 months after the last dose of niraparib to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

A10–5 ASSESSMENT OF SAFETY FOR ATEZO+NIRA ARM

A10–5.1 SAFETY PLAN FOR ATEZO+NIRA ARM

The anticipated important safety risks are outlined below (see Sections A10–5.1.1, A10–5.1.2, and A10–5.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A10–5.1.4.

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. ECGs will be done throughout treatment as outlined in the schedule of activities to monitor for QTc prolongation. 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. Adverse events will be reported as described in Sections 5.2–5.6 in the protocol body.

A10–5.1.1 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, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). See Appendix 6 and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A10–5.1.2 Risks Associated with Niraparib

The following are classified as risks associated with niraparib: hematological toxicity (thrombocytopenia, anemia, neutropenia [including febrile neutropenia]), hypertension (including hypertensive crisis), myelodysplastic syndrome and acute myeloid leukemia, second primary malignancies other than myelodysplastic syndrome and acute myeloid leukemia, embryofetal toxicity, pneumonitis, thromboembolic events, and posterior reversible encephalopathy syndrome.

Refer to the Niraparib Investigator's Brochure for a detailed description of all anticipated risks for niraparib.

A10–5.1.3 Risks Associated with Combination Use of Atezolizumab and Niraparib

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and niraparib: rash, hepatic, musculoskeletal, hematologic, cardiac, and renal toxicity events.

A10–5.1.4 Management of Patients Who Experience Adverse Events in Atezo+Nira Arm

A10–5.1.4.1 Dose Modifications

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

Niraparib dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., surgery, unrelated medical events, patient vacation, or holidays). Patients should be placed back on study therapy within 28 days of the scheduled interruption, unless otherwise discussed with the Sponsor.

All treatment interruptions and dose reductions (including any missed doses) and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Niraparib dose reduction will be allowed based on treatment side effects.
Dose reductions to 1 capsule QD (100 mg) will be allowed (see Table A10-5). No further dose reductions will be allowed. The timing of efficacy or safety evaluations should not be affected by dose interruptions or reductions.

Niraparib Dose Modifications for Non-Hematologic Toxicity

Treatment with niraparib must be interrupted for any treatment-related non-hematologic Grade 3 or 4 event unless it is deemed by the investigator to be related to atezolizumab treatment (see Appendix 6), in which case treatment with niraparib may continue without interruption. If toxicity is appropriately resolved to Grade 1 or better within 28 days of interruption, the patient may restart treatment with niraparib with a dose-level reduction according to Table A10-4 unless prophylaxis is considered feasible. If the event recurs at a similar or worse grade, treatment should be interrupted.

If the toxicity requiring dose interruption has not resolved to Grade 1 or better during a maximum 4-week (28-day) dose interruption period, or the patient has already undergone a dose reduction (to a minimum dose of 100 mg QD), or both, the patient must permanently discontinue treatment with niraparib. Once the dose of niraparib has been reduced, any re-escalation must be discussed with the Sponsor. Note that treatment with atezolizumab may continue if discontinuation criteria as outlined in Appendix 6 have not been met. Blood pressure and heart rate should be routinely monitored during treatment with niraparib (see Table A10-7).

Table A10-4 Niraparib Dose Reductions for Non-Hematologic Toxicity

Event	Dose
Initial dose	200 mg once daily
Dose reduction for treatment-related Grade 3 or 4 adverse event or serious adverse event that persists despite treatment/prophylaxis [a]	100 mg once daily
Continued treatment-related Grade 3 or 4 adverse event or serious adverse event >28 days	Discontinue niraparib

[a] Prophylaxis includes, but is not limited to, medications to prevent nausea, vomiting, diarrhea, constipation, headache, back pain, myalgia, arthralgia, insomnia, decreased appetite, or dry mouth.

Niraparib Dose Modifications for Hematologic Toxicity

The dose interruption and modification criteria for niraparib for hematologic toxicities will be based on blood counts and are outlined in Table A10-5.

Table A10-5 Management of Hematologic Toxicities

Laboratory Abnormality	Intervention
Platelet count 25,000 to <75,000/μL	Niraparib must be interrupted until platelet count is ≥100,000/μL with twice weekly CBC monitored until recovery. After recovery, niraparib may then be resumed at same dose with monitoring of blood counts once weekly for 3 weeks. In the United Kingdom: After recovery, niraparib must then be resumed at a reduced dose with monitoring of blood counts once weekly for 3 weeks.
Further occurrence of platelet count 25,000 to <75,000/μL	Niraparib must be interrupted until platelet count is ≥100,000/μL with twice weekly CBC monitored until recovery. Niraparib may then be resumed at a reduced dose; after recovery, blood counts are monitored once weekly for 3 weeks to ensure the safety of the new dose level. (Dose not to be decreased below 100 mg daily.) In the United Kingdom: Permanently discontinue niraparib. Twice weekly CBC monitoring is recommended until platelet count is ≥100,000/μL.
Platelet count <25,000/μL	Niraparib must be interrupted until platelet count is ≥100,000/μL with twice weekly CBC monitored until recovery. Niraparib may then be resumed at a reduced dose; after recovery, blood counts are monitored once weekly for 3 weeks to ensure the safety of the new dose level. (Dose not to be decreased below 100 mg daily.)
Neutrophil <1000/μL	Niraparib must be interrupted until neutrophil counts are ≥1500/μL with twice weekly CBC monitored until recovery. Niraparib may then be resumed at a reduced dose; after recovery, blood counts once weekly for 3 weeks to ensure the safety of the new dose level. (Dose not to be decreased below 100 mg daily.)

Table A10-5 Management of Hematologic Toxicities (cont.)

Laboratory Abnormality	Intervention
Hemoglobin ≤8 g/dL	Niraparib must be interrupted until hemoglobin is ≥9 g/dL with once or twice weekly CBC monitored until recovery. Niraparib may then be resumed at a reduced dose; after recovery, blood counts once weekly for 3 weeks to ensure the safety of the new dose level.
Hematologic adverse reaction requiring transfusion	For patients with platelet count ≤10,000/μL, prophylactic platelet transfusion per guidelines should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or prophylactic transfusion at a higher platelet count, such as ≤20,000/μL.

Note: If blood counts do not recover within 28 days to normal values (i.e., platelets ≥100,000/μL, hemoglobin ≥9 g/dL, neutrophils ≥1500/μL), niraparib should be discontinued.

If clinically indicated, use of G-CSF is allowed according to current American Society of Clinical Oncology guidelines. If clinically indicated, RBC transfusions are allowed according to institutional guidelines.

If the hematologic toxicity does not recover to the specified level within 4 weeks (28 days) of dose interruption and/or the patient has already undergone one dose reduction (to a minimum dose of 100 mg QD), then niraparib should be discontinued.

Any patient requiring transfusion of platelets or RBCs (1 or more units) or hematopoietic growth factor support may undergo a niraparib dose reduction upon recovery if study treatment is resumed.

The Medical Monitor is available to advise as needed regarding potential re-escalation following dose reduction.

It is strongly recommended that the patient be referred to a hematologist for further evaluation if transfusions are required on more than one occasion or if the treatment-related hematologic toxicities have not recovered to Grade 1 or better within 4 weeks. If a diagnosis of MDS/AML is confirmed by a hematologist, the patient must permanently discontinue niraparib.

Note that treatment with atezolizumab may continue at the investigator's discretion if discontinuation criteria as outlined in Appendix 6 have not been met.
The Medical Monitor is available to advise as needed.

A10–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Appendix 6). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day

of oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator.
The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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.

Niraparib treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Section A10–5.1.4.1 and Table A10-6).

If atezolizumab is discontinued, niraparib can be continued until documentation of progressive disease if the patient is likely to derive clinical benefit, as determined by the investigator. For patients enrolled in the United Kingdom, if atezolizumab is discontinued, niraparib must be discontinued. If niraparib is discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section A10–4.1.2 for information on dose interruptions for reasons other than toxicity (e.g., surgical procedures).

A10–5.1.4.3 Management Guidelines for Adverse Events

These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Table A10-6 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Nira Arm

Event	Action to Be Taken
Niraparib-related toxicities	
Grade 1 or 2	• Follow niraparib dose modification in Section A10–5.1.4.1. • Continue atezolizumab.
Grade 3	• Follow niraparib dose modification in Section A10–5.1.4.1. • Continue atezolizumab.
Grade 4	• Follow niraparib dose modification in Section A10–5.1.4.1. • Atezolizumab may continue at the discretion of the investigator per medical judgment.
Atezolizumab-related toxicities	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue niraparib.
Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Continue niraparib.
Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Niraparib may continue at the discretion of the investigator per medical judgment.

Atezo = atezolizumab; Nira = niraparib.

A10–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO+NIRA ARM (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 in the protocol body for reporting instructions). Adverse events of special interest for the Atezo + Nira arm 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 in the protocol body)
- 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.
- Pneumonitis
- Colitis

- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10\times$ upper limit of normal
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, HLH, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, and optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- MDS, AML, and secondary cancers as outlined in the secondary malignancies reporting section (see Section A10–5.3.5)
- Embryofetal toxicity should be reported as outlined in the pregnancy reporting section (see Section A10–5.3)
- Myelitis
- Facial paresis

A10–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+NIRA ARM

A10–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab and 6 months after the last dose of niraparib. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study 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 when updated information on the course and outcome of the pregnancy becomes available.

A10–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 3 months after the last dose of niraparib. 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. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to niraparib. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A10–5.3.3 Abortions

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

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.

A10–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male 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 in the protocol body).

A10–5.3.5 Secondary Malignancies

Any MDS, AML, or secondary cancers (new malignancies other than mUC) should be classified to as adverse events of special interest and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 in the protocol body).

A10–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+NIRA ARM

Table A10-7 Schedule of Activities for Atezo+Nira Arm

Assessment/Procedure	Stage 1 Screen [a] Days –28 to –1	Treatment Cycles (21-Day Cycles) [b]				Stage 2 Screen [c] (see Appendix 7) or Treat Discon [d]	Follow-Up
		Cycles 1 and 2 [b]			Cycles ≥3		
		Day 1 [b]	Day 8 (±1 D)	Day 15 (±1 D)	Day 1 (±3 D)		Q3M (±7 D)
Informed consent	See Appendix 7.					x [e, f]	
Molecular profile of urothelial carcinoma (if available)		Whenever updated information becomes available					
Vital signs [g]		x	x	x	x	x	
Weight [h]		x			x	x	
Complete physical examination [i]						x	
Limited physical examination [j, h]		x			x		
ECOG Performance Status [h]		x			x	x	
ECG [k, h]		x			x (Cycle 4)	x [f]	
Hematology [l]		x [m]	x	x	x [m]	x [n]	
Chemistry [o]		x [m]	x	x	x [m]	x [n]	
Coagulation (PT/INR and aPTT)		x			x	x [f, n]	
TSH, free T3 (or total T3), free T4 [p]		x [m, n]				x	
HIV, HBV, and HCV testing						x [f, n]	
C-reactive protein						x [f, n]	
LDH						x [f, n]	
Pregnancy test [q]		x			x	x [n]	x [q]
Urinalysis [r]		x			x	x [f, n]	
Serum autoantibody sample [s]		Perform if a patient experiences a suspected immune-mediated adverse event.					
PK samples		Refer to Table A10-8 and Table A10-9.					
ADA samples		Refer to Table A10-8 and Table A10-9.					

Table A10-7 Schedule of Activities for Atezo+Nira Arm (cont.)

Assessment/Procedure	Stage 1 Screen [a] Days –28 to –1	Treatment Cycles (21-Day Cycles) [b]				Stage 2 Screen [c] (see Appendix 7) or Treat Discon [d]	Follow-Up
		Cycles 1 and 2 [b]			Cycles ≥3		
		Day 1 [b]	Day 8 (±1 D)	Day 15 (±1 D)	Day 1 (±3 D)		Q3M (±7 D)
Biomarker samples	See Appendix 7.	Refer to Table A10-8 and Table A10-9.					
Blood sample for RBR (optional) [t]		x					
Tumor biopsy		x [u]					
Tumor biopsy (optional)		x [v]					
Tumor response assessments		x [w, x, y]					
Concomitant medications [z]		x	x	x	x	x	
Adverse events [aa]		x	x	x	x	x	x
Atezolizumab administration [bb, cc]		x			x		
Niraparib treatment dispensed/collected [dd, ee]		x [ff]			x [ff]	x	
Compliance Check of Patient Diary [ff]			x	x	x	x	
Survival follow-up and anti-cancer treatment							x [gg]

ADA = anti-drug antibody; Atezo = atezolizumab; CT = computed tomography; D = days; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; hBcAb = hepatitis B core antibody; hBsAb = hepatitis B surface antibody; hBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IRR = infusion-related reaction; Nira = niraparib; PK = pharmacokinetic; Q3M = every 3 months; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; TB = tuberculosis; TCZ = tocilizumab; Treat = treatment; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Patients who fail the first screening for study eligibility (Stage 1) may qualify for two re-screenings (for a total of three screenings per patient) at investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the initiation of study treatment may be used; such tests do not need to be repeated for screening or re-screening.

[b] Treatment must be initiated no later than 7 days after treatment assignment. Patients will return to the clinic on Days 1, 8, and 15 of Cycle 1 and Cycle 2, but only on Day 1 for subsequent cycles. The increased frequency of visits in Cycle 1 and Cycle 2 is necessary to monitor hematologic and chemistry parameters for the safety of niraparib dosing.

Table A10-7 Schedule of Activities for Atezo+Nira Arm (cont.)

[c] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details) or unacceptable toxicity during Stage 1 treatment may be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.2 of the protocol body) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 or patients who have discontinued Stage 2 treatment will then undergo follow-up assessments.

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before randomization.

[f] Assessments to be performed only for patients undergoing Stage 2 screening.

[g] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, 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. For the first infusion, vital signs should be measured within 60 minutes prior to 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.

[h] Assessment may be performed within 24 hours prior to dosing during the treatment period.

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

[j] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] ECG recording will be obtained during screening, and two ECGs will be obtained on both Day 1 of Cycle 1 and Day 1 of Cycle 4. One ECG should be obtained pre-treatment, and the other ECG should be obtained 30 minutes after the end of the atezolizumab infusion and 2 hours post-niraparib administration. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording. ECGs are recommended to be performed prior to coinciding blood draws, including for PK, ADA, and biomarker sample collection.

[l] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[m] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

Table A10-7 Schedule of Activities for Atezo+Nira Arm (cont.)

[n] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[o] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide (if considered standard of care in the region), *serum troponin (at baseline, if considered standard of care/required per local clinical practice, and as clinically indicated during the study),* glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. For U.K. patients, amylase and lipase must be included on Day 1 of each treatment cycle.

[p] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[q] All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum 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. During follow-up, pregnancy tests will be performed at 3 and 6 months. If a pregnancy test was performed within 96 hours prior to Day 1 of Cycle 1, it does not have to be repeated.

[r] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[s] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[t] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[u] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator (Stage 1 only). Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 for tissue sample requirements.

[v] Consenting patients may undergo optional tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the discretion of the investigator.

[w] Patients will undergo tumor assessments at baseline, every 9 weeks (±1 week) for the first 54 weeks following treatment initiation, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until loss of clinical benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new, non–protocol-specified anti-cancer therapy.

[x] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[y] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (Day 1 of Cycle 1).

Table A10-7 Schedule of Activities for Atezo+ Nira Arm (cont.)

[z] Includes 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 study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[aa] 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 related to study treatment or trial-related procedures until a final outcome can be reported.

[bb] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The infusion on Day 1 of Cycles 1 and 4 should be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[cc] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details).

[dd] Niraparib will be administered by mouth at a fixed dose of 200 mg daily.

[ee] On Day 1 of Cycles 1, 2, and 4, patients should take their tablets at the clinic, as directed by site personnel. Patients in the expansion phase should also take their tablets at the clinic on Day 15 of Cycle 1 after the niraparib PK draw has been completed (see Table A10-9 below for details on the PK schedule).

[ff] Patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.

[gg] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a 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. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table A10-8 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Nira Arm: Preliminary Phase

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Niraparib PK (plasma) • Biomarker (plasma, serum, and PBMC)
	30 (±10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
	2 hours after niraparib administration [a]	• Niraparib PK (plasma)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, and PBMC)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)
	30 minutes after atezolizumab infusion [a]	• Atezolizumab PK (serum)
	2 hours after niraparib administration [a]	• Niraparib PK (plasma)
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)

ADA = anti-drug antibody; Atezo+Nira = atezolizumab plus niraparib; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: For visits where both PK and ECG are performed, there is no specific window for PK collection. Sites should adhere to the PK schedule whenever possible.

[a] Niraparib should be administered orally 30 minutes prior to the atezolizumab infusion on Day 1 of Cycles 1 and 4.

Table A10-9 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+Nira Arm: Expansion Phase

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Niraparib PK (plasma) [a] • Biomarker (plasma, serum, and PBMC)
	30 (±10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
	2 hours after niraparib administration [b]	• Niraparib PK (plasma)
Day 15 of Cycle 1	Prior to study treatment	• Niraparib PK (plasma) [a]
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Niraparib PK (plasma) [a] • Biomarker (plasma, serum, and PBMC)
	2 hours after niraparib administration	• Niraparib PK (plasma)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Niraparib PK (plasma) [a] • Biomarker (plasma and serum)
	30 minutes after atezolizumab infusion [b]	• Atezolizumab PK (serum)
	2 hours after niraparib administration [b]	• Niraparib PK (plasma)
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)

ADA = anti-drug antibody; Atezo+Nira = atezolizumab plus niraparib; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

[a] Niraparib PK samples are to be drawn prior to dosing with niraparib.

[b] Niraparib should be administered orally 30 minutes prior to the atezolizumab infusion on Day 1 of Cycles 1 and 4.

A10–7 REFERENCES

Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet 2010;376:245–251.

Bajrami I, Frankum J, Konde A, et al. Genome-wide profiling of genetic synthetic lethality identifies CDK12 as a novel determinant of PARP1/2 inhibitor sensitivity. Cancer Res 2014;74:287–297.

Bentley J, Diggle CP, Harnden P, et al. DNA double strand break repair in human bladder cancer is error prone and involves microhomology-associated end-joining. Nucleic Acids Res 2004;32:5249–5259.

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;54:307–314.

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;56:739–745.

Booth L, Cruickshanks N, Ridder T, et al. PARP and CHK inhibitors interact to cause DNA damage and cell death in mammary carcinoma cells. Cancer Biol Ther 2013;14:458–465.

Butte MJ, Keir ME, Phamduy TB, et al. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–122.

Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 2014;507:315–322.

Cavanagh H, Rogers KM. The role of BRCA1 and BRCA2 mutations in prostate, pancreatic and stomach cancers. Hered Cancer Clin Pract 2015;13:16.

Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–6587.

Chen JJ, Silver D, Cantor S, et al. BRCA1, BRCA2, and Rad51 operate in a common DNA damage response pathway. Cancer Res 1999;59(7 Suppl):1752s–1756s.

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.

De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC Study 30986. J Clin Oncol 2012;30:191–199.

Duan W, Gao L, Aguila B, et al. Fanconi anemia repair pathway dysfunction, a potential therapeutic target in lung cancer. Front Oncol 2014;4:368.

Engert F, Kovac M, Baumhoer D, et al. Osteosarcoma cells with genetic signatures of BRCAness are susceptible to the PARP inhibitor talazoparib alone or in combination with chemotherapeutics. Oncotarget 2017;8:48794–48806.

Erdal E, Haider S, Rehwinkel J, et al. A prosurvival DNA damage-induced cytoplasmic interferon response is mediated by end resection factors and is limited by Trex1. Genes Dev 2017;31:353–369.

Fehrenbacher L, Spira A, Ballinger M, et al. 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;387:1837–1846.

Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009;361:123–134.

Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol 2011;12:852–861.

Gottipati P, Vischioni B, Schultz N, et al. Poly(ADP-ribose) polymerase is hyperactivated in homologous recombination-defective cells. Cancer Res 2010;70:5389–5398.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–723.

Jiao S, Xia W, Yamaguchi H, et al. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin Cancer Res 2017.

Johnson SF, Cruz C, Greifenberg AK, et al. CDK12 inhibition reverses de novo and acquired PARP inhibitor resistance in BRCA wild-type and mutated models of triple-negative breast cancer. Cell Rep 2016;17:2367–2381.

Kaelin WG, Jr. The concept of synthetic lethality in the context of anticancer therapy. Nat Rev Cancer 2005;5:689–698.

Kang J, D'Andrea AD, Kozono D. A DNA repair pathway-focused score for prediction of outcomes in ovarian cancer treated with platinum-based chemotherapy. J Natl Cancer Inst 2012;104:670–681.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–622.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.

Konstantinopoulos PA, Sachdev JC, Schwartzberg L, et al. Dose-finding combination study of niraparib and pembrolizumab in patients (pts) with metastatic triple-negative breast cancer (TNBC) or recurrent platinum-resistant epithelial ovarian cancer (OC). Ann Oncol 2017;28(suppl 5):v403–427.

Konstantinopoulos PA, Spentzos D, Karlan BY, et al. Gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer. J Clin Oncol 2010;28:3555–3561.

Kummar S, Ji J, Morgan R, et al. A phase I study of veliparib in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas. Clin Cancer Res 2012;18:1726–1734.

Lajud SA, Nagda DA, Yamashita T, et al. Dual disruption of DNA repair and telomere maintenance for the treatment of head and neck cancer. Clin Cancer Res 2014;20:6465–6478.

Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012;366:1382–1392.

Lombardi AJ, Hoskins EE, Foglesong GD, et al. Acquisition of relative interstrand crosslinker resistance and PARP inhibitor sensitivity in Fanconi anemia head and neck cancers. Clin Cancer Res 2015;21:1962–1972.

Lord CJ, Ashworth A. The DNA damage response and cancer therapy. Nature 2012;481:287–294.

Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373:1697–1708.

McCabe N, Turner NC, Lord CJ, et al. Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. Cancer Res 2006;66:8109–8115.

Mersch J, Jackson MA, Park M, et al. Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian. Cancer 2015;121:269–275.

Michels J, Vitale I, Saparbaev M, et al. Predictive biomarkers for cancer therapy with PARP inhibitors. Oncogene 2014;33:3894–3907.

Min A, Im SA, Yoon YK, et al. RAD51C-deficient cancer cells are highly sensitive to the PARP inhibitor olaparib. Mol Cancer Ther 2013;12:865–877.

Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 2016;375:2154–2164.

Murai J, Yang K, Desuphong G, et al. The USP1/UAF1 complex promotes double-strand break repair through homologous recombination. Mol Cell Biol 2011;31:2462–2469.

Plimack ER, Dunbrack RL, Brennan TA, et al. Defects in DNA repair genes predict response to neoadjuvant cisplatin-based chemotherapy in muscle-invasive bladder cancer. Eur Urol 2015;68:959–967.

Pollard J, Reaper P, Peek A, et al. Pre-clinical combinations of ATR and PARP inhibitors: defining target patient populations and dose schedule. Cancer Res 2016;76 (14 Suppl):3711.

Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (iMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2018;391(10122):748–757.

Rimar KJ, Tran PT, Matulewicz RS, et al. The emerging role of homologous recombination repair and PARP inhibitors in genitourinary malignancies. Cancer 2017;123:1912–24.

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;387:1909–1920.

Sandhu SK, Schelman WR, Wilding G, et al. The poly(ADP-ribose)polymerase inhibitor niraparib (MK4827) in *BRCA* mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. Lancet Oncol 2013;14:882–892.

Stefansson OA, Jonasson JG, Johannsson OT, et al. Genomic profiling of breast tumours in relation to BRCA abnormalities and phenotypes. Breast Cancer Res 2009;11:R47.

Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol 2017;18:75–87.

Tang Y, Hamed HA, Poklepovic A, et al. Poly (ADP-ribose) polymerase 1 modulates the lethality of CHK1 inhibitors in mammary tumors. Mol Pharmacol 2012;82:322–332.

Tecentriq® (atezolizumab) Summary of Product Characteristics, Genentech.

Tecentriq® (atezolizumab) U.S. Package Insert, Genentech.

Turner NC, Ashworth A. Biomarkers of PARP inhibitor sensitivity. Breast Cancer Res Treat 2011;127:283–286.

Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 2004;4:814–819.

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;23:4602–4608.

Wooster R, Bignell G, Lancaster J, et al. Identification of the breast cancer susceptibility gene BRCA2. Nature 1995;378:789–792.

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;187:1113–1119.

Yu H, Pak H, Hammond-Martel I, et al. Tumor suppressor and deubiquitinase BAP1 promotes double-strand break repair. Proc Natl Acad Sci USA 2014;111:285–290.

Zhang X, Li M, Momocilovic O, et al. Functional annotation of cancer driver genes in breast cancer patient-derived xenografts to identify a novel target for PARP inhibitors. J Clin Oncol 2016;34(15 suppl):e23192.

Appendix 11
Study Details Specific to Atezo+Magro Arm

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A11–1 BACKGROUND ON ATEZO+MAGRO ARM

A11–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (Atezo) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that targets programmed death-ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed death-1 (PD-1) and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. 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 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 cancer patients 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 (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, hypophysitis, myocarditis, and myasthenia gravis, have been observed (see Appendix 6). To date, these events have been manageable with treatment.

Atezolizumab (Tecentriq®) is approved for the treatment of urothelial carcinoma (UC), non–small-cell lung cancer (NSCLC), 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.

A11–1.2 BACKGROUND ON MAGROLIMAB

Magrolimab (Magro) is an anti-human CD47 monoclonal antibody that enables phagocytosis of human cancer cells by blocking CD47, a potent survival signal for macrophages. However, blockade of CD47 in tumors can enhance macrophage phagocytosis of cancer cells. In nonclinical studies, this results in a profound anti-tumor effect against solid tumors and hematologic malignancies. Nonclinical combinations with a checkpoint inhibitor (anti–PD-1) show synergistic anti-tumor effects and increases in CD8+ T cells when combined with anti-CD47.

Most normal tissues are unaffected by CD47 blockade because they lack pro-phagocytic signals. However, RBCs are a notable exception because CD47 expression helps regulate the turnover of RBCs. Administration of magrolimab results in an acute drop in hemoglobin due to phagocytosis of aging erythrocytes. However, in patients with solid tumors and lymphoma, a compensatory reticulocytosis and the generation of new,

younger RBCs results in a gradual resolution of the acute anemia despite continued treatment. Furthermore, in clinical and nonclinical studies, the administration of an initial low priming dose followed by maintenance doses of magrolimab substantially reduces the risk of severe anemia.

Another prominent clinical adverse reaction is hemagglutination, typically occurring after the initial priming or first maintenance dose of drug. Hemagglutination findings are generally transient, are not correlated with clinical symptoms, and have not required dose reductions in patients treated with priming and maintenance doses of magrolimab. Other common treatment-related adverse events observed include mild headaches, dizziness, fatigue, nausea, photopsia, fever, chills, urine discolorations, mild transient visual disturbances, arthralgia, hyperbilirubinemia (predominately unconjugated), back pain, abdominal pain, and infusion reactions.

Magrolimab is administered as an IV infusion and is currently being studied in five ongoing clinical trials. In two ongoing single-agent Phase I studies (SCI-CD47-001 [NCT02216409] in patients with advanced solid tumors and lymphomas and SCI-CD47-002 [NCT02678338] in patients with relapsed or refractory acute myeloid leukemia [AML]), dose escalation is ongoing. Three combinations trials have also been initiated: The first combines magrolimab with rituximab in patients with non-Hodgkin lymphoma; the second combines magrolimab with cetuximab in patients with solid tumors and colorectal cancer; the third evaluates magrolimab monotherapy activity in patients with AML and myelodysplastic syndrome (MDS) and magrolimab in combination with azacitidine in untreated patients with AML ineligible for standard induction chemotherapy and untreated patients with high-risk MDS.

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

A11–2 RATIONALE FOR ATEZO+MAGRO ARM

A11–2.1 THE PD-L1 PATHWAY

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).

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.

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 NSCLC, UC, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors, have made a significant impact on the treatment of patients with UC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A11–2.2 CD47 ANTAGONISM

CD47 is a surface glycoprotein that is widely expressed on cancer cells and normal tissues (Brown 2001). It consists of an extracellular immunoglobulin superfamily domain linked to five transmembrane spanning regions and a short intracellular cytoplasmic domain (Brown 2001). It binds to a variety of integrins and thrombospondin-1; however, its interaction with signal receptor protein-alpha (SIRP-α) is thought to be the major mediator of its function as a negative checkpoint regulator of phagocytosis.

CD47 binding to the receptor SIRP-α on the surface of the innate immune system, such as macrophages and dendritic cells, initiates a signal transduction cascade that blocks phagocytosis. In this way CD47 functions as an inhibitor of phagocytosis by delivering a dominant inhibitory signal to phagocytic cells (Blazar et al. 2001; Okazawa et al. 2005). However, the complex process of phagocytosis depends on the relative balance of pro-phagocytic and anti-phagocytic inputs. Most normal cells, apart from aging RBCs (Oldenborg 2004; Okazawa et al. 2005), lack expression of pro-phagocytic signals (Jaiswal et al. 2009; Majeti et al. 2009; Chao et al. 2012) and are unaffected by CD47 blockade. In contrast, most cancer cells, including UC cells, express pro-phagocytic signals on their cell surface (Chao et al. 2012). As a consequence, effective phagocytosis requires two events: a silencing of the CD47/SIRP-α inhibition pathway and interaction of the pro-phagocytic signal with its receptor. Cancer cells exhibit increased expression of CD47, presumably to prevent phagocytic elimination by innate immune cells (Jaiswal et al. 2010). When CD47 is blocked from interacting with SIRP-α, pro-phagocytosis signals dominate, enabling phagocytosis of the cancer cells, which

results in inhibition of tumor growth and metastasis (Majeti et al. 2009; Chao et al. 2011a; Chao et al. 2011b; Edris et al. 2012a; Edris et al. 2012b; Kim et al. 2012; Willingham et al. 2012; Pang et al. 2013).

A11–2.3 BENEFIT-RISK ASSESSMENT

Immunotherapy in metastatic UC (mUC) has shown significant promise. Results from the pivotal multicenter Phase II study GO29293 (iMvigor210) and Phase III study GO29294 (iMvigor211) showed that durable responses were achieved in second-line post-platinum patients with mUC who received atezolizumab monotherapy (Rosenberg et al. 2016; Powles et al. 2018). In iMvigor210 Cohort 2, the objective response rate (ORR) in all patients was 15%, and responses were seen in all PD-L1 immunochemistry subgroups and the median survival in all patients was 7.9 months. Importantly, atezolizumab was well tolerated, with a low rate of treatment-related Grade 3 or 4 adverse events and discontinuations due to adverse events (Rosenberg et al. 2016). In iMvigor211, as of 13 March 2017, a median overall survival of 8.6 months, an ORR of 13.4% (10.5, 16.9), and a median duration of response (DOR) of 21.7 months was observed in the intent-to-treat (ITT) population. Atezolizumab continued to be well tolerated with a lower rate of treatment-related Grade 3 or 4 adverse events and fewer discontinuations due to adverse events than chemotherapy. Despite the promise of single-agent checkpoint inhibition, only a small percentage of patients experience benefit, highlighting the need for combinations. One potential mechanism for converting otherwise resistant cancers is manipulation of the phagocytosis checkpoint system via anti-CD47 antibodies, resulting in macrophage mediated phagocytosis and cross-presentation of tumor antigens to T cells with subsequent proliferation of CD8 cells.

Nonclinical work has evaluated the anti-tumor effect of magrolimab in a xenograft model of human bladder cancer. Immunodeficient male mice were injected subcutaneously with 639V cancer cells transduced with a green fluorescent protein–luciferase-encoding lentivirus. Mice were then either administered daily intraperitoneal magrolimab or phosphate-buffered saline (PBS). All PBS-treated mice were euthanized after 4 weeks of treatment because of high tumor burden; however, mice treated with magrolimab showed no substantial tumor growth at the end of 4 weeks, and no significant tumor growth was observed after an additional 4 weeks of observation (FortySeven Inc., data on file).

Nonclinical work has also evaluated the combination of monoclonal antibodies to SIRP-α (CD47 receptor) and PD-1 (Yanagita et al. 2017). Tumor-bearing mice (harboring CT-26 colon cancer) treated with only SIRPα antibody had no reduction in tumor growth compared with placebo. Although treatment with an anti-PD1 monoclonal antibody showed decreases in tumor volume at Day 20, the combination of both SIRPα and PD-1 antibodies markedly enhanced tumor growth suppression ($p<0.01$).

In summary, the safety profile of atezolizumab in combination with magrolimab continues to be defined. Overlapping toxicities include anemia and infusion-related reactions (IRRs) and safety will be monitored closely.

Considering the high therapeutic need in the second-line setting for patients with mUC for tolerable and effective treatment, and the compelling nonclinical data and anticipated safety profile for the combination of atezolizumab and magrolimab, the benefit–risk assessment favors moving forward with the evaluation of the combination in patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.5.

A11–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+MAGRO ARM

A11–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 840 mg every 2 weeks (Q2W) (840 mg on Days 1 and 15 of each 28-day cycle). The average concentration following the 840 mg Q2W dose is expected to be equivalent to that of 1200 mg every 3 weeks (Q3W), the approved dose for atezolizumab (Tecentriq® U.S. Package Insert; Tecentriq SmPC). Anti-tumor activity has been observed across doses ranging from 1 to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached, and no dose-limiting toxicities (DLTs) were observed at any dose. The fixed dose of 840 mg Q2W (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 pharmacokinetic, efficacy, and safety data (see the Atezolizumab Investigator's Brochure for details).

A11–3.2 RATIONALE FOR MAGROLIMAB DOSE AND SCHEDULE

Magrolimab will be administered on a 28-day cycle. During Cycle 1, patients will receive a 1-mg/kg priming dose on Day 1 followed by three weekly doses of 30 mg/kg on Days 8, 15, and 22. During Cycle 2, patients will receive weekly doses of 30 mg/kg on Days 1, 8, 15, and 22. For all subsequent cycles, patients will receive 30 mg/kg on Days 1 and 15. Magrolimab will be administered by IV injection.

In the solid tumor study (5F9-CD47 001), 30-mg/kg doses of magrolimab resulted in drug concentrations that far exceeded those associated with anti-tumor efficacy in nonclinical models (100 mcg/mL) and were higher than concentrations associated with objective responses in 2 patients with solid tumors (Forty Seven Inc., data on file). Population pharmacokinetic (PK) modeling and simulation predicts that the proposed dosing regimen of 30 mg/kg weekly loading followed by 30 mg/kg Q2W results in

steady-state concentrations in the range of 300–1000 mcg/mL. Therefore, the proposed dose regimen of 30 mg/kg Q2W starting in Week 9 is anticipated to maximally affect the molecular target and be both safe and efficacious. This dose and this schedule were chosen on the basis of effects observed in nonclinical and clinical studies, PK–pharmacodynamic modeling results, and observed clinical safety data, as described below (see Table A11-1).

Table A11-1 Treatment Schedule for Atezo+Magro Arm

	Cycle 1				Cycle 2				Cycle 3+	
Day	1	8	15	22	1	8	15	22	1	15
Atezolizumab 840 mg IV	x		x		x		x		x	x
Magrolimab 1 mg/kg IV	x									
Magrolimab 30 mg/kg IV		x	x	x	x	x	x	x	x	x

Atezo = atezolizumab.

Magrolimab will be dosed using a prime/maintenance schedule. The priming dose was implemented as a safety measure to protect against the potential for severe anemia (an identified risk given the mechanism of action of magrolimab and the presence of CD47 on aging RBCs). In nonclinical studies, the premature loss of aging RBCs was compensated for by an ensuring reticulocytosis, and the initial anemia resolved as aged RBCs were replaced with younger cells. These studies also found that the potential for severe anemia was ameliorated by administration of a low priming dose of magrolimab that results in a mild-to-moderate anemia and stimulates reticulocytosis.

The doses for magrolimab were established in Study SCI-CD47-001. Part A established the recommended priming dose of magrolimab; Parts B and C identified the optimal maintenance dose.

Part A of the study enrolled patients in dose cohorts of 0.1, 0.3, 1.0 and 3.0 mg administered weekly using a modified accelerated dose-titration design. The optimal priming dose of 1.0 mg/kg was identified because it was the dose level at which no more than 1 of 6 patients experienced a DLT. No patients experienced a DLT at the 1.0-mg/kg level. Two patients treated at the 3-mg/kg level experienced DLTs (Grade 3 abdominal pain during infusion and Grade 3 hemagglutination with headache).

In Parts B and C of the study, all patients received a Week 1 priming dose of 1 mg/kg followed by weekly maintenance dosing beginning at Week 2 of 3, 10, 20, and 30 mg/kg. A 3+3 study design was used to determine the maximum tolerated dose of 45 mg/kg.

A11–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+MAGRO ARM

A11–4.1 SAFETY EVALUATION IN ATEZO+MAGRO ARM

Because of the potential for overlapping hematologic toxicities and IRRs identified for both atezolizumab and magrolimab, special caution will be taken by performing a planned safety evaluation (see Section 3.1.4 in protocol body). Randomization to the Atezo+Magro arm will be paused after the enrollment of 6 patients until all of the patients in that arm have completed a safety evaluation of at least 1 cycle (28 days) of treatment. Patients who withdraw prior to 28 days will not be replaced, and the safety evaluation will be based on the available data at the time all remaining patients have a follow-up of 28 days. If the combination is sufficiently safe, randomization will be resumed.

A11–4.2 TREATMENT IN ATEZO+MAGRO ARM

A11–4.2.1 Formulation, Packaging, and Handling

A11–4.2.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

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

A11–4.2.1.2 Magrolimab

Magrolimab is supplied in single-use, 10-mL vials containing 200 mg of the antibody. The magrolimab drug product is a sterile, clear to slightly opalescent, colorless, preservative-free liquid intended for IV injection.

For information on the formulation and handling of magrolimab, see the pharmacy manual and the Magrolimab Investigator's Brochure.

A11–4.2.2 Dosage, Administration, and Compliance

Patients in the Atezo+Magro arm will receive treatment as outlined in Table A11-1 and Table A11-2 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 in the protocol body for details). Treatment must be initiated no later than 7 days after treatment assignment.

Table A11-2 Treatment Regimen for Atezo+Magro Arm

Cycle	Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
Cycle 1	28 days	• Atezolizumab 840 mg IV on Days 1 and 15 • Magrolimab 1 mg/kg IV on Day 1 • Magrolimab 30 mg/kg IV on Days 8, 15, and 22
Cycle 2	28 days	• Atezolizumab 840 mg IV on Days 1 and 15 • Magrolimab 30 mg/kg IV on Days 1, 8, 15, and 22
Cycles 3+	28 days	• Atezolizumab 840 mg IV on Days 1 and 15 • Magrolimab 30 mg/kg IV on Days 1 and 15

Atezo = atezolizumab; Magro = magrolimab.

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab or magrolimab are available. Nonclinical safety assessment suggests that the primary toxicity to be anticipated with overdose of HuF59-G4 may be anemia.

A11–4.2.2.1 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle.

Administration of atezolizumab 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A11-3.

Table A11-3 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. Premedication for magrolimab should be given as described in Section A11–4.2.2.2. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during the infusion and 30 (±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, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

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

Guidelines for medical management of IRRs for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A11–5.1.4. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

A11–4.2.2.2 Magrolimab Administration

Magrolimab will be administered on a 28-day cycle. Magrolimab should be administered 1 hour after the completion of the atezolizumab infusion. During Cycle 1, patients will receive a 1-mg/kg priming dose on Day 1 followed by doses of 30 mg/kg on Days 8, 15, and 22. In Cycle 2, patients will receive weekly doses of 30 mg/kg on Days 1, 8, 15, and 22. For all subsequent cycles, patients will receive 30 mg/kg on Days 1 and 15. Magrolimab will be administered by IV injection. The priming dose should be infused over 3 hours (±30 minutes), and all maintenance doses should be infused over 2 hours (±30 minutes). Patients should be premedicated with acetaminophen 500–650 mg and

oral or IV diphenhydramine 25–50 mg or a comparable regimen (see Table A11-5, management of infusion reactions) for the first two doses of magrolimab (includes the priming dose). The last recorded body weight of a patient should be used for calculating the magrolimab dose. The dose administered should be within 10% of the calculated dose.

The dose of magrolimab may be decreased to 20 mg/kg for Grade ≥3 adverse events that are assessed as being related to magrolimab at the investigator's discretion. Guidelines for magrolimab treatment interruption or discontinuation because of toxicities are provided in Section A11–5.1.4.2. Magrolimab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. If the time interval between magrolimab doses is greater than 4 weeks on account of missed doses, then repriming is required prior to restarting weekly doses.

Vital signs are recommended to be measured within 60 minutes of the infusion, and during and after the infusion if clinically indicated.

A11–4.2.3 Stage 2 Treatment

Patients who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1 in the protocol body) may be given the option of receiving a different treatment combination during Stage 2, as outlined in Table A11-4, provided they meet eligibility criteria (see Section 4.1 in the protocol body). Patients who experience unacceptable toxicity related to magrolimab may also be eligible to receive treatment during Stage 2, provided they meet eligibility criteria.

Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A11-4 Stage 2 Treatment Regimens Available for the Atezo+Magro Arm

Study Treatment	Appendix
Atezo + EV	Appendix 9
Atezo + SG	Appendix 13

Atezo = atezolizumab; EV = enfortumab vedotin; Magro = magrolimab; SG = sacituzumab govitecan.

Refer to Appendix 13 for details specific to the Atezo+SG arm.

A11–4.3 CONCOMITANT THERAPY FOR ATEZO+MAGRO ARM

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 study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A11–4.3.1 Cautionary Therapy for Atezo+Magro Arm

A11–4.3.1.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor-α(TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α 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 (see Appendix 6 for details) or injection-site or systemic reactions associated with magrolimab (see Table A11-5).

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 A11-4.3.2) may be used during the study at the discretion of the investigator.

A11–4.3.2 Prohibited Therapy for Atezo + Magro Arm

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, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2 in the protocol body), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances outlined in Section A11–4.3.3.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin 2) are prohibited within 4 weeks or 5 half-lives of the drug, 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.

A11–4.3.3 Permitted Therapy for Atezo + Magro Arm

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

- Oral contraceptives with a failure rate of < 1% per year (see Section A11–4.4)
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin at a stable dose)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section A11–4.3.2)
- 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

- Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  After 2 cycles of treatment, palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy.
- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator. See Appendix 6 for further information.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections A11–4.3.1 and A11–4.3.2) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-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 5).

A11–4.4 CONTRACEPTION REQUIREMENTS FOR ATEZO+MAGRO ARM

Contraception requirements for women and men in the Atezo+Magro arm are outlined below:

- Women of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use contraception, 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 last dose of study treatment.

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

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

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

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 4 months after the last dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

A11–5 ASSESSMENT OF SAFETY FOR ATEZO+MAGRO ARM

A11–5.1 SAFETY PLAN FOR ATEZO+MAGRO ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and magrolimab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A11–5.1.1, A11–5.1.2, and A11-5.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A11-5.1.4.

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. Because of the potential for overlapping hematologic toxicities and IRRs identified for both atezolizumab and magrolimab, special caution will be taken by performing a planned safety evaluation of the first 6 patients randomized to the Atezo+Magro arm. Randomization to the Atezo+Magro arm will be paused after the enrollment of 6 patients until all of the patients in that arm have completed a safety evaluation of 28 days (one prime dose 7 days prior to Cycle 1 plus one 21-day cycle). If the combination is sufficiently safe, the randomization will be resumed.

Administration of study treatment 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. Adverse events will be reported as described in Sections 5.2–5.6 in the protocol body.

A11–5.1.1 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, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). See Appendix 6 and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A11–5.1.2 Risks Associated with Magrolimab

As of 24 July 2018, a total of 242 patients have been treated with magrolimab both as monotherapy and in combination with the anti-tumor antibodies such as rituximab and cetuximab. Across all study populations, the most common treatment-related effects observed are anemia, fatigue, infusion-related reaction, headache, pyrexia, chills, nausea, and blood bilirubin increased.

Anemia is the most common treatment-related adverse event in clinical studies and is typically manifested as a decline in hemoglobin of about 0.5 g/dL to 1.5 g/dL observed within the first 1–2 weeks of treatment. Significant drops in hemoglobin level (2 g/dL or higher) have also been observed in early doses. Life-threatening cases of anemia have occurred in clinical studies with magrolimab. Participants with significant medical conditions (such as unstable angina, ischemic heart disease, or other significant cardiovascular disease) are at an increased risk for complications of anemia, which could be fatal.

There is a possibility that treatment with magrolimab may interfere with the assessment of RBC phenotyping. Magrolimab binds to CD47 on RBCs and can mask detection of antibodies to minor antigens to the participant's RBCs and ABO/rhesus (Rh) phenotype.

IRRs have occurred in patients treated with magrolimab and most often associated with the initial two treatments of magrolimab. The most common adverse events associated with the IRRs included chills, pyrexia, back pain, nausea, vomiting, hypotension, dyspnea and headache.

Pneumonitis has been infrequently observed in patients receiving magrolimab. Generally, immune-related adverse events have not been observed in clinical use with magrolimab. In contrast to T-cell checkpoint inhibitors, magrolimab primarily exerts its anti-tumor efficacy through macrophage-mediated phagocytosis of tumor cells. Nonspecific T-cell or other host immune responses that are seen with T-cell checkpoint inhibitors have not been observed with magrolimab in nonclinical studies. Additionally, no events of macrophage activation syndrome (MAS) or HLH have been reported in clinical studies.

Thromboembolic events, including deep vein thromboses and pulmonary embolisms, have been reported in some participants receiving magrolimab, sometimes early in therapy. Available data for magrolimab do not support a clear or consistent relationship between clinical thromboembolic events and magrolimab use.

Refer to the Magrolimab Investigator's Brochure for a detailed description of all anticipated risks for magrolimab.

A11–5.1.3 Risks Associated with Combination Use of Atezolizumab and Magro

The adverse events of IRRs and anemia are potential overlapping toxicities associated with combination use of atezolizumab and magrolimab.

A11–5.1.4 Management of Patients Who Experience Adverse Events in Atezo+Magro Arm

A11–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab in this study. The dose of magrolimab may be decreased to 20 mg/kg at the investigator's discretion.
The Medical Monitor is available to advise as needed (see Section A11–4.2.2.2).

In general, magrolimab dose reductions to 20 mg/kg may be considered for magrolimab drug-related toxicities that are Grade 3 or 4; however, the following are generally not reasons for dose reduction:

- Grade 3 anemia

  Grade 3 hemolytic anemia that is medically significant, requiring hospitalization or prolongation of existing hospitalization, disabling or limiting self-care activities of daily life, may result in dose reduction.

- Grade 3 indirect/unconjugated hyperbilirubinemia that resolves to Grade ≤ 2 with supportive care within 1 week and is not associated with other clinically significant consequences
- Grade 3 elevation in ALT, AST, or ALP that resolves to Grade ≤ 2 with supportive care within 1 week and is not associated with other clinically significant consequences

- Transient Grade 3 nausea, vomiting, diarrhea, local reactions, influenza-like symptoms, myalgias, fever, headache, pain during the infusion, or skin toxicity that resolves to Grade ≤2 within ≤72 hours after medical management (e.g., supportive care, including immunosuppressant treatment) has been initiated
- Grade 3 fatigue that resolves to Grade ≤2 within 2 weeks on study
- Grade 3 magrolimab-related infusion reactions in the absence of an optimal pretreatment regimen, which is defined as acetaminophen or a comparable nonsteroidal anti-inflammatory agent, plus an antihistamine and corticosteroids
- Grade 3 tumor lysis syndrome or electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia, etc.) that resolve to Grade ≤2 or baseline within 1 week
- Grade 3 or 4 lymphopenia or leukopenia
- Any Grade 3 autoimmune toxicity that clinically resolves to Grade ≤2 within 7 days of initiating therapy
- Grade 3 diarrhea or skin toxicity that resolves to Grade ≤1 in <7 days after medical management (e.g., immunosuppressant treatment) has been initiated
- Other single laboratory values out of normal range that have no clinical correlate and resolve to Grade ≤2 or to baseline within 7 days with adequate medical management
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites

Patients who are deemed to require further dose reductions below 20 mg/kg of magrolimab should be removed from study treatment with magrolimab.

A11–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table A11-5). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for >12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for >12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator.

The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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.

Magrolimab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table A11-5). If a patient misses three or more consecutive doses during the combination treatment period, the investigator will decide whether the patient should discontinue magrolimab permanently; the Medical Monitor is available to advise as needed. If magrolimab is withheld for >28 days because of toxicity, the patient should be discontinued from magrolimab. However, if the investigator believes the patient is likely to derive clinical benefit, magrolimab can be resumed after being withheld for >28 days. The decision to re-challenge patients with magrolimab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. If the time interval between magrolimab doses is >4 weeks on account of missed doses, a repriming period is required prior to restarting weekly doses. If repriming is necessary, atezolizumab should be held during the repriming week and restarted when the 30 mg/kg weekly dosing of magrolimab begins.

If atezolizumab is discontinued, magrolimab should also be discontinued. If magrolimab is discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section A11-4.2.2 for information on dose interruptions for reasons other than toxicity.

A11–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 6 for atezolizumab-related adverse events and in Table A11-5. Table A11-5 integrates management guidelines for those adverse events where both atezolizumab and magrolimab have developed guidance. Table A11-5 also includes generic guidance for how to manage magrolimab when atezolizumab-associated adverse events occur. Section A11–5.1.4.4 includes management guidelines for magrolimab-associated adverse events. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases. For cases in which management guidelines are not covered in Appendix 6, the Magrolimab Investigator's Brochure, or the protocol, patients should be managed as deemed appropriate by the investigator according to best medical judgment.

Table A11-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Magro Arm

Event	Action to Be Taken
IRRs, CRS, and anaphylaxis	
General guidance	• Guidelines for management of IRRs and CRS for atezolizumab are provided in Appendix 6. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue atezolizumab and magrolimab.
IRR, Grade 1	• Follow guidelines for atezolizumab in Appendix 6. • For anaphylaxis precautions, see Appendix 5.
IRR, Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • For anaphylaxis precautions, see Appendix 5. • For magrolimab: Stop the magrolimab infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV or equivalent and/or 500 to 750 mg oral paracetamol/acetaminophen. Remain at bedside and monitor patient until resolution of symptoms. Corticosteroid therapy may also be administered at the discretion of the investigator. If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate when symptoms resolve. If symptoms recur, then stop infusion and disconnect the patient from the infusion apparatus; no further magrolimab will be administered at that visit. The amount of study drug infused must be recorded on the electronic Case Report Form. Patients who experience an infusion reaction of Grade 2 during the 4-hour post-infusion observation period that does not resolve during that time should be observed for 24 hours or until the adverse event resolves, with vital sign measurements every 4 hours and additional evaluations as medically indicated for the management of the adverse event.

Atezo = atezolizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; Magro = magrolimab.

Table A11-5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+Magro Arm (cont.)

Event	Action to Be Taken
IRRs, CRS, and anaphylaxis	
IRR, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • For anaphylaxis precautions, see Appendix 5. • For magrolimab: Stop infusion and permanently discontinue magrolimab. Begin an IV infusion of normal saline, and treat the patient as follows: administer bronchodilators, epinephrine 0.2 to 1 mg of a 1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV or equivalent, as needed. Administer aggressive symptomatic treatment. All patients will be observed for an additional 24 hours or longer until the adverse event resolves, with vital sign measurements every 4 hours and additional evaluations as medically indicated for the management of the adverse event.
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue magrolimab.
Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Continue magrolimab.
Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Magrolimab may be continued at the discretion of the investigator per medical judgment.

Atezo = atezolizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; Magro = magrolimab.

A11–5.1.4.4 Magrolimab Anemia Management Guidelines

Anemia, Blood Cross-Matching, and Packed RBC Transfusion Procedures

In clinical studies, anemia is the most common treatment-related adverse event and is typically manifested as a decline in hemoglobin of about 0.5 g/dL to 1.5 g/dL observed in the first 1 to 2 weeks of treatment. In patients with no other significant diseases or medical conditions, this decrease in hemoglobin level has been acceptable. However, for patients with significant diseases or medical conditions, such as unstable angina, ischemic heart disease, or uncontrolled diabetes mellitus, treatment-related anemia could be life threatening or fatal. Significant drops in hemoglobin level (2 g/dL or higher) have also been observed in early doses.

Magrolimab binds to RBCs and leads to erythrophagocytosis. This, coupled with anemia from other causes in patients with cancers, means that care has to be taken with RBC cross-matching and packed RBC transfusions. There is a possibility that treatment with

magrolimab may obscure assessment of RBC phenotyping, although this has not been observed in patients to date.

At baseline, prior to initiation of magrolimab therapy, blood cell ABO phenotyping for minor antigens, type and screen (ABO/Rh), and direct antibody testing (DAT) will be performed to facilitate, together with the prior phenotype, allocation of properly cross-matched blood should a blood transfusion be warranted.

For patients after exposure to magrolimab:

- ABO, Rh, and DAT may be pan-reactive due to magrolimab binding to RBCs. Therefore, if a non-urgent transfusion is ordered by the investigator, perform the following procedures:
    1. Front type: EGA treat cells (×2 maximum) and warm wash ×4 (minimum) with 0.9% saline.
    2. Back type: Perform reverse anti-human globulin for both A and B.
    3. If a valid ABO type cannot be obtained, mark the final report as invalid and notify the transfusion service for the site.
- Antibody screen

If a pan-agglutinin/warm autoantibody is present in low-ionic-strength solution, repeat the antibody screen with polyethylene glycol (PeG). Perform PeG adsorption studies and elution studies.

Blood Components for Transfusion

For all elective red cell transfusions, leukocyte-reduced units matched for the phenotype of the patients (as described above) will be used. Where exact matching for all specified blood groups proves impractical (e.g., for MNS), local sites will decide on the best matched donor units to be used. Cytomegalovirus (CMV) matching (i.e., CMV seronegative units for CMV-seronegative patients) will not be required for this study because it will limit the inventory for antigen matching.

If cross-match is incompatible, the RBC units that are Coombs cross-match incompatible will be selected (e.g., phenotype-matched or least incompatible) for issue at the discretion of the local sites' transfusion Service Medial Director or equivalent person, where available.

For emergency transfusions, the transfusion laboratory may consider using emergency Group O Rh−negative units if phenotyped units are not available.

Blood plasma therapy will be blood-type specific. Platelets will be blood-type compatible whenever possible, and if not, will have been tested and found not to have high titer anti-A or anti-B.

A11–5.1.5 Atezo+Magro-Specific Safety Definition

Adverse event severity grading for hemagglutination and microangiopathy:

- Grade 1: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that are asymptomatic or mild, not requiring intervention
- Grade 2: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that require medical intervention
- Grade 3: Evidence of hemagglutination/microangiopathy on peripheral blood smear AND associated clinical sequelae that are medically significant, requiring hospitalization or prolongation of existing hospitalization, disabling, or limited self-care activities of daily living
- Grade 4: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that are life threatening or require urgent intervention
- Grade 5: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that result in death

A11–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO+MAGRO ARM (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 in the protocol body for reporting instructions). Adverse events of special interest for the Atezo+Magro arm 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 in the protocol body)
- 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.

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10\times$ upper limit of normal

- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, and optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade $\geq$2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

A11–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+MAGRO ARM

A11–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab and 4 months after the last dose of magrolimab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study 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 when updated information on the course and outcome of the pregnancy becomes available.

A11–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within

4 months after the last dose of magrolimab. 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. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to magrolimab. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnancy partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A11–5.3.3 Abortions

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

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.

A11–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male 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 in the protocol body).

A11–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+MAGRO ARM

Table A11-6 Schedule of Activities for Atezo+Magro Arm

	Stage 1 Screen [a]	Treatment Period (28-day cycles) [b]										Stage 2 Screen [c] (see Appendix 7) or Treat Discon [d]	Follow-Up Q3M (±7 days)
		Cycle 1				Cycle 2				Cycles > 3			
Day (±days)	Day –28 to –1	Day 1	Day 8 (±1)	Day 15 (± 1)	Day 22 (± 1)	Day 1 (± 3)	Day 8 (±1)	Day 15 (± 1)	Day 22 (± 1)	Day 1 (± 3)	Day 15 (± 1)		
Informed consent	See Appendix 7.											x [e, f]	
Vital signs [g]		x	x	x	x	x	x	x	x	x	x	x	
Molecular profile of urothelial carcinoma (if available)		Whenever updated information becomes available											
Weight [h, i]		x				x				x		x	
Complete physical examination [j]												x	
Limited physical examination [k, i]		x	x	x	x	x	x	x	x	x	x		
ECOG Performance Status [i]		x	x	x	x	x	x	x	x	x	x	x	
ECG [l, i]		Perform as clinically indicated.										x [f]	
Hematology [m]		x [n]	x	x	x	x	x	x	x	x	x	x [o]	
Chemistry [p]		x [n]	x	x	x	x	x	x	x	x	x	x [o]	
Peripheral smear and D-dimer		x				x				x		x	
ABO typing and DAT		x [q]											
Coagulation (PT/INR and aPTT)												x [f, o]	
TSH, free T3 (or total T3), free T4 [r]		x [n, o]										x [o]	
HIV, HBV, and HCV testing												x [f, o]	
C-reactive protein												x [f, o]	
LDH		x				x				x		x [f, o]	

Table A11-6 Schedule of Activities for Atezo+Magro (cont.)

	Stage 1 Screen [a]	Treatment Period (28-day cycles) [b]										Stage 2 Screen [c] (see Appendix 7) or Treat Discon [d]	Follow-Up Q3M (±7 days)
		Cycle 1				Cycle 2				Cycles > 3			
Day (±days)	Day –28 to –1	Day 1	Day 8 (±1)	Day 15 (± 1)	Day 22 (± 1)	Day 1 (± 3)	Day 8 (±1)	Day 15 (± 1)	Day 22 (± 1)	Day 1 (± 3)	Day 15 (± 1)		
Pregnancy test [s]	See Appendix 7.					x				x		x [o]	x [s]
Urinalysis [t]		x				x				x		x [f, o]	
Serum autoantibody sample [u]		Perform if a patient experiences a suspected immune-mediated adverse event											
PK samples		Refer to Table A11-7.											
ADA samples		Refer to Table A11-7.											
Biomarker samples		Refer to Table A11-7.											
Blood sample for RBR (optional) [v]		x											
Tumor biopsy		x [w]											
Tumor biopsy (optional)		x [x]											
Tumor response assessments		x [y, z, aa]											
Concomitant medications [bb]		x	x	x	x	x	x	x	x	x	x	x	
Adverse events [cc]		x	x	x	x	x	x	x	x	x	x	x	x
Atezolizumab administration [dd, ee]		x		x		x		x		x	x		
Magrolimab administration [ee, ff]		x	x	x	x	x	x	x	x	x	x		
Survival follow-up and anti-cancer treatment													x [gg]

Table A11-6 Schedule of Activities for Atezo+Magro (cont.)

ADA = anti-drug antibody; Atezo = atezolizumab; CT = computed tomography; DAT = direct antiglobulin test; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; PK = pharmacokinetic; Q3M = every 3 months; RBR = Research Biosample Repository; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; TB = tuberculosis; TCZ = tocilizumab; Treat = treatment; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Patients who fail their first screening for study eligibility (Stage 1) may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the initiation of study treatment may be used; such tests do not need to be repeated for screening or re-screening.

[b] Treatment must be initiated no later than 7 days after treatment assignment.

[c] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details) or unacceptable toxicity may be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.2 in the protocol body) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 or patients who have discontinued Stage 2 treatment will then undergo follow-up assessments.

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[f] Assessments to be performed only for patients undergoing Stage 2 screening.

[g] Vital signs include respiratory rate, pulse rate, pulse oximetry, and systolic and diastolic blood pressure while the patient is in a seated position, 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. For the first infusion, vital signs should be measured within 60 minutes prior to 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.

[h] The last recorded body weight of a patient should be used for calculating the magrolimab dose. The dose administered should be within 10% of the calculated dose.

[i] Assessment may be performed within 24 hours prior to dosing during the treatment period.

Table A11-6 Schedule of Activities for Atezo+Magro (cont.)

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

[k] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] ECG recordings will be obtained during screening. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[n] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[o] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[p] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide (if considered standard of care in the region), *serum troponin (at baseline, if considered standard of care/required per local clinical practice, and as clinically indicated during the study),* glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. For U.K. patients, amylase and lipase must be included on Day 1 of each treatment cycle.

[q] Testing should be sent for ABO phenotyping for minor antigens and type and screen (ABO/Rh) and direct antiglobulin test prior to infusion at Day 1 of Cycle 1.

[r] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1, and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[s] All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum 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. During follow-up, pregnancy tests will be performed at 3 and 6 months. If a pregnancy test was performed within 96 hours prior to Day 1 of Cycle 1, it does not have to be repeated.

[t] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[u] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody.

[v] 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.

Table A11-6 Schedule of Activities for Atezo+Magro (cont.)

[w] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by investigator (see Section 3.1.1 in the protocol body for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 in the protocol body for tissue sample requirements.

[x] Consenting patients may undergo optional tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[y] Patients will undergo tumor assessments at baseline, every 9 weeks (± 1 week) for the first 54 weeks following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays until loss of clinical benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new, non–protocol-specified anti-cancer therapy.

[z] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[aa] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

[bb] Includes 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 study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[cc] 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.

[dd] Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle. The initial infusion of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Starting with Day 1 of Cycle 2, atezolizumab should be given within ± 3 days of scheduled date (i.e., Day 1 of each 28-day cycle).

[ee] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by investigator (see Section 3.1.1 in the protocol body for details).

Table A11-6 Schedule of Activities for Atezo+Magro (cont.)

[ff] Magrolimab will be administered by IV infusion. During Cycle 1, patients will receive a priming dose of 1 mg/kg on Day 1 followed by doses of 30 mg/kg via IV on Days 8, 15, and 22 of a 28-day cycle. During Cycle 2, weekly doses of 30 mg/kg will be administered on Days 1, 8, 15, and 22. For all subsequent cycles, patients will receive 30 mg/kg on Days 1 and 15. Patients should be premedicated with acetaminophen 500–650 mg and oral or IV diphenhydramine 25–50 mg or comparable regimen for the priming dose (Day 1 of Cycle 1) and the first loading dose administration (Day 8 of Cycle 1). Magrolimab should be administered 1 hour after the completion of the atezolizumab infusion.

[gg] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and clinic visits approximately every 3 months until death (unless patient withdraws consent or Sponsor terminates study). If a patient requests to be withdrawn from follow-up, this request must be documented in source documents and signed by investigator. If the patient withdraws from study, study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table A11-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+Magro Arm: Preliminary and Expansion Phases

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Magrolimab PK (serum) • Magrolimab ADA (serum) • Biomarker (plasma, serum, and PBMC)
	30 (±10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
	1 hour after end of magrolimab infusion	• Magrolimab PK (serum)
Day 8 of Cycle 1	Prior to study treatment	• Magrolimab PK (serum)
	1 hour after end of magrolimab infusion	• Magrolimab PK (serum)
Day 22 of Cycle 1	Prior to study treatment	• Magrolimab PK (serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Magrolimab PK (serum) • Magrolimab ADA (serum) • Biomarker (plasma, serum, and PBMC)
Day 1 of Cycle 4 and Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Magrolimab PK (serum) • Magrolimab ADA (serum) • Biomarker (plasma and serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Magrolimab PK (serum) • Magrolimab ADA (serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Magrolimab PK (serum) • Magrolimab ADA (serum) • Biomarker (plasma and serum)

ADA = anti-drug antibody; Atezo+Magro = atezolizumab plus magrolimab; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

A11–7 REFERENCES

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;54:307–314.

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;56:739–745.

Blazar BR, Lindberg FP, Ingulli E, et al. CD47 (integrin-associated protein) engagement of dendritic cell and macrophage counterreceptors is required to prevent the clearance of donor lymphohematopoietic cells. J Exp Med 2001;194:541–549.

Brown E. Integrin-associated protein (CD47): an unusual activator of G protein signaling. J Clin Invest 2001;107:1499–1500.

Butte MJ, Keir ME, Phamduy TB, et al. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–122.

Chao MP, Alizadeh AA, Tang C, et al. Therapeutic antibody targeting of CD47 eliminates human acute lymphoblastic leukemia. Cancer Res 2011a;71:1374–1384.

Chao MP, Majeti R, Weissman IL. Programmed cell removal: a new obstacle in the road to developing cancer. Nat Rev Cancer 2011b;12:58–67.

Chao MP, Weissman IL, Majeti R. The CD47-SIRPα pathway in cancer immune evasion and potential therapeutic implications. Curr Opin Immunol 2012;24:225–232.

Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–6587.

De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC Study 30986. J Clin Oncol 2012;30:191–199.

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.

Edris B, Weiskopf K, Volkmer AK, et al. Antibody therapy targeting the CD47 protein is effective in a model of aggressive metastatic leiomyosarcoma. Proc Natl Acad Sci USA 2012a;109:6656–6661.

Edris B, Weiskopf K, Weissman IL, et al. Flipping the script on macrophages in leiomyosarcoma. Oncoimmunology 2012b;1:1202–1204.

Fehrenbacher L, Spira A, Ballinger M, et al. 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;387:1837–1846.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–723.

Jaiswal S, Chao MP, Majeti R, et al. Macrophages as mediators of tumor immunosurveillance. Trends Immunol 2010;31:212–219.

Jaiswal S, Jamieson CH, Pang WW, et al. CD47 is upregulated on circulating hematopoietic stem cells and leukemia cells to avoid phagocytosis. Cell 2009;138:271–285.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–422.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.

Kim D, Wang J, Willingham SB, et al. Anti-CD47 antibodies promote phagocytosis and inhibit the growth of human myeloma cells. Leukemia 2012;26:2538–2545.

Majeti R, Chao MP, Alizadeh AA, et al. CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. Cell 2009;138:286–299.

Okazawa H, Motegi S, Ohyama N, et al. Negative regulation of phagocytosis in macrophages by the CD47-SHPS-1 system. J Immunol 2005;174:2004–2011.

Oldenborg PA. Role of CD47 in erythroid cells in autoimmunity. Leuk Lymphoma 2004;45:1319–1327.

Pang WW, Pluvinage JV, Price EA, et al. Hematopoietic stem cell and progenitor cell mechanisms in myelodysplastic syndromes. Proc Natl Acad Sci USA 2013;110:3011–3016.

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;387:1909–1920.

Tecentriq® (atezolizumab) Summary of Product Characteristics, Genentech.

Tecentriq® (atezolizumab) U.S. Package Insert, Genentech.

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;23:4602–4608.

Willingham SB, Volkmer JP, Gentles AJ, et al. The CD47-signal regulatory protein alpha (SIRPα) interaction is a therapeutic target for human solid tumors. Proc Natl Acad Sci USA 2012;109:6662–6667.

Yanagita T, Murata Y, Tanaka D, et al. Anti-SIRPα antibodies as a potential new tool for cancer immunotherapy. JCI Insight 2017;12:e89140.

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;187:1113–1119.

Appendix 12
Study Details Specific to Atezo+Tira Arm

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A12–1 BACKGROUND ON ATEZO+TIRA ARM

A12–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that targets programmed death-ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed death-1 (PD-1) and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. 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 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 cancer patients 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 has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, myocarditis, and nephritis, have been observed (see the Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab (Tecentriq®) 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.

A12–1.2 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/kappa mAb derived in Open Monoclonal Technology (OMT) rats that binds T-cell Immunoreceptor with Immunoglobulin and Immunoreceptor Tyrosine-Based Inhibition Motif [ITIM] domains (TIGIT) and prevents its interaction with the poliovirus receptor (PVR). The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and consists of two heavy chains (456 amino acid residues each) and two light chains (220 amino acid residues each).

The inhibitory immunoreceptor TIGIT has been shown to limit the effector function of tumor-associated lymphocytes. TIGIT is an immunoglobulin (Ig) super family member

expressed on subsets of activated T cells and natural killer (NK) cells, and found highly expressed in tumor tissue and in tumor-infiltrating immune cells in many human cancers, including, but not limited to NSCLC, breast cancer, multiple myeloma (MM), and non-Hodgkin lymphoma (NHL). In multiple tumor types, TIGIT is coordinately expressed with PD-1 (Yu et al. 2009; Johnston et al. 2014; Manieri et al. 2017). Genetic ablation or antibody blockade of TIGIT has been shown to enhance NK cell killing, CD4+ and CD8+ T-cell activation, and effector function in vitro and in vivo in nonclinical models (Yu et al. 2009; Johnston et al. 2014; Stanietsky et al. 2009; Joller et al. 2011). In the nonclinical tumor models, TIGIT interacted with high affinity to CD155 (also known as PVR), which also has an activating counter-receptor CD226. Activation of TIGIT on T cells and NK cells was demonstrated to limit proliferation, effector cytokine production, and killing of target tumor cells (Yu et al. 2009; Stanietsky et al. 2009; Johnston et al. 2014).

Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of the tumor-specific T-cell responses, which may result in improved meaningful anti-tumor activity when tiragolumab is used in combination with other cancer immunotherapies and administered with chemotherapy. The available nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in cancer patients.

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

A12–2 RATIONALE FOR ATEZO+TIRA ARM

A12–2.1 THE PD-L1 PATHWAY

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).

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.

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, urothelial carcinoma, 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).

A12–2.2 THE TIGIT PATHWAY

TIGIT is an immune inhibitory receptor that is a member of the immunoglobulin super family (Yu et al. 2009). TIGIT is expressed on the surface of activated T cell and NK cell subsets and interacts with high affinity with CD155 (also known as PVR) (Yu et al. 2009). Genetic ablation of TIGIT in T cells in mice results in exacerbated T-cell responses in nonclinical models of autoimmune and viral infections, demonstrating the role of TIGIT in inhibiting T-cell responses (Joller et al. 2011; Johnston et al. 2014). TIGIT expression is elevated in the tumor microenvironment in many human tumors, is concordantly expressed with other checkpoint immune-receptors such as PD-1 on the surface of T cells, and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014; Manieri et al. 2017). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014; Wang et al. 2015; Manieri et al. 2017; Farkas et al. 2018).

TIGIT is expressed in a wide variety of human tumors, including most solid tumors, such as NSCLC, urothelial, breast cancer, melanoma, and hematological tumors, such as MM and NHL, and fluorescence activated cell sorting (FACS) analysis of T cells isolated from fresh tumor samples revealed that TIGIT and PD-1 are also co-expressed on tumor infiltrating T cells (Johnston et al. 2014; Yadav et al. 2016; Yang 2016; Guillerey at al. 2018; Le Goux et al. 2017). TIGIT expression ranged from 30%–80% and 50%–80% on tumor-infiltrating CD4+ and CD8+ T cells, respectively (Johnston et al. 2014). Furthermore, overexpression of TIGIT, OX40L, and CD8+ were significantly associated with prognosis for recurrence-free survival and overall survival in muscle invasive bladder cancer (Le Goux et al. 2017).

Therefore, TIGIT is a potential target for therapeutic intervention, aimed at restoring the immune response against the tumor. Agents that inhibit TIGIT's interaction with PVR may inhibit an important source of tumor-associated immune suppression and therefore may enhance the activity of other immune-based therapies. Nonclinical studies using genetically deficient mice and blocking antibodies have revealed a key role for TIGIT in regulating T-cell responses in cancer. Together these data support the hypothesis that

anti-TIGIT may reactivate anti-tumor immunity and provide clinical benefits to patients with cancer.

A12–2.3 COMBINED INHIBITION OF THE PD-L1/PD-1 AND TIGIT PATHWAYS

Durable clinical benefit is limited to a minority of patients treated with single-agent PD-L1/PD-1 inhibitors. Therapies targeting the mechanisms of resistance to anti-PD-L1/PD-1 therapies are needed to improve outcomes in patients with solid cancers. Resistance to PD-L1/PD-1 blockade may result in the expression of multiple co-inhibitory receptors on the surface of effector T cells. Nonclinical tumor models have shown that TIGIT selectively suppressed the effector function of chronically stimulated CD8+ T cells, and that inhibiting both TIGIT and PD-L1/PD-1 resulted in superior efficacy compared with single-agent treatments (Johnston et al. 2014). Hence, respectively targeting both TIGIT and PD-L1 with tiragolumab and atezolizumab in patients, may enhance the efficacy of PD-1/PD-L1 blockade across different cancer types.

A12–2.4 CLINICAL STUDIES OF TIRAGOLUMAB

Tiragolumab is currently under investigation in two ongoing clinical studies in patients with solid tumors (Studies GO30103 and GO40290).

A12–2.4.1 Clinical Study of Tiragolumab as a Single Agent or in Combination with Atezolizumab

Study GO30103 is a first-in-human, open-label, multicenter, global, dose-escalation/dose-expansion Phase I study designed to evaluate the safety, tolerability, and pharmacokinetics of tiragolumab as a single agent (Phase Ia) and in combination with atezolizumab (Phase Ib) in patients with locally advanced, recurrent, or metastatic incurable tumors, including urothelial cancer, renal cell cancer, NSCLC, head and neck squamous cell carcinoma, esophageal cancer, colorectal cancer (CRC), gastric cancer, cholangiocarcinoma, and triple-negative breast cancer.

As of the data cutoff date of 3 December 2018, 42 patients had received tiragolumab monotherapy at doses of 2–1200 mg, and 164 patients had received tiragolumab at doses of 2–600 mg in combination with 1200-mg atezolizumab. The best observed response with tiragolumab monotherapy was prolonged stable disease in 8 of 42 patients, with some patients (including 1 patient with CRC) experiencing a decrease in tumor size. Among 164 patients receiving tiragolumab in combination with atezolizumab, a complete response was observed in 3 patients (including 1 patient with esophageal cancer), a partial response was observed in 22 patients (including patients with esophageal cancer), and stable disease was observed in 38 patients. Among 4 patients with urothelial cancer receiving tiragolumab in combination with atezolizumab, a confirmed partial response was observed in 3 patients.

No maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), or clear dose-related trends in the incidence or severity of adverse events have been determined for tiragolumab as a single agent or in combination with atezolizumab. A fatal case of hepatic toxicity culminating in fulminant liver failure occurred in a patient with metastatic head and neck cancer receiving single-agent tiragolumab at the highest dose cleared for enrollment (1200 mg) (see the Tiragolumab Investigator's Brochure for details). No other fatal cases of fulminant liver failure have been observed.

Overall, tiragolumab as a single agent or in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile is observed to be consistent across different solid tumor indications.

A12–2.4.2 Clinical Study of Tiragolumab in Combination with Atezolizumab in PD-L1–Selected Patients with NSCLC

Study GO40290 is a global, multicenter, randomized, blinded, placebo-controlled Phase II study designed to evaluate the safety and efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated, locally advanced unresectable, or metastatic PD-L1–selected NSCLC.

As of the primary clinical cutoff date of 30 June 2019, a total of 135 patients with a PD-L1 TPS $\geq$1% were included in the intent-to-treat (ITT) population and were randomly assigned to receive tiragolumab plus atezolizumab (n=67) or placebo plus atezolizumab (n=68). Of the enrolled patients, 43.0% of patients had a TPS $\geq$50% relative to 57.0% of patients with a TPS 1%–49%, 59.3% had non-squamous histology compared with 40.7% of patients who had squamous histology, and 10.4% of patients were never-smokers versus 89.6% who had smoked. These three stratification factors were well balanced between treatment groups. Demographics were also generally well balanced between treatment groups, with a median age of 68 years in both the tiragolumab plus atezolizumab and placebo plus atezolizumab arms. There were more females (41.8% vs. 29.4%) and more White patients (62.7% vs. 58.8%) in the tiragolumab plus atezolizumab arm compared with the placebo plus atezolizumab arm.

In the ITT population, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (31.3%) than in the placebo plus atezolizumab arm (16.2%). In the subgroup of patients with TPS $\geq$50%, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (n=29; 55.2% [95% CI: 35.4%, 75.0%]) than the placebo plus atezolizumab arm (n=29; 17.2% [95% CI: 1.8%, 32.7%]). Of note, responders in the tiragolumab plus atezolizumab arm included patients with both squamous and non-squamous histology.

[redacted]

[redacted]

To date, most adverse events have been Grade 1 or Grade 2. Serious adverse events, Grade 3–5 adverse events, adverse events leading to discontinuation, and adverse events leading to death have been balanced between the two treatment arms. Serious and high-grade treatment-related adverse events have also been balanced between the two treatment arms. Immune-mediated adverse events were balanced between the two treatment arms, with the exception of a higher frequency of infusion-related reaction (IRR) and rash reported in the atezolizumab plus tiragolumab arm. Discontinuation due to adverse events was low (approximately 6% in both arms). A fatal case of Epstein-Barr virus (EBV) reactivation and possible secondary hemophagocytic lymphohistiocytosis (HLH) was reported in Study GO40290 in a [redacted] year-old male in [redacted] with metastatic lymphoepithelioma-like carcinoma subtype of NSCLC (PD-L1 positive), which can be associated with EBV infection in [redacted] patients.

Overall, tiragolumab in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile seems to be consistent as reported across different solid tumor indications.

Refer to the Tiragolumab Investigator's Brochure for additional details on all ongoing and planned clinical studies

A12–2.5 BENEFIT-RISK ASSESSMENT

The preliminary safety and efficacy data from the ongoing studies of tiragolumab as a single agent or in combination with atezolizumab across different solid tumor indications support a favorable benefit–risk profile for tiragolumab. This favorable benefit–risk profile, the potential for TIGIT as a target for therapeutic intervention in urothelial cancer, and the significant unmet medical need in this indication are key reasons for the current study.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.5.

A12–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+TIRA ARM

A12–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed

across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities (DLTs) 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 pharmacokinetic (PK), efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A12–3.2 RATIONALE FOR TIRAGOLUMAB DOSE AND SCHEDULE

Tiragolumab will be administered at a fixed dose of 600 mg IV Q3W (600 mg on Day 1 of each 21-day cycle). The fixed dose of 600 mg IV Q3W was selected on the basis of available clinical PK, efficacy, and safety data from the combined Phase Ia/Phase Ib Study GO30103, with single-agent tiragolumab or tiragolumab in combination with atezolizumab. In the Phase Ia portion of the study with tiragolumab as a single agent, the MTD was not reached, and no DLTs were observed in dose escalation. [redacted] Prolonged stable disease was observed in patients in the Phase Ia portion of the study at tiragolumab doses beginning at 400 mg. In the Phase Ib portion of the study with tiragolumab plus atezolizumab, the MTD was not reached. Anti-tumor activity, as measured by radiographic partial responses, was observed across doses for tiragolumab beginning at 30 mg and ranging up to 600 mg in combination with 1200 mg atezolizumab.

Refer to the Tiragolumab Investigator's Brochure for additional details.

A12–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+TIRA ARM

A12–4.1 TREATMENT IN ATEZO+TIRA ARM

A12–4.1.1 Formulation, Packaging, and Handling

A12–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

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

A12–4.1.1.2 Tiragolumab

The tiragolumab drug product will be supplied in single-use, 15-mL glass vials. The vials contain 10 mL of tiragolumab drug product and are buffered in histidine solution

containing polysorbate 20, sucrose, L-methionine, and WFI. The approximate concentration of tiragolumab antibody in the vials is 60 mg/mL.

For information on the formulation and handling of tiragolumab, see the pharmacy manual and the Tiragolumab Investigator's Brochure.

A12–4.1.2 Dosage, Administration, and Compliance

Treatment in the Atezo+Tira arm will be administered as outlined in Table A12-1.

For the mUC Cohort, patients in the Atezo+Tira arm will receive treatment until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Patients in the MIBC Cohorts 1 and 2 will undergo surgery after Cycle 3; treatment in Cycle 4 should be reinitiated 4–6 weeks after surgery, but can be reinitiated up to 12 weeks after surgery if surgical complications arise (see Table A12-1).
For patients in the mUC Cohort, Stage 2 treatment must begin within 3 months after the patient has experienced disease progression per RECIST v1.1 or unacceptable toxicity in Stage 1. However, it is recommended that patients begin Stage 2 treatment as soon as possible. Atezolizumab will be administered prior to administration of tiragolumab. It is recommended that treatment be initiated as soon as possible and no later than 7 days after randomization.

Table A12-1 Treatment Regimen for Atezo+Tira Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Tiragolumab 600 mg IV on Day 1 of each cycle

Atezo+Tira = atezolizumab+tiragolumab.

Note: For MIBC Cohorts 1 and 2, patients will receive treatment for a total of 17 cycles. Treatment in Cycles 1–3 will be administered prior to surgery. Treatment in Cycle 4 should be reinitiated 4–6 weeks after surgery, but can be reinitiated up to 12 weeks after surgery if surgical complications arise.

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

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab or tiragolumab are available.

A12–4.1.2.1 Atezolizumab

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

Administration of atezolizumab 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A12-2.

Table A12-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • After the infusion of atezolizumab, the patient begins a 30-minute observation period. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during the infusion and at 30 (±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, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Guidelines for medical management of IRRs for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A12–5.1.4.2. Atezolizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

A12–4.1.2.2 Tiragolumab

Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle with a post-infusion observation period as described in Table A12-3.

Administration of tiragolumab 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 5. Tiragolumab infusions will be administered per the instructions outlined in Table A12-3.

Table A12-3 Administration of First and Subsequent Tiragolumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the tiragolumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Tiragolumab should be infused over 60 (±10) minutes. • After the infusion of tiragolumab, the patient begins a 60-minute observation period. • Record vital signs every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. • Patients will be informed about the possibility of delayed post-infusion symptoms and will be 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, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Tiragolumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±10) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient tolerated the previous infusion of tiragolumab well without infusion-associated adverse events, the observation period may be reduced to 30 minutes. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 15 (±10) minutes after the infusion.

Guidelines for medical management of IRRs for tiragolumab are provided in Appendix 6.

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A12–5.1.4.2. Tiragolumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with tiragolumab should be based on the

investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

A12–4.1.2.3 Stage 2 Treatment

Patients in the mUC Cohort who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1 in the protocol body) will be given the option of receiving a different treatment combination during Stage 2, as outlined in Table A12-4, provided they meet eligibility criteria (see Section 4.1 in the protocol body). Patients who experience unacceptable toxicity related to tocilizumab may also be eligible to receive treatment during Stage 2, provided they meet eligibility criteria.

Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A12-4 Stage 2 Treatment Regimens Available for the Atezo+Tira Arm

Study Treatment	Appendix
Atezo+EV	Appendix 9
Atezo+SG	Appendix 13

Atezo = atezolizumab; EV = enfortumab vedotin; SG = sacituzumab govitecan; Tira = tiragolumab.

Refer to Appendix 13 for details specific to the Atezo+SG arm.

A12–4.2 CONCOMITANT THERAPY FOR ATEZO+TIRA ARM

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 study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A12–4.2.1 Permitted Therapy for Atezo+Tira Arm

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

- Oral contraceptives with a failure rate of < 1% per year (see Section A12–4.3)
- 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 A12–4.2.3)
- 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
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab and tiragolumab may be continued during palliative radiotherapy.
- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

Premedication with antihistamines, antipyretics, 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 therapies other than those defined as cautionary or prohibited therapies (see Sections A12–4.2.2 and A12–4.2.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-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 5).

A12–4.2.2 Cautionary Therapy for Atezo+Tira Arm

A12–4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab and tiragolumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α 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 and tiragolumab therapy (refer to Appendix 6 for details).

A12–4.2.2.2 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 A12–4.2.3) may be used during the study at the discretion of the investigator.

A12–4.2.3 Prohibited Therapy for Atezo+Tira Arm

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 [mUC Cohort] and Section 4.1.4 [MIBC Cohorts] in the protocol body), and during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined above in Section A12-4.2.1.
- Investigational therapy (other than protocol-mandated study treatment) 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 treatment with atezolizumab and/or tiragolumab, and for 5 months after the final dose of atezolizumab and for 90 days after the final dose of tiragolumab.

- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug (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 and/or tiragolumab.

A12–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO+TIRA ARM

Contraception requirements for men and women in the Atezo + Tira arm are outlined below:

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, 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 and for 90 days after the final dose of tiragolumab.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and 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 acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 90 days after the final dose of tiragolumab. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

A12–5 ASSESSMENT OF SAFETY FOR ATEZO+TIRA ARM

A12–5.1 SAFETY PLAN FOR ATEZO+TIRA ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and tiragolumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A12–5.1.1, A12–5.1.2, and A12–5.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A12–5.1.4.

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 and tiragolumab 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. Adverse events will be reported as described in Sections 5.2–5.6. An Internal Monitoring Committee and Scientific Oversight Committee will review safety data throughout the study as described in Section 3.1.6 in the protocol body.

A12–5.1.1 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, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to HLH. Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A12–5.1.2 Risks Associated with Tiragolumab

IRRs and immune-mediated hepatitis are identified risks of tiragolumab. Lymphopenia is an identified risk of tiragolumab when used in combination with atezolizumab and chemotherapies.

Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell

proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events). Refer to Appendix 6 of the protocol and Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of anticipated safety risks for tiragolumab.

A12–5.1.2.1 Infusion-Related Reactions

Because tiragolumab is a therapeutic monoclonal antibody and targets immune cells, IRRs associated with hypersensitivity reactions and/or target-mediated cytokine release may occur. Clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

IRRs have been reported in patients treated with tiragolumab, with or without atezolizumab. The majority of events were mild to moderate and manageable.

To minimize the risk and sequelae of IRRs, the initial dose of tiragolumab will be administered over 60 minutes followed by a 60-minute observation period. Subsequent infusions and observation times may be shortened if the preceding infusion is well tolerated. All infusions of tiragolumab will be administered in an appropriate medical setting.

Refer to Section A12–4.1.2.2 for detailed guidance on administration of tiragolumab in this study. Refer to Appendix 5 for guidance on anaphylaxis precautions and Appendix 6 for guidance on management of IRRs.

A12–5.1.2.2 Immune-Mediated Hepatitis

The use of tiragolumab to block the immune inhibitory receptor TIGIT serves to increase a baseline T-cell and NK-cell immune response, especially in combination with other checkpoint inhibitors (CPIs) (i.e., atezolizumab). A disruption in the functioning of immune checkpoint molecules may lead to imbalances in immunologic tolerance that results in an unchecked immune response, including immune-mediated hepatitis.

Refer to Appendix 6 for guidance on the management of immune-mediated hepatitis.

A12–5.1.2.3 Lymphopenia

The IgG1 backbone of tiragolumab with the intact Fc-effector function may lead to antibody-dependent cell-mediated cytotoxicity-mediated reduction in lymphocyte count. Lymphopenia is an identified risk with tiragolumab in combination with atezolizumab and chemotherapies. Transient decreases in lymphocyte count without clinical sequelae have been observed in patients treated with tiragolumab, with or without atezolizumab.

Patients with a lymphocyte count $<$500 cells/mL will be excluded from this study (see Sections 4.1.1.2 and 4.1.3), and CBCs will be monitored regularly during the study (see Section A12–6).

A12–5.1.2.4 Immune-Mediated Adverse Events

Nonclinical models have suggested a role of TIGIT signaling interruption in autoimmunity. In a knockout model (TIGIT–/–), loss of TIGIT signaling resulted in hyperproliferative T-cell responses and exacerbation of experimental autoimmune encephalitis (EAE). TIGIT–/– and wild-type B6 mice were immunized with myelin oligodendrocyte glycoprotein peptide in an EAE using suboptimal doses. In contrast to the wild-type B6 mice, the majority of the TIGIT–/– mice developed severe EAE (Joller et al. 2011).

Clinical experience with therapeutic agents intended to enhance anti-tumor T-cell responses has demonstrated that development of autoimmune inflammatory conditions is a general risk and may therefore be considered a potential risk of tiragolumab. Such immune-mediated adverse events have been described for virtually all organ systems and include, but are not limited to, colitis, pneumonitis, endocrinopathies, ocular toxicity, pancreatic toxicity, neurologic toxicity, cardiac toxicity, nephritis, myositis, and severe cutaneous adverse reactions.

Patients with a history of autoimmune disease will be excluded from this study (see Sections *4.1.2.2* and 4.1.4.1).

Management guidelines for individual suspected immune-mediated adverse events are provided in Appendix 6.

A12–5.1.2.5 Embryofetal Toxicity

Embryofetal toxicity is a potential risk with tiragolumab. Administration of tiragolumab is expected to have adverse effects on pregnancy based on the expression of TIGIT on decidual NK and $CD8^+$ T cells (Powell et al. 2017; van der Zwan et al. 2018; Vento-Tormo et al. 2018), and the expected role of these cells in the recognition and response to foreign fetal, placental, and viral antigens at the maternal-fetal interface as well as maintenance of maternal-fetal tolerance. No reproductive or teratogenicity studies in animals have been conducted with tiragolumab. There are no clinical studies of tiragolumab in pregnant women. Tiragolumab should not be administered to pregnant women.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of embryofetal toxicity.

A12–5.1.3 Risks Associated with Combination Use of Atezolizumab and Tiragolumab

Based on results from clinical data with tiragolumab and atezolizumab, there are known and potential overlapping toxicities in patients treated with tiragolumab plus atezolizumab. Because the expected pharmacologic activity of these two molecules is

to increase adaptive T-cell immune responses, there is the possibility of heightened immune responses.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a list of identified risks associated with tiragolumab in combination with atezolizumab. Based on the mechanism of action of tiragolumab and atezolizumab, additional immune-mediated adverse events are potential overlapping toxicities associated with combination use of tiragolumab plus atezolizumab.

Based on clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with tiragolumab and atezolizumab will be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with immune CPIs to date has been incorporated into the design and safety management plan (see Section A12–5.1) in order to reduce the potential risks to participating patients. Patients with a history of autoimmune disease will be excluded from this study (see Sections 4.1.2 and 4.1.4). Patients previously treated with approved or experimental CIT will also be excluded from participation in this study. Owing to the risks of active viral infection and viral reactivation (see Section A12–2.4), patients with active infection (including, but not limited to, HIV, hepatitis B virus, hepatitis C virus, EBV, known and/or suspected chronic active EBV infection, or tuberculosis) and/or patients with recent severe infections will be excluded from this study (see Sections 4.1.2 and 4.1.4).

A12–5.1.4 Management of Patients Who Experience Specific Adverse Events in the Atezo+Tira Arm

A12–5.1.4.1 Dose Modifications

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

A12–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab and tiragolumab may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before study treatment can be resumed. If study treatment is withheld for > 12 weeks, the patient will be discontinued from study treatment. However, study treatment may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Study treatment can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. Atezolizumab and tiragolumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

On the basis of the available characterization of mechanism of action, tiragolumab may cause adverse events similar to, but independent of, atezolizumab. Tiragolumab may also exacerbate the frequency or severity of atezolizumab-related adverse events or may have non-overlapping toxicities with atezolizumab. Because these scenarios may not be distinguishable from each other in the clinical setting, immune-mediated adverse events should generally be attributed to both agents, and dose interruptions or treatment discontinuation in response to immune-mediated adverse events should be applied to both tiragolumab and atezolizumab. If atezolizumab is discontinued, tiragolumab should also be discontinued. If tiragolumab is discontinued, atezolizumab should also be discontinued.

Refer to Section A12–4.1.2 for information on dose interruptions for reasons other than toxicity.

A12–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Table A12-5 and Appendix 6. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

For cases in which management guidelines are not covered in Appendix 6, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table A12-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tira Arm

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reactions	• Guidelines for management of IRRs and CRS for atezolizumab are provided in Appendix 6. Follow these same guidelines for tiragolumab. [a] • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue the causative agent.
Pulmonary, hepatic, GI, endocrine, ocular, immune-mediated myocarditis, pancreatic, dermatologic, neurologic, immune-mediated meningoencephalitis, renal, and systemic immune activation	• Guidelines for management of these events are provided in Appendix 6 for atezolizumab. Follow these same guidelines for tiragolumab. [a]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue tiragolumab.

GI = gastrointestinal; CRS = cytokine release syndrome; IRR = infusion-related reaction.

[a] Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab, as outlined in Appendix 6, are also applicable to tiragolumab.

A12–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR THE ATEZO+TIRA ARM (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 the Atezo+Tira arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.4.2)
- 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.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10\times$ upper limit of normal
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, HLH, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, and optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, or toxic epidermal necrolysis)

- Myelitis
- Facial paresis

A12–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN THE ATEZO+TIRA ARM

A12–5.3.1 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 atezolizumab and 5 months after the final dose of tiragolumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail 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 when updated information on the course and outcome of the pregnancy becomes available.

A12–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 90 days after the last dose of tiragolumab. 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 e-mailing the form using the fax number or e-mail address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the course pregnancy partner and the outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A12–5.3.3 Abortions

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

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

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

A12–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male 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).

A12–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+TIRA ARM

Table A12-6 Schedule of Activities for Atezo+Tira Arm (mUC Cohort)

Assessment/Procedure	Stage 1 Screening [a] Days –28 to –1	Treatment Cycles (21-Day Cycles) Cycle ≥ 1 [b] Day 1 (±3 D)	Stage 2 Screen [c] (see Appendix 7) or Treat Discon [d]	Follow-Up Q3M (± 7 D)
Informed consent	See Appendix 7.		x [e, f]	
Molecular profile of urothelial carcinoma (if available)		Whenever updated information becomes available		
Vital signs [g]		x	x	
Weight [h]		x	x	
Complete physical examination [i]			x	
Limited physical examination [j, h]		x		
ECOG Performance Status [h]		x	x	
ECG [k, h]		Perform as clinically indicated.	x [f]	
Hematology [l]		x [m]	x [n]	
Chemistry [o]		x [m]	x [n]	
Coagulation (PT/INR and aPTT)			x [f, n]	
TSH, free T3 (or total T3), and free T4 [p]		x [m, n]	x [n]	
HIV, HBV, and HCV testing			x [f, n]	
C-reactive protein		x	x [f, n]	
LDH			x [f, n]	
Pregnancy test [q]		x	x [n]	x [q]
Urinalysis [r]		x	x [f, n]	
Serum autoantibody sample [s]		Perform if a patient experiences a suspected immune-related adverse event.		
PK samples		Refer to Table A12-7.		
ADA samples		Refer to Table A12-7.		

Table A12-6 Schedule of Activities for Atezo+Tira Arm (mUC Cohort) (cont.)

Assessment/Procedure	Stage 1 Screening [a] Days –28 to –1	Treatment Cycles (21-Day Cycles) Cycle ≥ 1 [b] Day 1 (±3 D)	Stage 2 Screen [c] (see Appendix 7) or Treat Discon [d]	Follow-Up Q3M (± 7 D)
Biomarker samples	See Appendix 7.	Refer to Table A12-7.		
Blood sample for RBR (optional) [t]		x		
Tumor biopsy		x [u]		
Tumor biopsy (optional)		x [v]		
Tumor response assessments		x [w, x, y]		
Concomitant medications [z]		x	x	
Adverse events [aa]		x	x	x [aa]
Atezolizumab administration [bb, cc]		x		
Tiragolumab administration [cc, dd]		x		
Survival follow-up and anti-cancer treatment				x [ee]

ADA = anti-drug antibody; CT = computed tomography; D = day; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q3M = every 3 months; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; TB = tuberculosis; Treat = treatment; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Patients who fail their first screening for study eligibility (Stage 1) may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the initiation of study treatment may be used; such tests do not need to be repeated for screening or re-screening.

[b] Treatment must be initiated no later than 7 days after treatment assignment.

[c] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 in protocol body for details) or unacceptable toxicity may be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.2 in protocol body) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

Table A12-6 Schedule of Activities for Atezo+Tira Arm (mUC Cohort) (cont.)

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 or patients who have discontinued Stage 2 treatment will then undergo follow-up assessments.

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[f] Assessments to be performed only for patients undergoing Stage 2 screening.

[g] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, 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. 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 the infusion and at 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 the infusion and at 30 (±10) minutes after the infusion.

[h] Assessment may be performed within 24 hours prior to dosing during the treatment period.

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

[j] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] ECG recordings will be obtained during screening. It is recommended that patients 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, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[m] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

[n] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[o] Chemistry panel (serum or plasma) includes 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, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. For U.K. patients, amylase and lipase must be included on Day 1 of each treatment cycle.

Table A12-6 Schedule of Activities for Atezo+Tira Arm (mUC Cohort) (cont.)

[p] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[q] All women of childbearing potential will have a serum pregnancy test at screening. Urine or serum 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. During follow-up, pregnancy tests will be performed at 3 and 6 months. If a pregnancy test was performed within 96 hours prior to Day 1 of Cycle 1, it does not have to be repeated.

[r] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[s] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[t] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[u] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 in protocol body for tissue sample requirements.

[v] Consenting patients may undergo optional tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[w] Patients will undergo tumor assessments at baseline, every 9 weeks (±1 week) for the first 54 weeks following treatment initiation, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays until loss of clinical benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new, non–protocol-specified anti-cancer therapy.

[x] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[y] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

[z] Includes 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 study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[aa] 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.

Table A12-6 Schedule of Activities for Atezo+Tira Arm (mUC Cohort) (cont.)

[bb] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[cc] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 in protocol body for details).

[dd] Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle. The initial dose of tiragolumab will be delivered over 60 (± 10) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 10) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[ee] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a 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. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table A12-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Tira Arm (mUC Cohort)

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarker (plasma, serum, PBMC) [a]
	30 (± 10) minutes after the end of atezolizumab infusion	• Atezolizumab PK (serum)
	30 (± 10) minutes after the end of tiragolumab infusion	• Tiragolumab PK (serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarker (plasma, serum, PBMC) [a]
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum)
Day 1 of Cycles 4 and 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarker (plasma, serum) [a]

ADA = anti-drug antibody; Atezo = atezolizumab; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; Tira = tiragolumab.

Note: On the basis of emerging safety 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. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Biomarker collections are applicable only after approval from local regulatory authorities.

Table A12-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Tira Arm (mUC Cohort) (cont.)

Visit	Time	Sample Type
Day 1 of Cycle 12	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum)
Day 1 of Cycle 16 and every fourth cycle thereafter	Prior to study treatment	• Atezolizumab PK (serum) [a] • Atezolizumab ADA (serum) [a] • Tiragolumab PK (serum) • Tiragolumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarker (plasma, serum) [b]

ADA = anti-drug antibody; Atezo = atezolizumab; PK = pharmacokinetic; Tira = tiragolumab.

Note: On the basis of emerging safety 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. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Atezolizumab PK and ADA samples are not required after Cycle 16 and before the treatment discontinuation visit.

[b] Biomarker collections are applicable only after approval from local regulatory authorities.

Table A12-8 Schedule of Activities for Atezo+Tira Arm (MIBC Cohorts)

Assessment/Procedure	Screening [a] Days –28 to –1	Treatment Cycles (21-Day Cycles)/Surgery: Cycle 1 [b] Day 1	Cycles 2–3 Day 1 (±3 D)	Surgery [c]	Cycles 4–17 [d] Day 1 (±3 D)	Treat Discon [e]	Follow-Up Q3M (± 7 D) [f]
Molecular profile of urothelial carcinoma (if available)	See Appendix 7.	Whenever updated information becomes available					
Vital signs [g]		x	x		x	x	
Weight [h]		x	x		x	x	
Complete physical examination [i]						x	
Limited physical examination [j, h]		x	x		x		
ECOG Performance Status [h]		x	x		x	x	
ECG [k, h]		Perform as clinically indicated.					
Hematology [l]		x [m]	x [m]		x [m]	x	
Chemistry [n]		x [m]	x [m]		x [m]	x	
TSH, free T3 (or total T3), and free T4 [o]		x [m]				x	
C-reactive protein		x	x		x	x	
Pregnancy test [p]		x	x		x	x	x [p]
Urinalysis [q]		x	x		x		
Serum autoantibody sample [r]		Perform if a patient experiences a suspected immune-related adverse event.					
PK samples		Refer to Table A12-9.					
ADA samples		Refer to Table A12-9.					
Biomarker samples		Refer to Table A12-9.					

Table A12-8 Schedule of Activities for Atezo + Tira Arm (MIBC Cohorts) (cont.)

Assessment/Procedure	Screening [a]	Treatment Cycles (21-Day Cycles)/Surgery				Treat Discon [e]	Follow-Up Q3M (± 7 D) [f]
		Cycle 1 [b]	Cycles 2–3	Surgery [c]	Cycles 4–17 [d]		
	Days –28 to –1	Day 1	Day 1 (±3 D)		Day 1 (±3 D)		
Blood sample for RBR (optional) [s]	See Appendix 7.	x					
Stool sample (optional) [t]		x [t]					
Tumor biopsy		x [u]			x [u]		
Tumor response assessments					x [v, w]		
Concomitant medications [x]		x	x		x	x	
Adverse events [y]		x	x		x	x	x
Atezolizumab administration [z, aa]		x	x		x		
Tiragolumab administration [aa, bb]		x	x		x		
Cystectomy				x [cc]			
Lymph node dissection				x [cc]			
Survival follow-up and anti-cancer treatment							x [dd]

ADA = anti-drug antibody; CT = computed tomography; D = day; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MIBC = muscle invasive bladder cancer; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q3M = every 3 months; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; Treat = treatment; TSH = thyroid-stimulating hormone.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

This table is not applicable to France.

Table A12-8 Schedule of Activities for Atezo + Tira Arm (MIBC Cohorts) (cont.)

[a] Patients who fail their first screening for study eligibility may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the initiation of study treatment may be used; such tests do not need to be repeated for screening or re-screening.

[b] Treatment must be initiated no later than 7 days after treatment assignment.

[c] A minimum of 7 days between time of last infusion and surgery is required.

[d] Treatment in Cycle 4 should be reinitiated 4–6 weeks after surgery, but can be reinitiated up to 12 weeks after surgery if surgical complications arise.

[e] Patients will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients.

[f] Patients should return for follow-up visits every 3 months until 24 months after the treatment discontinuation visit. Patients may then continue with standard-of-care treatment with their doctor

[g] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, 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. 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 the infusion and at 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 the infusion and at 30 (±10) minutes after the infusion.

[h] Assessment may be performed within 24 hours prior to dosing during the treatment period.

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

[j] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] It is recommended that patients 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, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[m] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

Table A12-8 Schedule of Activities for Atezo + Tira Arm (MIBC Cohorts) (cont.)

[n] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. For U.K. patients, amylase and lipase must be included on Day 1 of each treatment cycle.

[o] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[p] All women of childbearing potential will have a serum pregnancy test at screening. Urine or serum 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. During follow-up, pregnancy tests will be performed at 3 and 6 months. If a pregnancy test was performed within 96 hours prior to Day 1 of Cycle 1, it does not have to be repeated.

[q] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[r] Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[s] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[t] Stool samples will be collected before surgery for cystectomy and lymph node dissection, preferably after Day 1 of Cycle 3. Patients who consent to providing optional stool samples will receive the collection device on or before Day 1 of Cycle 3.

[u] During the study (i.e., up to 24 months after the treatment discontinuation visit), patients will undergo tumor biopsy sample collection at the time of disease recurrence as determined by the investigator (see Section 4.5.7 in the protocol body for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or disease recurrence, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 in protocol body for tissue sample requirements.

[v] Patients will undergo tumor assessments at baseline, within 4 weeks prior to resuming systemic therapy following surgery, and then every 12 weeks (±2 weeks) while on treatment and until 24 months (104 weeks) after the treatment discontinuation visit, regardless of dose delays, or until disease recurrence, whichever occurs first (see Section 3.1.3 in the protocol body for details). Tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease recurrence.

[w] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[x] Includes 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 study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[y] 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.

Table A12-8 Schedule of Activities for Atezo + Tira Arm (MIBC Cohorts) (cont.)

[z] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[aa] Treatment will continue until unacceptable toxicity or disease recurrence (as defined in Section 4.5.7) or until completion of 14 cycles post-surgery, whichever comes first.

[bb] Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle. The initial dose of tiragolumab will be delivered over 60 (± 10) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 10) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[cc] A specimen from surgical resection (i.e., radical cystectomy) along with an associated pathology report and tissue from lymph node dissection must be submitted. See Section 4.5.8 in protocol body for tissue sample requirements.

[dd] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months for 24 months after the treatment discontinuation visit (unless the patient withdraws consent or the Sponsor terminates the study). If a 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. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table A12-9 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+Tira Arm (MIBC Cohorts)

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarker (blood, PBMC, plasma, serum, and urine) [a]
	30 (± 10) minutes after the end of atezolizumab infusion	• Atezolizumab PK (serum)
	30 (± 10) minutes after the end of tiragolumab infusion	• Tiragolumab PK (serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarker (PBMC, plasma and serum) [a]
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarker (blood and urine)
Surgery for cystectomy	Prior to surgery	• Biomarker (blood, PBMC, and urine) [a]
Day 1 of Cycles 4 and 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarker (plasma, serum in Cycles 4 and 8) [a] • Biomarker (blood and urine, Cycle 4) [a]

ADA = anti-drug antibody; Atezo = atezolizumab; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; Tira = tiragolumab.

Notes: On the basis of emerging safety 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. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

This table is not applicable to France.

[a] Biomarker collections are applicable only after approval from local regulatory authorities.

Table A12-9 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Tira Arm (MIBC Cohorts) (cont.)

Visit	Time	Sample Type
Day 1 of Cycle 6 (~3 months post-cystectomy)	At visit	• Biomarker (blood and urine) [a]
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarker (plasma, serum) [a]

ADA = anti-drug antibody; Atezo = atezolizumab; PK = pharmacokinetic; Tira = tiragolumab.

Notes: On the basis of emerging safety 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. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

This table is not applicable to France.

[a] Biomarker collections are applicable only after approval from local regulatory authorities.

A12–7 REFERENCES

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.

Butte MJ, Keir ME, Phamduy TB, et al. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Chen L, Deng H, Lu M, et al. B7-H1 expression associates with tumor invasion and predicts patient's survival in human esophageal cancer. Int J Clin Exp Pathol 2014;7:6015–23.

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.

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.

Dhupar R, Van Der Kraak L, Pennathur A, et al. Targeting immune checkpoints in esophageal cancer: a high mutational load tumor. Ann Thorac Surg 2017;103:1340–49.

Farkas AM, Audenet F, Anastos H, et al. Tim-3 and TIGIT mark Natural Killer cells susceptible to effector dysfunction in human bladder cancer. J Immunol 2018;200(Suppl 1):124–14.

Fehrenbacher L, Spira A, Ballinger M, et al. 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.

Guillerey C, Harjunpää H, Carrié N, et al. TIGIT immune checkpoint blockade restores CD8+ T cell immunity against multiple myeloma. Blood 2018;132:1689–94.

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.

Johnston RJ, Comps-Agrar L, Hackney J, et al. The immunoreceptor TIGIT regulates antitumor and antiviral CD8(+) T cell effector function. Cancer Cell 2014;26:923–37.

Joller N, Hafler JP, Brynedal B, et al. Cutting edge: TIGIT has T cell-intrinsic inhibitory functions. J Immunol 2011;186:1338–42.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.

Le Goux C, Vacher S, Pignot G, et al. mRNA expression levels of genes involved in antitumor immunity: identification of a 3-gene signature associated with prognosis of muscle-invasive bladder cancer. Oncoimmunology 2017;6:e1358330.

Manieri NA, Chiang EY, and Grogan JL. TIGIT: a key inhibitor of the cancer immunity cycle. Trends Immunol 2017;38:20–8.

Ohigashi Y, Sho M, Yamada Y, et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. Clin Cancer Res 2005;11:2947–53.

Powell RM, Lissauer D, Tamblyn J, et al. Decidual T cells exhibit a highly differentiated phenotype and demonstrate potential fetal specificity and a strong transcriptional response to IFN. J Immunol 2017;199:3406–17.

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.

Stanietsky N, Simic H, Arapovic J, et al. The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity. Proc Natl Acad Sci USA 2009;106:17858–63.

Tecentriq® (atezolizumab) U.S. Package Insert, Genentech.

van der Zwan A, Bi K, Norwitz ER, et al. Mixed signature of activation and dysfunction allows human decidual $CD8^+$ T cells to provide both tolerance and immunity. Proc Natl Acad Sci USA 2018;115:385–90.

Vento-Tormo R, Efremova M, Botting RA, et al. Single-cell reconstruction of the early maternal-fetal interface in humans. Nature 2018;563:347–53.

Wang F, Hou H, Wu S, et al. TIGIT expression levels on human NK cells correlate with functional heterogeneity among healthy individuals. Eur J Immunol 2015;45:2886–97.

Yadav M, Green C, Ma C, et al. Tigit, CD226 and PD-L1/PD-1 are highly expressed by marrow-infiltrating T cells in patients with multiple myeloma. Blood 2016;128:2102.

Yang Z. Expression and function of tigit in B-cell non-hodgkin lymphoma. Blood 2016;128:4138.

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.

Yu X, Harden K, Gonzalez LC, et al. The surface protein TIGIT suppresses T cell activation by promoting the generation of mature immunoregulatory dendritic cells. Nat Immunol 2009;10:48–57.

Zhao JJ, Zhou ZQ, Wang P, et al. Orchestration of immune checkpoints in tumor immune contexture and their prognostic significance in esophageal squamous cell carcinoma. Cancer Manag Res 2018;10:6457–68.

Appendix 13
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A13–1 BACKGROUND ON ATEZO+SG ARM

A13–1.1 BACKGROUND ON ATEZOLIZUMAB

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

A13–1.2 BACKGROUND ON TROP-2 AND SACITUZUMAB GOVITECAN

Trophoblast cell-surface antigen 2 (Trop-2) is a transmembrane calcium signal transducer glycoprotein of the TACSTD gene family that is expressed in many tumors. Trop-2 is a cell-surface marker of trophoblast cells that is expressed in many solid tumors at higher levels compared with normal tissue. Trop-2 binds several cellular proteins, including IGF-1, claudin-1, claudin-7, cyclin D1, and protein kinase C, and has been implicated in the regulation of tumor growth, invasion, and spread. Through activation of the ERK1/2-MAPK pathway, Trop-2 also contributes to cell cycle progression and could play a role in stem-cell biology through deregulation of stem-cell functions via the Notch, Hedgehog, and Wnt pathways. Overexpression of Trop-2 has been reported in most human epithelial cancers, including urothelial, oral, head and neck, thyroid, lung, esophageal, gastric, colorectal, pancreatic, breast, renal, uterine, cervical, ovarian, and glioma (Goldenberg et al. 2018).

Sacituzumab govitecan is a Trop-2–directed antibody–drug conjugate (ADC) consisting of three components:

1. A humanized IgG1κ monoclonal antibody hRS7, which binds to Trop-2
2. SN-38, a topoisomerase I inhibitor and active metabolite of irinotecan
3. A proprietary hydrolyzable linker (CL2A) that couples hRS7 to SN-38

Pharmacology data suggest that sacituzumab govitecan binds to Trop-2–expressing cancer cells and undergoes internalization with the subsequent release of SN-38 via hydrolysis of the linker. Upon release, SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I–induced single-stranded DNA breaks, resulting in DNA damage that leads to apoptosis. The hydrolyzable linker of sacituzumab govitecan may also permit release of SN-38 in the acidic microenvironment of the tumor; this bystander effect allows for the killing of low- or even non-Trop-2 expressing tumor cells.

Sacituzumab govitecan is approved for the treatment of urothelial carcinoma and breast cancer.

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

A13–2 RATIONALE FOR ATEZO+SG ARM

A13–2.1 THE PD-L1 PATHWAY

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).

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.

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, urothelial carcinoma, 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).

Sacituzumab govitecan has shown anti-tumor activity in nonclinical and clinical studies and is currently being evaluated in patients with metastatic solid cancers (Bardia et al. 2019; Tagawa et al. 2019b; Petrylak et al. 2020). Sacituzumab govitecan is currently being evaluated in patients who have progressed after both platinum chemotherapy and checkpoint immunotherapy, and who have progressed after checkpoint immunotherapy, but were ineligible for platinum therapy, with comparable response rates. In patients who had previously received both chemotherapy and checkpoint immunotherapy (n = 45), investigators observed a response rate of 31% a median progression-free survival (PFS) of 7.3 months and a median overall survival (OS0 of 16.3 months. Within the platinum-ineligible, but checkpoint immunotherapy experienced cohort (n = 18), investigators observed a response rate of 28%, with a reduction in tumor size observed in 61% of patients; the median PFS and OS were not reported.

A13–2.2 BENEFIT-RISK ASSESSMENT

Sacituzumab govitecan is currently being evaluated in patients with metastatic urothelial carcinoma (mUC), who have progressed after both platinum chemotherapy and checkpoint inhibitor (CPI), and who have progressed after CPI, but were ineligible for platinum therapy in separate cohorts of a Phase II study (TROPHY-U-01) (Tagawa et al. 2019a; Petrylak et al. 2020). Response rates were comparable between each cohort; in patients who had previously received both chemotherapy and CPI (n = 45), investigators observed a response rate of 31%, a median PFS of 7.3 months, and a median OS of 16.3 months. Within the platinum-ineligible, but CPI experienced cohort (n = 18), investigators observed a response rate of 28%, with a reduction in tumor size observed in 61% of patients; the median PFS and OS were not reported.

Combining sacituzumab govitecan, an ADC that can cause tumor-cell death with possible neoantigen release, with atezolizumab, an immune-stimulating agent, could have promising therapeutic potential in urothelial carcinoma (UC). Because of the potential for overlapping toxicities, a minimum of 6 patients in the atezolizumab plus sacituzumab govitecan (Atezo+SG) arm must complete a safety evaluation before additional patients can be enrolled in that arm (see Section 3.1.4 for details).

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.5.

A13–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+SG ARM

A13–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab.

A13–3.2 RATIONALE FOR SACITUZUMAB GOVITECAN DOSE AND SCHEDULE

Sacituzumab govitecan will be administered at a dose of 10 mg/kg on Days 1 and 8 of each 21-day cycle, which is an approved dosage of sacituzumab govitecan. Additional safety and efficacy information can be found in the Sacituzumab Govitecan Investigator's Brochure.

A13–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+SG ARM

A13–4.1 TREATMENT IN ATEZO+SG ARM

A13–4.1.1 Formulation, Packaging, and Handling

A13–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

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

A13–4.1.1.2 Sacituzumab Govitecan

Sacituzumab govitecan will be supplied by the Sponsor as a sterile, off-white to yellowish lyophilized powder in a single-dose glass vial. The vial contains approximately 180 mg of sacituzumab govitecan for reconstitution.

For information on the formulation and handling of sacituzumab govitecan, see the pharmacy manual.

A13–4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + SG arm will receive treatment as outlined in Table A13-1 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1). Treatment must be initiated no later than 7 days after treatment assignment.

Table A13-1 Treatment Regimen for Atezo + SG Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Sacituzumab govitecan 10 mg/kg by IV infusion on Days 1 and 8 [a] • Atezolizumab 1200 mg by IV infusion on Day 1 [b]

Atezo = atezolizumab; SG = sacituzumab govitecan.

[a] There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[b] The atezolizumab infusion should be initiated approximately 60 minutes following completion of the sacituzumab govitecan infusion.

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

Refer to Section A13–5.1.4 for information on treatment interruptions for patients who experience toxicities. Treatment interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.4. No safety data related to overdosing of atezolizumab are available. Sacituzumab govitecan doses in excess of the recommended dose may be associated with exposure-related toxicities, such as neutropenia and diarrhea. These toxicities, frequently associated with chemotherapies, should be managed through supportive care to prevent serious consequences (such as dehydration and infection) and provide symptomatic relief, in accordance with institutional guidelines.

A13–4.1.2.1 Sacituzumab Govitecan

Sacituzumab govitecan will be administered by IV infusion at a dose of 10 mg/kg on Days 1 and 8 of each 21-day cycle.

Administration of sacituzumab govitecan 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 5.

First infusion: Administer infusion over 3 hours. Observe patients during the infusion and for at least 30 minutes following the initial dose, for signs or symptoms of infusion-related reactions (IRRs).

Subsequent infusions: Administer infusion over 1 to 2 hours if prior infusions were tolerated. Observe patients during the infusion and for at least 30 minutes after infusion.

Prior to each dose of sacituzumab govitecan, premedication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting is recommended as follows:

- Premedicate with antipyretics, H1 and H2 blockers prior to infusion; corticosteroids may be used for patients who have had prior infusion reactions
- Premedicate with a two- or three-drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK1 receptor antagonist, as well as other drugs as indicated)

Following administration of sacituzumab govitecan, no further premedication for atezolizumab will be allowed.

Guidelines for the medical management of IRRs for sacituzumab govitecan are provided in Section A13–5.1.4.

Guidelines for dose modifications, treatment interruptions, or discontinuations because of toxicities are provided in Section A13–5.1.4.

A13–4.1.2.2 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. Atezolizumab should be administered approximately 60 minutes after completion of the sacituzumab govitecan infusion.

Administration of atezolizumab 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A13-2.

Table A13-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during the infusion and at 30 (±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-pyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Guidelines for medical management of IRRs for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A13–5.1.4.

A13–4.2 CONCOMITANT THERAPY FOR ATEZO+SG ARM

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 study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A13–4.2.1 Permitted Therapy for Atezo+SG Arm

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

- Colony-stimulating factors (CSFs), such as granulocyte colony-stimulating factors (G-CSFs) and erythropoiesis-stimulating agents (ESAs), which are to be administered per local practice/institutional guidelines or the American Society of Clinical Oncology guidelines for hematopoietic CSFs (Smith et al. 2015) and American Society of Clinical Oncology/American Society of Hematology guidelines for ESAs (Bohlius et al. 2019)
- Oral contraceptives
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Megestrol acetate administered as an appetite stimulant after initiation of study treatment
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section A13–4.2.3)
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Bisphosphonates and denosumab for the prevention of skeletal events
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease).

  Treatment with atezolizumab and sacituzumab govitecan may be continued during palliative radiotherapy.
- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.

- The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

  Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

- Anti-convulsant therapy, if required, is administered at a stable dose.

  Treatment with atezolizumab may be continued during radiotherapy. Treatment with sacituzumab govitecan should be withheld for 1 week prior to radiotherapy and for 2 weeks after radiotherapy.

Premedication with antihistamines, anti-pyretics, 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 with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-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 5).

A13–4.2.2 Cautionary Therapy for Atezo + SG Arm

A13–4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α 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 Section A13–5.1.4 for guidelines for managing specific adverse events).

A13–4.2.2.2 Strong UDP Glucuronosyltransferase Family 1 Member A1 Inhibitors or Inducers

Co-administration of sacituzumab govitecan with strong inhibitors of UDP glucuronosyltransferase 1A1 (UGT1A1) may increase systemic exposure to the active metabolite, SN-38 (the cytotoxic component of sacituzumab govitecan), resulting in an

increase in the exposure to sacituzumab govitecan and a potential risk of neutropenia. Conversely, concomitant use of UGT1A1 inducers could decrease exposure to sacituzumab govitecan. Therefore, patients who are receiving strong inhibitors of UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir) or strong UGT1A1 inducers concomitantly with sacituzumab govitecan should be closely monitored for severe neutropenia.

A13–4.2.2.3 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 A13–4.2.3) may be used during the study at the discretion of the investigator.

A13–4.2.3 Prohibited Therapy for Atezo + SG Arm

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 4.4), and during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A13–4.2.1).
- Investigational therapy (other than protocol-mandated study treatment) 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 treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, 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.

A13–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO+SG ARM

Contraception requirements for women and men in the Atezo + SG arm are outlined below:

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, 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 last dose of atezolizumab and for 6 months after the last dose of sacituzumab govitecan.

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

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

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

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

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for 3 months after the last dose of sacituzumab govitecan. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 3 months after the last dose of sacituzumab govitecan to avoid exposing the embryo.

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

A13–5 ASSESSMENT OF SAFETY FOR ATEZO+SG ARM

A13–5.1 SAFETY PLAN FOR ATEZO+SG ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and sacituzumab govitecan in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A13–5.1.1, A13-5.1.2, and A13–5.1.3). Guidelines for management of patients who experience adverse events are provided in Section A13–5.1.4.

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. Because of the potential for overlapping toxicities, a minimum of 6 patients in the Atezo+SG arm must complete a safety evaluation before additional patients can be enrolled in that arm (see Section 3.1.4 for details). Administration of atezolizumab and sacituzumab govitecan 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. Adverse events will be reported as described in Sections 5.2–5.6.

A13–5.1.1 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, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A13–5.1.2 Risks Associated with Sacituzumab Govitecan

Sacituzumab govitecan has been associated with risks such as the following: IRRs, gastrointestinal toxicities, infectious toxicities (may involve sepsis, pneumonia), fatigue, and hematologic toxicities. Patients who are homozygous for the UGT1A1*28 allele are potentially at increased risk for neutropenia, febrile neutropenia, and anemia and may be at increased risk for other adverse events following initiation of sacituzumab govitecan treatment. There is also a risk of embryofetal toxicity based on sacituzumab govitecan’s mechanism of action. Refer to Section 6 of Sacituzumab Govitecan Investigator's Brochure for a detailed description of anticipated risks for sacituzumab govitecan.

A13–5.1.3 Risks Associated with Combination Use of Atezolizumab and Sacituzumab Govitecan

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and sacituzumab govitecan: gastrointestinal events, dermatologic events, and hepatic events.

A13–5.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo + SG Arm

A13–5.1.4.1 Dose Modifications

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

For management of drug-related toxicities, the dose of sacituzumab govitecan can be reduced by 2.5 mg/kg (i.e., one dose level) up to two times, as outlined in Table A13-3.

Table A13-3 Suggested Dose Reductions for Sacituzumab Govitecan

	Initial Dose	First Dose Reduction	Second Dose Reduction
Sacituzumab govitecan	10 mg/kg	7.5 mg/kg	5 mg/kg

If further dose reduction is indicated for sacituzumab govitecan after two dose reductions, sacituzumab govitecan should be discontinued. After dose reduction, the dose of sacituzumab govitecan may not be escalated.

A13–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for more than 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for more than 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for more than 12 weeks if the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption should 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.

Sacituzumab govitecan treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If treatment-related Grade ≥ 3 non-hematologic toxicity attributed to sacituzumab govitecan prevents dose resumption by more than 3 weeks, or for more than 5 weeks in total, permanently

discontinue sacituzumab govitecan. The decision to re-challenge patients with sacituzumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed

If either atezolizumab or sacituzumab govitecan is discontinued, the other drug can be continued if the patient is likely to derive clinical benefit, as determined by the investigator. The Medical Monitor is available to advise as needed. Refer to Section A13–4.1.2 for information on dose interruptions for reasons other than toxicity (e.g., surgical procedures).

A13–5.1.4.3 Management Guidelines for Adverse Events

Patients are required to have an ANC of $\geq 1.5 \times 10^9$/L (1500/μL) on Day 1 or each cycle and an ANC of $\geq 1.0 \times 10^9$/L (1000/μL) on Day 8 of each cycle to receive treatment with sacituzumab govitecan. Guidelines for management of hematologic toxicities and other toxicities (including guidelines for dose modification and treatment interruption or discontinuation) are provided in Table A13-4. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm

Event	Action to Be Taken
IRRs, CRS, and anaphylaxis	
General guidelines	• Guidelines for management of IRRs and CRS for atezolizumab are provided in Appendix 6. • Guidelines for management of IRRs for sacituzumab govitecan are provided below. • For anaphylaxis precautions, see Appendix 5.
IRR to sacituzumab govitecan, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR to sacituzumab govitecan, Grade 2	• Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, administer oral premedication with antihistamine and anti-pyretic and monitor closely for IRRs. Corticosteroids may be used for patients who have had prior infusion reactions. • For recurrent Grade 2 IRRs that fail to recover within 6 hours despite optimal management, sacituzumab govitecan should be permanently discontinued.

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; IRR = infusion-related reaction; G-CSF = granulocyte colony-stimulating factor; LFT = liver function test; PO = orally; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
IRRs, CRS, and anaphylaxis (cont.)	
IRR to sacituzumab govitecan, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue sacituzumab govitecan and contact the Medical Monitor. [a]
Hemophagocytic lymphohistiocytosis	• Follow guidelines for atezolizumab in Appendix 6. • Withhold sacituzumab govitecan and contact the Medical Monitor for guidance.

Atezo + SG = atezolizumab plus sacituzumab govitecan; CRS = cytokine release syndrome; IRR = infusion-related reaction; G-CSF = granulocyte colony-stimulating factor; LFT = liver function test; PO = orally; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the patient is likely to derive clinical benefit. The decision to re-challenge patients with the study treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. .

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A13–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the assessment of benefit-risk by the investigator and in alignment with the protocol requirements for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity	
General guidelines	• Because nausea, vomiting, and diarrhea are frequent sacituzumab govitecan-associated toxicities that potentially overlap with atezolizumab-associated toxicities, appropriate treatment, including fluid and electrolyte replacement (as needed), is required to minimize the risk of serious consequences, such as dehydration. <u>Diarrhea</u> • Dietary modification should be recommended for the management of diarrhea, including adequate fluid intake to maintain hydration. • Administer antibiotics as clinically indicated. • For excessive cholinergic responses to study treatment (e.g., abdominal cramping, diarrhea, salivation), administer appropriate premedication (e.g., atropine) for subsequent treatments. <u>Nausea and Vomiting</u> • Because sacituzumab govitecan is considered to be moderately emetogenic, premedication with a two- or three-drug anti-emetic regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK1 receptor antagonist, as well as other drugs as indicated) should be administered prior to sacituzumab govitecan infusion. • If nausea and vomiting are persistent, a three-drug regimen, including a 5-HT3 inhibitor (ondansetron or palonosetron, or other agents according to local practices), an NK1-receptor antagonist (fosaprepitant or aprepitant), and dexamethasone (10 mg PO or IV), may be administered. • Anticipatory nausea can be treated with olanzapine.

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea or colitis, Grade 1	• Follow guidelines for atezolizumab in Appendix 6. • Continue sacituzumab govitecan. • Initiate symptomatic treatment such as the following: – Loperamide can be administered at the onset of treatment-related diarrhea (after infectious causes are ruled out) at an initial dose of 4 mg, followed by 2 mg with every episode of diarrhea to a maximum dose of 16 mg/day. – If diarrhea is not resolved after 24 hours, consider adding diphenoxylate/atropine and/or opium tincture, as clinically indicated. –If diarrhea persists, consider adding octreotide 100–150 μg SC three times per day, or treat as per institutional guidelines.
Diarrhea or colitis, Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • Withhold sacituzumab govitecan. • Initiate symptomatic treatment such as the following: – Loperamide can be administered at the onset of treatment-related diarrhea (after infectious causes are ruled out) at an initial dose of 4 mg, followed by 2 mg with every episode of diarrhea to a maximum dose of 16 mg/day. – If diarrhea is not resolved after 24 hours, consider adding diphenoxylate/atropine and/or opium tincture, as clinically indicated. – If diarrhea persists, consider adding octreotide 100–150 μg SC three times per day, or treat as per institutional guidelines. • If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan. [b] If not, permanently discontinue sacituzumab govitecan and contact the Medical Monitor. [a]

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea or colitis, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold sacituzumab govitecan. • Treat with IV fluids and consider hospitalization. • Initiate symptomatic treatment such as the following: – Loperamide can be administered at the onset of treatment-related diarrhea (after infectious causes are ruled out) at an initial dose of 4 mg, followed by 2 mg with every episode of diarrhea to a maximum dose of 16 mg/day. – If diarrhea is not resolved after 24 hours, consider adding diphenoxylate/atropine and/or opium tincture, as clinically indicated. – If diarrhea persists, consider adding octreotide 100–150 μg SC three times per day, or treat as per institutional guidelines. • First and second occurrence: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan; reduce the dose by one level if event does not resolve within 1 week after interrupting treatment and is not manageable with anti-diarrheal agents. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Third occurrence: Permanently discontinue sacituzumab govitecan and contact the Medical Monitor. [a]
Nausea or vomiting, Grade 3	• Continue atezolizumab. For persistent nausea that does not respond to treatment and for all vomiting events, withhold sacituzumab govitecan. • Manage per institutional guidelines. • First and second occurrence: If sacituzumab govitecan is withheld and event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan; reduce the dose by one level if event does not resolve within 1 week after interrupting treatment and is not manageable with anti-emetic agents. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Third occurrence: Permanently discontinue sacituzumab govitecan and contact the Medical Monitor. [a]

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Nausea or vomiting, Grade 4	• Withhold atezolizumab and sacituzumab govitecan. • Manage per institutional guidelines. • If event resolves to Grade 2 or better within 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab. [a] • First and second occurrence: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan; reduce the dose by one level if event does not resolve within 1 week after interrupting treatment and is not manageable with anti-emetic agents. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Third occurrence: Permanently discontinue sacituzumab govitecan and contact the Medical Monitor. [a]

Atezo + SG = atezolizumab plus sacituzumab govitecan; IRR = infusion-related reaction; G-CSF = granulocyte colony-stimulating factor; LFT = liver function test; PO = orally; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the patient is likely to derive clinical benefit. The decision to re-challenge patients with the study treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A13–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the assessment of benefit-risk by the investigator and in alignment with the protocol requirements for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Neutropenia	
General guidelines	• Sacituzumab govitecan should only be administered if Day 1 ANC $\geq 1.5 \times 10^9$/L (1500/μL) and Day 8 ANC $\geq 1.0 \times 10^9$/L (1000/μL). • The routine prophylactic use of growth factors is not required; however, prophylactic administration may be considered and should comply with American Society of Clinical Oncology guidelines. Growth factors may be administered to patients who have experienced febrile neutropenia or Grade 3 or Grade 4 neutropenia and to patients at high risk of poor clinical outcomes, including those with prolonged neutropenia, ANC $< 0.1 \times 10^9$/L (100/μL), febrile neutropenia, or serious infections.
Neutropenia, Grade 3 or 4	• Withhold atezolizumab and sacituzumab govitecan. • At first occurrence, initiate G-CSF prophylaxis for subsequent dosing. • If event resolves to Grade 2 or better within 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab and contact the Medical Monitor. [a] • If Grade 3–4 neutropenia does not resolve within 3 weeks or with G-CSF support, contact the Medical Monitor and refer the patient to a hematologist for further investigations **Grade 4 neutropenia lasting ≥7 days (or less if clinically indicated), febrile neutropenia, or neutropenia that delayed dosing by 2–3 weeks:** • First occurrence: If event resolves to Grade 1 or better (Day 1) or to Grade 2 or better (Day 8) within 3 weeks after interrupting treatment, resume sacituzumab govitecan. [b] If not, permanently discontinue sacituzumab govitecan. [a] • Second and third occurrence: If event resolves to Grade 1 or better (Day 1) or to Grade 2 or better (Day 8) within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by one level. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Fourth occurrence: Permanently discontinue sacituzumab govitecan and contact the Medical Monitor. [a] **All other cases of Grade 3 or 4 neutropenia:** • If event resolves to Grade 1 or better (Day 1) or to Grade 2 or better (Day 8) within 3 weeks after interrupting treatment, resume sacituzumab govitecan. [b] If not, permanently discontinue sacituzumab govitecan. [a]

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Atezo + SG = atezolizumab plus sacituzumab govitecan; IRR = infusion-related reaction; G-CSF = granulocyte colony-stimulating factor; LFT = liver function test; PO = orally; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the patient is likely to derive clinical benefit. The decision to re-challenge patients with the study treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A13–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the assessment of benefit-risk by the investigator and in alignment with the protocol requirements for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Dermatologic events	
Dermatologic event, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue sacituzumab govitecan.
Dermatologic event, Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Withhold sacituzumab govitecan. **Event that has delayed treatment by 2–3 weeks or event that persists for ≥48 hours despite optimal medical management:** • First and second occurrence: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by one level. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Third occurrence: Permanently discontinue sacituzumab govitecan and contact the Medical Monitor. [a] **All other Grade 3 events:** • If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan. [b] If not, permanently discontinue sacituzumab govitecan. [a]
Dermatologic event, Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold sacituzumab govitecan. • First and second occurrence: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by one level. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Third occurrence: Permanently discontinue sacituzumab govitecan and contact the Medical Monitor. [a]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6. • Withhold sacituzumab govitecan. • If event resolves to Grade 1 or better, resume sacituzumab govitecan. • Permanently discontinue sacituzumab govitecan if withheld for >3 weeks or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed.

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Atezo + SG = atezolizumab plus sacituzumab govitecan; IRR = infusion-related reaction; G-CSF = granulocyte colony-stimulating factor; LFT = liver function test; PO = orally; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the patient is likely to derive clinical benefit. The decision to re-challenge patients with the study treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A13–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the assessment of benefit–risk by the investigator and in alignment with the protocol requirements for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin	
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin ≤ 2 × ULN	• Continue atezolizumab and sacituzumab govitecan.
AST/ALT > 3 × ULN to 5 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue atezolizumab and sacituzumab govitecan. • Monitor LFTs at least weekly. • Consider patient referral to a hepatologist and liver biopsy. **Suspected immune-mediated events of > 5 days' duration:** • Consider withholding atezolizumab. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If atezolizumab is withheld and event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks after event onset, resume atezolizumab. [d, e] If not, permanently discontinue atezolizumab and contact the Medical Monitor. [a]
AST/ALT > 5 × ULN to < 10 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue atezolizumab. Withhold sacituzumab govitecan. • If event resolves to AST/ALT ≤ 5 × ULN within 3 weeks after interrupting treatment, resume sacituzumab govitecan. If not, permanently discontinue sacituzumab govitecan. [a] • Monitor LFTs at least weekly. • Consider patient referral to hepatologist and liver biopsy. **Suspected immune-mediated events:** • Withhold atezolizumab and sacituzumab govitecan. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 3 weeks after interrupting treatment, resume sacituzumab govitecan. [b] If not, permanently discontinue sacituzumab govitecan and contact the Medical Monitor. [a] • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN with 12 weeks after event onset, resume atezolizumab. [d, e] If not, permanently discontinue atezolizumab and sacituzumab govitecan and contact the Medical Monitor. [a]

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin > 2 × ULN	• Investigate causes for elevated bilirubin and initiate treatment as indicated per institutional guidelines. • Use best medical judgment when determining whether to continue study treatment.
AST/ALT > 3 × ULN with total bilirubin > 2 × ULN	• Withhold atezolizumab and sacituzumab govitecan. • Monitor LFTs every 48–72 hours until decreasing and then monitor weekly. • Refer patient to hepatologist and consider liver biopsy. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN while within 3 weeks after interrupting treatment, resume sacituzumab govitecan with dose reduced by one level. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks after event onset, resume atezolizumab. [d, e] If not, permanently discontinue atezolizumab and contact the Medical Monitor. [a] • Permanently discontinue atezolizumab and sacituzumab govitecan for life-threatening hepatic events and contact the Medical Monitor.
AST/ALT > 10 × ULN	• Permanently discontinue atezolizumab and contact the Medical Monitor. [a] Withhold sacituzumab govitecan. • Monitor LFTs every 48–72 hours until decreasing and then monitor weekly. • Refer patient to hepatologist and consider liver biopsy. • Consider administering 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent or escalating the corticosteroid dose. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN, taper corticosteroids over ≥ 1 month. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 3 weeks after interrupting treatment, resume sacituzumab govitecan with dose reduced by one level. [b, c] If not, permanently discontinue sacituzumab govitecan. [a]

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Atezo + SG = atezolizumab plus sacituzumab govitecan; IRR = infusion-related reaction; G-CSF = granulocyte colony-stimulating factor; LFT = liver function test; PO = orally; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the patient is likely to derive clinical benefit. The decision to re-challenge patients with the study treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. .

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A13–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the assessment of benefit-risk by the investigator and in alignment with the protocol requirements for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Endocrine events	
Hypothyroidism, Grade 1	• Follow guidelines for atezolizumab in Appendix 6. • Continue sacituzumab govitecan.
Hypothyroidism, Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • Consider withholding sacituzumab govitecan. • When symptoms are controlled and thyroid function is improving, resume sacituzumab govitecan. [b]
Hypothyroidism, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold sacituzumab govitecan. • When symptoms are controlled and thyroid function is improving, resume sacituzumab govitecan. [b]
Hyperthyroidism, Grade 1	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Follow guidelines for atezolizumab in Appendix 6. • Continue sacituzumab govitecan. **TSH < 0.1 mU/L:** • Follow guidelines for Grade 2 hyperthyroidism.
Hyperthyroidism, Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • Consider withholding sacituzumab govitecan. • When symptoms are controlled and thyroid function is improving, resume sacituzumab govitecan. [b]
Hyperthyroidism, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold sacituzumab govitecan. • When symptoms are controlled and thyroid function is improving, resume sacituzumab govitecan. [b]

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Atezo + SG = atezolizumab plus sacituzumab govitecan; IRR = infusion-related reaction; G-CSF = granulocyte colony-stimulating factor; LFT = liver function test; PO = orally; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the patient is likely to derive clinical benefit. The decision to re-challenge patients with the study treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A13–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the assessment of benefit-risk by the investigator and in alignment with the protocol requirements for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Sacituzumab govitecan-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab and sacituzumab govitecan.
Grade 3	• Continue atezolizumab. Withhold sacituzumab govitecan. **Non-hematologic toxicity that persists for > 48 hours despite optimal medical management requires dose hold until resolution to Grade 1. Contact the Medical Monitor prior to resuming treatment:** • First occurrence: Resume sacituzumab govitecan with the dose reduced by 25% (one level). • Second occurrence: Resume sacituzumab govitecan with the dose reduced by 50% (two levels). • Third occurrence: Permanently discontinue sacituzumab govitecan and contact the Medical Monitor. [a] **All other Grade 3 toxicities:** • If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan. [b] If not, permanently discontinue sacituzumab govitecan. [a]
Grade 4	• Withhold atezolizumab and sacituzumab govitecan . • If event improves resume atezolizumab. The Medical Monitor is available to advise as needed. If not, permanently discontinue atezolizumab. **Toxicity that has delayed treatment by 1–3 weeks or non-hematologic toxicity:** • First and second occurrence: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by one level. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Third occurrence: Permanently discontinue sacituzumab govitecan and contact the Medical Monitor. [a] **All other Grade 4 toxicities:** • If event resolves to Grade 1 or better while within 3 weeks after interrupting treatment, resume sacituzumab govitecan. [b] If not, permanently discontinue sacituzumab govitecan. [a]

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Atezo + SG = atezolizumab plus sacituzumab govitecan; IRR = infusion-related reaction; G-CSF = granulocyte colony-stimulating factor; LFT = liver function test; PO = orally; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the patient is likely to derive clinical benefit. The decision to re-challenge patients with the study treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A13–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the assessment of benefit-risk by the investigator and in alignment with the protocol requirements for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue sacituzumab govitecan.
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Sacituzumab govitecan may be continued at the discretion of the investigator per medical judgment.

Atezo + SG = atezolizumab plus sacituzumab govitecan; IRR = infusion-related reaction; G-CSF = granulocyte colony-stimulating factor; LFT = liver function test; PO = orally; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the patient is likely to derive clinical benefit. The decision to re-challenge patients with the study treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A13–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the assessment of benefit-risk by the investigator and in alignment with the protocol requirements for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

A13–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO+SG ARM (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 the Atezo + SG arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either 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.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, HLH, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

- Myelitis
- Facial paresis

A13–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+SACITUZUMAB GOVITECAN ARM

A13–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab or within 6 months after the last dose of sacituzumab govitecan. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study 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 when updated information on the course and outcome of the pregnancy becomes available.

A13–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 3 months after the last dose of sacituzumab govitecan. 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. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A13–5.3.3 Abortions

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

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

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

A13–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study 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).

A13–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+SG ARM

Table A13-5 Schedule of Activities for Patients Treated with Atezo + SG (Stages 1 and 2)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-day cycles) [a]				Treatment Discontinuation [d]	Follow-Up
		Cycle 1 [b]		Cycles ≥ 2			
	Day –28 to –1	Day 1	Day 8 [c]	Day 1 [c]	Day 8 [c]		Q3M
Molecular profile of bladder cancer (if available)	See Appendix 7.	Whenever updated information becomes available					
Vital signs [e]		x		x		x	
Weight [f]		x		x		x	
Complete physical examination [g]						x	
Limited physical examination [h, f]		x	x	x	x		
ECOG Performance Status [f]		x		x		x	
ECG [i, f]		x		x		x	
Hematology [j]		x [k, l]	x	x [k]	x	x	
Chemistry [m]		x [k, l]	x	x [k]	x	x	
C-reactive protein		x [k, l]		x [k]		x	
Coagulation (INR and aPTT)		Perform as clinically indicated.				x	
TSH, free T3 (or total T3), free T4 [n]		x [k, l, n]				x	
Viral serology (if applicable) [o]				x [o]		x [o]	x [o]
Pregnancy test [p]		x [k, l]		x		x	x [p]
Urinalysis [q]		x		x			
Serum autoantibody sample [r]		x [s]					
Serum PK sample		Refer to Table A13-6.					
Serum ADA sample		Refer to Table A13-6.					
Plasma, serum, and PBMC samples for biomarkers		Refer to Table A13-6.					

Table A13-5 Schedule of Activities for Patients Treated with Atezo + SG (Stages 1 and 2) (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-day cycles) [a]				Treatment Discontinuation [d]	Follow-Up
		Cycle 1 [b]		Cycles ≥ 2			
	Day –28 to –1	Day 1	Day 8 [c]	Day 1 [c]	Day 8 [c]		Q3M
Blood sample for RBR (optional) [t]	See Appendix 7.	x					
Tumor biopsy		x [u]					
Tumor biopsy (optional)		x [v]					
Tumor response assessments		x [w, x, y]					
Concomitant medications [z]		x	x	x	x	x	
Adverse events [aa]		x	x	x	x	x [aa]	x [aa]
Sacituzumab govitecan administration [bb, cc]		x	x	x	x		
Atezolizumab administration [bb, dd]		x		x			
Survival follow-up and anti-cancer treatment							x [ee]

ADA = anti-drug antibody; App = Appendix; Atezo + SG = atezolizumab plus sacituzumab govitecan; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBV = hepatitis B virus; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; Q3M = every 3 months; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.

[b] Treatment must be initiated no later than 7 days after treatment assignment.

[c] Visits can occur up to 2 days after the scheduled visit day.

[d] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed by the investigator (see Section 3.1.1 for details) may be used as the treatment discontinuation visit.

Table A13-5 Schedule of Activities for Patients Treated with Atezo + SG (Stages 1 and 2) (cont.)

[e] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion of each drug and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion of each drug. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion of each drug and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[f] Assessment may be performed within 24 hours prior to dosing during the treatment period.

[g] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[j] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[k] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

[l] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[m] Chemistry panel (serum or plasma) includes 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, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. For UK patients, amylase and lipase must be included on Day 1 of each treatment cycle.

[n] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[o] Patients with a positive quantitative HBV DNA at screening will undergo additional HBV DNA tests on Day 1 of every third cycle (i.e., Cycles 3, 6, 9, etc.), at treatment discontinuation (±7 days), and at 3, 6, 9, and 12 months (±14 days at each timepoint) after treatment discontinuation. Study treatment and procedures may proceed while HBV DNA is being processed, but results should be reviewed by the investigator as soon as they are available. If HBV DNA increases to ≥500 IU/mL, consultation with a hepatologist or gastroenterologist with specialty in hepatitis B is recommended. The Medical Monitor is available to advise as needed.

[p] All women of childbearing potential will have a urine or serum pregnancy test performed at specified visits during treatment and at 3 months and 6 months after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. If a pregnancy test was performed within 96 hours prior to Day 1 of Cycle 1, it does not have to be repeated.

[q] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

Table A13-5 Schedule of Activities for Patients Treated with Atezo + SG (Stages 1 and 2) (cont.)

[r] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[s] Autoantibody analysis should be repeated for patients who develop signs or symptoms suggestive of autoimmune disease (e.g., lupus erythematosus). For patients who show evidence of immune-mediated toxicity, additional samples may be considered.

[t] 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.

[u] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 for tissue sample requirements.

[v] Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation, if deemed clinically feasible, and may undergo additional on-treatment biopsies at any other time during the study at the investigator's discretion.

[w] Patients will undergo tumor assessments at baseline, every 9 weeks (± 1 week) for the first 54 weeks following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1. Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[x] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the tumor assessment schedule described above (see Footnote “v”). Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[y] For patients who undergo screening for Stage 2: Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.

[z] Includes 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 study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[aa] 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.

Table A13-5 Schedule of Activities for Patients Treated with Atezo + SG (Stages 1 and 2) (cont.)

[bb] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).

[cc] Sacituzumab govitecan will be administered by IV infusion at a dose of 10 mg/kg on Day 1 and 8 of each 21-day cycle. Sacituzumab govitecan should be administered prior to the atezolizumab infusion. Sacituzumab govitecan should be infused over approximately 3 hours on first infusion and over 1 hour on subsequent infusions, if the first infusion is well tolerated.

[dd] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Refer to Section A13–4.1.2.2 for details on atezolizumab infusions (including measurement of vital signs).

[ee] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a 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. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table A13-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + SG Arm: Preliminary and Expansion Phases

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	•Atezolizumab PK (serum) •Atezolizumab ADA (serum) •Sacituzumab govitecan PK (serum) •Sacituzumab govitecan ADA (serum) •Biomarker (plasma, serum, PBMC)
	30 (± 10) minutes after sacituzumab govitecan infusion	•Sacituzumab govitecan PK (serum)
	30 (± 10) minutes after atezolizumab infusion	•Atezolizumab PK (serum)
Day 8 of Cycle 1	Prior to study treatment	•Sacituzumab govitecan PK (serum)
Day 1 of Cycle 2	Prior to study treatment	•Atezolizumab PK (serum) •Atezolizumab ADA (serum) •Biomarker (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to study treatment	•Atezolizumab PK (serum) •Atezolizumab ADA (serum) •Sacituzumab govitecan PK (serum) •Sacituzumab govitecan ADA (serum)
	30 minutes after sacituzumab govitecan infusion	•Sacituzumab govitecan PK (serum)
Day 8 of Cycle 3	Prior to study treatment	•Sacituzumab govitecan PK (serum)
Day 1 of Cycle 4	Prior to study treatment	•Atezolizumab PK (serum) •Atezolizumab ADA (serum) •Biomarker (plasma, serum)
Day 1 of Cycle 5	Prior to study treatment	•Sacituzumab govitecan PK (serum) •Sacituzumab govitecan ADA (serum)
	30 (± 10) minutes after sacituzumab govitecan infusion	•Sacituzumab govitecan PK (serum)
Day 1 of Cycle 7	Prior to study treatment	•Sacituzumab govitecan PK (serum) •Sacituzumab govitecan ADA (serum)
	30 (± 10) minutes after sacituzumab govitecan infusion	•Sacituzumab govitecan PK (serum)

ADA = anti-drug antibody; Atezo + SG = atezolizumab plus sacituzumab govitecan; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety 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. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

For all sacituzumab govitecan PK -Total antibody, free SN-38, SN-38 glucuronide, and total SN-38 will be tested.

Table A13-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + SG Arm: Preliminary and Expansion Phases (cont.)

Visit	Time	Sample Type
Day 1 of Cycle 8	Prior to study treatment	•Atezolizumab PK (serum) •Atezolizumab ADA (serum) •Biomarker (plasma, serum)
Day 1 of Cycle 9	Prior to study treatment	•Sacituzumab govitecan PK (serum) •Sacituzumab govitecan ADA (serum)
	30 (± 10) minutes after sacituzumab govitecan infusion	•Sacituzumab govitecan PK (serum)
Day 1 of Cycle 11 and every third cycle thereafter (e.g., Cycles 14, 17, 20, etc.)	Prior to study treatment	•Sacituzumab govitecan PK (serum) •Sacituzumab govitecan ADA (serum)
	30 (± 10) minutes after sacituzumab govitecan infusion	•Sacituzumab govitecan PK (serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	•Atezolizumab PK (serum) •Atezolizumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	•Atezolizumab PK (serum) •Atezolizumab ADA (serum) •Sacituzumab govitecan PK (serum) •Sacituzumab govitecan ADA (serum) •Biomarker (plasma, serum)

ADA = anti-drug antibody; Atezo + SG = atezolizumab plus sacituzumab govitecan; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety 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. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

For all sacituzumab govitecan PK -Total antibody, free SN-38, SN-38 glucuronide, and total SN-38 will be tested.

A13–7 REFERENCES

Bardia A, Mayer IA, Vahdat LR, et al. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. N Engl J Med 2019;380:741–51.

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.

Bohlius J, Bohlke K, Castelli R, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. J Clin Oncol 2019;37:1336–51.

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.

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.

Fehrenbacher L, Spira A, Ballinger M, et al. 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.

Goldenberg DM, Stein R, Sharkey RM. The emergence of trophoblast cell-surface antigen 2 (TROP-2) as a novel cancer target. Oncotarget 2018;9:28989–9006.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.

Ocean AJ, Starodub AN, Bardia A, et al. Sacituzumab govitecan (IMMU-132), an anti-Trop-2-SN-38 antibody-drug conjugate for the treatment of diverse epithelial cancers: safety and pharmacokinetics. Cancer 2017;123:3843–54.

Petrylak DP, Tagawa ST, Jain RK, et al. Early results of TROPHY-U-01 Cohort 2: Sacituzumab govitecan (SG) in platinum-ineligible patients (pts) with metastatic urothelial cancer (mUC) who progressed after prior checkpoint inhibitor (CPI) therapy. J Clin Oncol 2020;38(15 Suppl):5027.

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.

Schmid P, Cruz C, Braiteh FS, et al. Atezolizumab in metastatic TNBC (mTNBC): long-term clinical outcomes and biomarker analyses [abstract]. Cancer Res 2017;77(13 Suppl):abstract 2986.

Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. New Eng J Med 2018;379:2108–21.

Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2015;33:3199–212.

Tagawa ST, Faltas BM, Lam ET, et al. Sacituzumab govitecan (IMMU-132) in patients with previously treated metastatic urothelial cancer (mUC): Results from a phase I/II study. J Clin Oncol 2019a;37(7 Suppl):3199–212.

Tagawa ST, Petrylak DP, Grivas P, et al. TROPHY-u-01: A phase II open-label study of sacituzumab govitecan (IMMU-132) in patients with advanced urothelial cancer after progression on platinum-based chemotherapy and/or anti-PD-1/PD-L1 checkpoint inhibitor therapy. J Clin Oncol 2019b;37(15 Suppl): TPS3153.

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 14
Study Details Specific to Atezo+TCZ Arm

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A14–1 BACKGROUND ON ATEZO+TCZ ARM

A14–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (Atezo) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that targets programmed death-ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed death-1 (PD-1) and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. 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 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 cancer patients 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 (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, hypophysitis, myocarditis, and myasthenia gravis, have been observed (see Appendix 6 for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab (Tecentriq®) is approved for the treatment of urothelial carcinoma (UC), non–small-cell lung cancer (NSCLC), 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.

A14–1.2 BACKGROUND ON TOCILIZUMAB

Tocilizumab (TCZ) is a recombinant humanized, anti-human monoclonal antibody of the IgG1 subclass directed against the soluble and membrane-bound interleukin 6 receptor (IL-6R). Tocilizumab binds specifically to both soluble IL-6R (sIL-6R) and membrane-bound IL-6R (mIL-6R) and has been shown to inhibit sIL-6R and mIL-6R–mediated signaling.

Interleukin 6 (IL-6) is a pleiotropic pro-inflammatory, multifunctional, cytokine produced by a variety of cell types. It has been shown to be involved in such diverse physiological processes as T-cell activation; induction of acute phase proteins; stimulation of hematopoietic precursor cell growth and differentiation; proliferation of hepatic, dermal and neural cells; bone metabolism; lipid metabolism; hepatoprotection; and fibrosis.

Elevated tissue and serum levels of IL-6 have been implicated in the disease pathology of several inflammatory and autoimmune disorders, including rheumatoid arthritis, Castleman's disease, systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, giant cell arteritis, Takayasu arteritis, systemic sclerosis, and cytokine release syndrome.

The IV formulation of tocilizumab is approved in the European Union, the United States, and Japan for rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis (sJIA), and polyarticular juvenile idiopathic arthritis (pJIA), and in the United States for cytokine release syndrome. IV tocilizumab is also approved in more than 75 other countries for the treatment of RA, in more than 70 additional countries for the treatment of sJIA, and over 65 other countries for the treatment of pJIA. In India and Japan, IV tocilizumab has additional indications for treatment in Castleman disease.

The SC formulation of tocilizumab is approved in more than 85 countries (including the European Union, the United States, New Zealand, Switzerland, Canada, Japan, South Korea, and Taiwan) for the treatment of RA. The subcutaneous (SC) formulation is also approved in the United States, the European Union, Brazil, and New Zealand for the treatment of giant cell arteritis (GCA), and in Japan for GCA and Takayasu arteritis.

A14–2 RATIONALE FOR ATEZO+TCZ ARM

A14–2.1 THE PD-L1 PATHWAY

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).

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.

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 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).

CIT agents, particularly immune checkpoint inhibitors, have made a significant impact on the treatment of patients with UC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A14–2.2 IL-6 AND CANCER

IL-6 is a pleotropic cytokine that binds both mIL-6R and sIL-6R receptors. This cytokine regulates the proliferation, migration, activation, morphology, and metabolic state of virtually all cells that partake in cancer formation and progression (Chang et al. 2014). The IL-6 signaling pathway is abnormally regulated in a variety of malignancies through numerous mechanisms, including the overexpression of IL-6, IL-6R, sIL-6R, gp130, JAK, and Stat3 (Chang et al. 2014).

Binding to the common signal transducing receptor chain glycoprotein 130 (gp130) initiates the activation of JAK/STAT3, MAPK, and PI3K pathways (Fisher et al. 2014). Soluble IL-6 and sIL-6R binding to gp130 (trans-signaling) is associated with the transition from acute to chronic inflammation and development of a pro-tumor state with shifts in the tumor microenvironment to include more tumor-associated macrophages, T-regulatory cells, and myeloid derived suppressor cells (Rose-John et al. 2006; Scheller et al. 2011; Fisher et al. 2014).

The nonclinical effect of IL-6 and PD-L1 blockade has been evaluated in murine models of pancreatic cancer (Mace et al. 2016). The combination showed efficacy in mice bearing subcutaneous models of pancreatic cancer compared with either the PD-L1 or IL-6 blockade alone ($p<0.03$ for MT5 subcutaneous tumors compared with PD-L1 alone) and was accompanied by an increase in T-effector lymphocytes.

Clinical evaluation of tocilizumab in cancer has been performed but not in combination with a checkpoint inhibitor. A Phase I trial combined carboplatin and doxorubicin with tocilizumab and interferon-α2b in patients with recurrent epithelial ovarian cancer (Dijkgraaf et al. 2015). In this dose-escalation study, patients received carboplatin and doxorubicin for 6 cycles. For the first 3 cycles, patients received 1, 2, 4, or 8 mg/kg of IV tocilizumab every 4 weeks. At the 8-mg/kg dose of tocilizumab, interferon-α2b was added after 3 patients had received and tolerated the 8-mg/kg dose without interferon-α2b. Twenty-one patients were assessed for response and of these patients,

3 patients had a complete response, 8 had a partial response, 6 had stable disease, and 3 had progressive disease. See Section 421 for the safety findings of this study.

Pharmacodynamic evaluations of peripheral blood mononuclear cells were performed after Cycles 3 and 6. Patients receiving the 8-mg/kg dose of tocilizumab (with and without interferon-α2b) showed a functional blockade of IL-6R with increased levels of serum IL-6 ($p = 0.02$) and sIL-6R ($p = 0.008$). In addition, effects were seen in the immune cells with T cells showing higher levels of activation and increased secretion of interferon-γ and tumor necrosis factor–α (TNF-α).

Internal evaluation of patients with metastatic UC (mUC) enrolled in prior atezolizumab studies found that patients with mUC have higher levels of plasma IL-6 (pg/mL) when compared with patients with other solid tumor types including melanoma, triple-negative breast cancer, and NSCLC. Furthermore, internal evaluation of first-line cisplatin-ineligible patients enrolled in Cohort 1 of Study GO29293 (IMvigor210; NCT02951767) found that patients with low levels of IL-6 had superior survival compared with those with high levels of IL-6. Additionally, in the same population, patients whose C-reactive protein (CRP) decreased during treatment had improved overall survival. Similar results were also observed in the Phase III NSCLC study (GO28915 [OAK]; NCT02008227). Atezolizumab-treated patients whose CRP level decreased during treatment had improved survival. This phenomenon, however, was not seen in patients treated on the docetaxel control arm of the Study GO28915 (OAK), regardless of treatment response. Although it is unclear whether improved survival is a correlative or causative effect in these studies, reduced inflammation during treatment may be beneficial, and the lung cancer findings suggest that the benefit of reduced inflammation may be specific to checkpoint inhibitors.

A14–2.3 BENEFIT-RISK ASSESSMENT

Immunotherapy in mUC has shown significant promise. Results from the pivotal multicenter Phase II study GO29293 (IMvigor210) and Phase III study GO29294 (IMvigor211) showed that durable responses were achieved in second-line post-platinum patients with mUC who received atezolizumab monotherapy (Rosenberg et al. 2016; Powles et al. 2018). In IMvigor210 Cohort 2, the objective response rate (ORR) in all patients was 15%, and responses were seen in all PD-L1 immunochemistry subgroups and the median survival in all patients was 7.9 months. Importantly, atezolizumab was well tolerated, with a low rate of treatment-related Grade 3 or 4 adverse events and discontinuations due to adverse events (Rosenberg et al. 2016). In IMvigor211, as of 13 March 2017, a median overall survival of 8.6 months, an ORR of 13.4% (10.5, 16.9), and a median duration of response (DOR) of 21.7 months was observed in the intent-to-treat (ITT) population. Atezolizumab continued to be well tolerated with a lower rate of treatment-related Grade 3 or 4 adverse events and fewer discontinuations due to adverse events than chemotherapy.

Despite the promise of single-agent checkpoint inhibition, only a small percentage of patients experience benefit, highlighting the need for combinations. One potential mechanism for converting otherwise resistant tumors is the manipulation of the immune system and microenvironment. The additional of tocilizumab, an IL-6R inhibitor, offers the potential to re-set the immune system by decreasing regulatory T (T_{reg}) cells, increasing effector T cells, and decreasing tumor-associated macrophages and myeloid-derived suppressor cells.

The safety profile of atezolizumab in combination with tocilizumab continues to be defined. Overlapping toxicities include rash, increased liver function values, hypersensitivity, infusion-related reactions (IRRs), gastrointestinal (GI) events, and hypothyroidism. Aggressive safety monitoring will be put into place to monitor for these adverse events. In addition, a safety evaluation will occur after 6 patients have been enrolled in the combination treatment arm.

Considering the high therapeutic need in the second-line treatment of patients with mUC for tolerable and effective treatment, the compelling clinical and nonclinical data for both atezolizumab and tocilizumab, as well as the anticipated safety profile of the combination, the benefit–risk assessment favors moving forward with the evaluation of the combination in patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.5.

A14–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+TCZ ARM

A14–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 840 mg every 2 weeks (Q2W) (840 mg on Days 1 and 15 of each 28-day cycle). The average concentration following the 840 mg Q2W dosage is expected to be equivalent to that of 1200 mg every 3 weeks (Q3W), the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert; Tecentriq Summary of Product Characteristics). Anti-tumor activity has been observed across doses ranging from 1 to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached, and no dose-limiting toxicities (DLTs) 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 pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A14–3.2 RATIONALE FOR TOCILIZUMAB DOSE AND SCHEDULE

Tocilizumab will be administered by IV infusion at a dose of 8 mg/kg every 4 weeks (Q4W) on Day 1 of each 28-day cycle, the approved dose for tocilizumab for the treatment of RA.

Although there have been few evaluations of tocilizumab in patients with cancer, the Phase I trial in recurrent epithelial cancer described above (see Section A14–2.2) evaluated tocilizumab in combination with cytotoxic chemotherapy (Dijkgraaf et al. 2015). Twenty-three patients enrolled in the study, and no DLT was established. The main Grade 3 or 4 adverse events were febrile neutropenia for <7 days (19%), ileus (19%), and nausea or vomiting (10%). Neutrophil counts were decreased in all dose groups, and in the 8-mg/kg tocilizumab cohort, 4 of 5 patients experienced Grade ≥3 neutropenia. The attribution of these events to tocilizumab is confounded, however, by the concomitant use of cytotoxic chemotherapy.

Overall, the available information, although not specific to tocilizumab and checkpoint inhibitors, suggests that tocilizumab 8 mg/kg IV Q4W in combination with atezolizumab is reasonable and expected to result in an acceptable safety profile.

A14–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+TCZ ARM

A14–4.1 SAFETY EVALUATION IN ATEZO+TCZ ARM

Because of the potential for overlapping toxicities identified for atezolizumab and tocilizumab (rash, increased liver function values, hypersensitivity, IRRs, GI events, and hypothyroidism), special caution will be taken with a planned safety evaluation (see Section 3.1.4 in the protocol body). Randomization to the atezolizumab plus tocilizumab (Atezo+TCZ) arm will be paused after the enrollment of 6 patients until all patients in that arm have completed a safety evaluation of at least 1 cycle (28 days) of treatment. Patients who withdraw before 28 days will not be replaced, and the safety evaluation will be based on the available data at the time all remaining patients have a follow-up of 28 days. If the combination is deemed to be sufficiently safe, randomization will be resumed.

A14–4.2 TREATMENT IN ATEZO+TCZ ARM

A14–4.2.1 Formulation, Packaging, and Handling

A14–4.2.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

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

A14–4.2.1.2 Tocilizumab

Tocilizumab will be supplied by the Sponsor as a sterile solution at a concentration of 20 mg/mL in single-use vials containing 4.0, 10.0, or 20.0 mL.

For information on the formulation and handling of tocilizumab, see the pharmacy manual and the Tocilizumab Investigator's Brochure.

A14–4.2.2 Dosage, Administration, and Compliance

Patients in the Atezo+TCZ arm will receive treatment as outlined in Table A14-1 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease; see Section 3.1.1 in the protocol body for details). Treatment must be initiated no later than 7 days after treatment assignment. Tocilizumab will be administered first. Atezolizumab will be administered 2 hours after the conclusion of the tocilizumab infusion.

Table A14-1 Treatment Regimen for Atezo+TCZ Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Tocilizumab 8 mg/kg IV on Day 1 • Atezolizumab 840 mg IV on Days 1 and 15

Atezo+TCZ = atezolizumab plus tocilizumab.

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. There are limited data available on overdose with tocilizumab. One case of accidental overdose was reported in which a patient with multiple myeloma received a single IV dose of 40 mg/kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received a single dose up to 28 mg/kg IV; dose-related neutropenia, however, was observed. No safety data related to atezolizumab overdose are available.

A14–4.2.2.1 Tocilizumab Administration

Tocilizumab will be administered by IV infusion at a dose of 8 mg/kg Q4W on Day 1 of each 28-day cycle. Each patient will receive 8 mg/kg tocilizumab (or 4 mg/kg in certain circumstances, as described in Section A14–5.1.4.3, with a maximum dose of 800 mg tocilizumab (for patients weighing >100 kg). The last recorded body weight of a patient should be used for calculating tocilizumab volumes for each infusion. The dose administered should be within 10% of the calculated dose. No premedication is required before tocilizumab infusions.

Administration of tocilizumab 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 5.

Medication volumes and additional details of the infusion preparation are provided in the pharmacy manual.

The infusion bag of tocilizumab may be stored at 2°C–8°C for 24 hours provided that the infusion is prepared aseptically and allowed to return to room temperature before administration. Tocilizumab should be infused into an arm vein over 60 (±15) minutes and will be administered at room temperature. In exceptional cases of infusion reactions, this time may be extended to up to 6 hours (hypersensitivity or anaphylaxis are described in Appendix 5). The infusion speed must be 10 mL/hr for 15 minutes and then increased to 130 mL/hr to complete the dosing over 60 minutes. The entire 100-mL content of the infusion bag must be administered. Normal saline (20 mL) will be administered following the infusion of study medication to flush the remaining study medication through the IV set.

Vital signs are recommended to be measured within 60 minutes prior to the infusion, during the infusion if clinically indicated, and 30 minutes (±10 minutes) after the infusion.

Guidelines for tocilizumab dose modifications, treatment interruptions, or discontinuations due to toxicities are provided in Section A14–5.1.4.

A14–4.2.2.2 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle. Atezolizumab should be administered 2 hours after the completion of the tocilizumab infusion.

Administration of atezolizumab 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A14-2.

Table A14-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during the infusion and 30 (±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, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

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

Guidelines for medical management of infusion-related reactions for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section 430. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

A14–4.2.3 Stage 2 Treatment

Patients who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1 in the protocol body) will be given the option of receiving a different treatment combination during Stage 2, as outlined in Table A14-3, provided they meet eligibility criteria (see Section 4.1 in the protocol body). Patients who experience unacceptable toxicity related to tocilizumab may also be eligible to receive treatment during Stage 2, provided they meet eligibility criteria.

Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2

treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A14-3 Stage 2 Treatment Regimens Available for the Atezo+TCZ Arm

Study Treatment	Appendix
Atezo+EV	Appendix 9
Atezo+SG	Appendix 13

Atezo = atezolizumab; EV = enfortumab vedotin; SG = sacituzumab govitecan; TCZ = tocilizumab.

Refer to Appendix 13 for details specific to the Atezo+SG arm.

A14–4.3 CONCOMITANT THERAPY FOR ATEZO+TCZ ARM

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 study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A14–4.3.1 Cautionary Therapy for Atezo+TCZ Arm

A14–4.3.1.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α 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 6 for details).

A14–4.3.1.2 Drug Interactions with Tocilizumab

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., IL-6) during chronic inflammation. Therefore, it is expected that for molecules that

antagonize cytokine activity, such as the tocilizumab, the formation of CYP450 enzymes could be normalized. When starting or stopping therapy, patients taking medications that are individually dose adjusted and metabolized via CYP450, 3A4, 1A2, or 2C9 (e.g., atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporin, or benzodiazepines) should be monitored as doses may need to be adjusted to maintain therapeutic effect. Given its long elimination half-life, the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

A14–4.3.1.3 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 A14–4.3.2) may be used during the study at the discretion of the investigator.

A14–4.3.1.4 Non-Live Vaccines

Non-live vaccines are allowed during the course of the study. At this time, there is insufficient experience with SARS-CoV-2 vaccines to support concrete recommendations concerning the use of SARS-CoV-2 vaccines in patients receiving tocilizumab.

Because of the immunosuppressant nature of tocilizumab, the impact on immunogenicity of mRNA vaccines cannot be completely ruled out. Based on available information within the current labelling about vaccination, it is recommended that all patients, particularly pediatric or elderly patients, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating tocilizumab therapy. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

A14–4.3.2 Prohibited Therapy for Atezo+TCZ Arm

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, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2 in the protocol body), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances outlined in Section A14–4.3.3.
- Immunization with any live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab and tocilizumab, and for 5 months after the last dose of atezolizumab or tocilizumab.

- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin 2) are prohibited within 4 weeks or 5 half-lives of the drug, 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.

A14–4.3.3 Permitted Therapy for Atezo+TCZ Arm

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

- Oral contraceptives with a failure rate of < 1% per year (see Section A14–4.4)
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin at a stable dose)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section A14–4.3.2)
- 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
- Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  After 2 cycles of treatment, palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy.
- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator. See Appendix 6 for further information.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections A14–4.3.1 and A14–4.3.2) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-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 5).

A14–4.4 CONTRACEPTION REQUIREMENTS FOR ATEZO+TCZ ARM

Contraception requirements for women in the Atezo+TCZ arm are outlined below:

- Women of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during treatment and for 5 months after the last dose of study treatment.

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

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

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

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 60 days after the last dose of tocilizumab to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

A14–5 ASSESSMENT OF SAFETY FOR ATEZO+TCZ ARM

A14–5.1 SAFETY PLAN FOR ATEZO+TCZ ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and tocilizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A14–5.1.1, A14–5.1.2, and A14–5.1.3). Guidelines for the management of patients who experience specific adverse events are provided in Section A14–5.1.4.

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. Because of the potential for overlapping toxicities such as rash, increased liver function values, hypersensitivity, dyspnea, infections, IRRs, GI events, and hypothyroidism identified for atezolizumab and tocilizumab, special caution will be taken with a planned safety evaluation. Randomization to the Atezo+TCZ arm will be paused after the enrollment of 6 patients until all patients in that arm have completed a safety evaluation of 28 days. If the combination is sufficiently safe, the randomization will be resumed.

Administration of study treatment 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. Adverse events will be reported as described in Sections 5.2–5.6 in the protocol body.

A14–5.1.1 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, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). See Appendix 6 and Section 6 of the Atezolizumab Investigator's Brochure for detailed description of anticipated safety risks for atezolizumab.

A14–5.1.2 Risks Associated with Tocilizumab

Clinical experience to date focuses on the non-oncology disease setting. On the basis of the safety data from the tocilizumab prescribing information, adverse drug reactions include severe infection (bacterial, viral and fungal), complications of diverticulitis including gastrointestinal perforation, serious hypersensitivity reactions including anaphylaxis, neutropenia, and hepatoxicity. Important potential risks include elevated lipid levels and potential risk of cardiovascular and cerebrovascular events, demyelinating disorders, immunogenicity, malignancies, thrombocytopenia, and the potential risk of bleeding.

Refer to the Tocilizumab Investigator's Brochure for a detailed description of all anticipated risks for tocilizumab.

A14–5.1.3 Risks Associated with Combination Use of Atezolizumab and Tocilizumab

The adverse events of rash, hepatotoxicity/liver function test increased, hypersensitivity, dyspnea, infections, IRRs, GI events, and hypothyroidism are potential overlapping toxicities with combination use of atezolizumab and tocilizumab.

A14–5.1.4 Management of Patients Who Experience Adverse Events in Atezo+TCZ Arm

A14–5.1.4.1 Dose Modifications

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

Dose modification or discontinuation of tocilizumab is required for serious infections, anaphylaxis, serious hypersensitivity, GI perforations, demyelinating disorders, elevated liver enzymes, neutropenia, and thrombocytopenia. Guidelines are presented below. If a patient's dose is reduced because of a toxicity that subsequently resolves, the patient may resume treatment at the original dose at the discretion of the investigator. The Medical Monitor is available to advise as needed. The timing of efficacy or safety evaluations should not be affected by dose interruptions or reductions.

A14–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table A14-4). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over $\geq$1 month to $\leq$10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for $>$12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for $>$12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for $>$12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator.

The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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.

Tocilizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table A14-4). If tocilizumab is withheld for ≥12 weeks after event onset, the investigator will decide whether the patient should discontinue tocilizumab permanently. The Medical Monitor is available to advise as needed.

If atezolizumab is discontinued, tocilizumab should also be discontinued. If tocilizumab is discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section A14–4.2.2 for information on dose interruptions for reasons other than toxicity (e.g., surgical procedures).

A14–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 6 for atezolizumab-related adverse events and below for events related to tocilizumab treatment. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Toxicity Management for Tocilizumab

Opportunistic Infections and Serious Infections

- Investigators should exercise caution when considering the use of tocilizumab in patients with a history of recurring infection or with underlying conditions (e.g., diabetes) which may predispose patients to infections. Tocilizumab should not be administered to patients with active infection. The effects of tocilizumab on high-sensitivity CRP, neutrophils, and the signs and symptoms of infection should be considered when evaluating a patient for a potential infection.
- Vigilance for timely detection of serious infection is recommended for patients receiving tocilizumab, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reaction. Patients must be instructed to contact their physician immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.
- If a patient develops a serious infection, administration of tocilizumab is to be interrupted until the infection is controlled. The investigator should consider the benefit–risk before resuming treatment with tocilizumab.

Gastrointestinal Perforations

- Timely diagnosis and appropriate treatment may reduce the potential for complications of diverticulitis and thus reduce the risk of GI perforations. Therefore, patients should be made aware of the symptoms potentially indicative of diverticular disease, and they should be instructed to alert their healthcare provider as soon as possible if these symptoms arise. In patients with a history of symptomatic diverticulosis, diverticulitis, or other chronic lower GI conditions that might predispose to perforations, the clinician should consider the benefit–risk profile before using tocilizumab. Discontinuation of tocilizumab is recommended for patients who develop immune-mediated colitis on study and is required for patients who develop GI perforations.

Demyelinating Disorders

- The effect of treatment with tocilizumab on demyelinating disorders is not known; events have rarely been reported. Patients should be closely monitored for signs and symptoms potentially indicative of central demyelinating disorders. Physicians should exercise caution when considering the use of tocilizumab in patients with preexisting or recent-onset demyelinating disorders. Treatment with tocilizumab should be interrupted during assessment of a potential demyelination event and be resumed only if the balance of benefits and risks of continuing study drug is favorable.

Table A14-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+TCZ Arm

Event	Action to Be Taken
IRRs and CRS	• For atezolizumab-related IRRs and CRS, please follow guidelines for atezolizumab in Appendix 6. • For tocilizumab: If a patient has symptoms of anaphylaxis or serious hypersensitivity or requires an interruption of the study drug because of symptoms of anaphylaxis or hypersensitivity, administration of tocilizumab must be discontinued permanently. The patient should be treated according to the standard of care for management of the hypersensitivity reaction. Blood samples for the presence of anti-tocilizumab antibodies and pharmacokinetic or pharmacodynamic assessment should be obtained at the time of the event and 8 weeks after the final dose.
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue tocilizumab.
ALT/AST increased	
Grade 1 >ULN –3.0× ULN	• Continue atezolizumab, monitor LFTs until values resolve to within normal limits. • For persistent increases (≥2 consecutive assessments at least 1 month apart), reduce tocilizumab dose to 4 mg/kg or interrupt tocilizumab until ALT/AST have normalized. • For patients with elevated LFTs at screening, dose reduction is not needed unless the ALT/AST increase reaches Grade 2 in severity.
Grade 2 >3.0–5.0× ULN	• Follow guidelines for atezolizumab in Appendix 6. • Hold tocilizumab until <3× ULN and follow recommendations above for Grade 1. For persistent increases >3× ULN, permanently discontinue tocilizumab.
Grade 3 or 4 >5.0× ULN	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue tocilizumab.
Additional guidance	• Discontinuation of tocilizumab is recommended with ALT or AST elevation >3× ULN combined with at least one of the following: Total bilirubin >2× ULN INR >1.5 Presence of worsening fatigue, nausea, vomiting, fever, rash or eosinophilia If patient's liver function tests have not returned to normal or to the patient's baseline level within 6 months (or sooner if deemed necessary by the investigator), the investigator should consider referral to a specialist.

Atezo = atezolizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; LFT = liver function test; LLN = lower limit of normal; NCI CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; TCZ = tocilizumab; ULN = upper limit of normal.

Table A14-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+TCZ Arm (cont.)

Event	Action to Be Taken
Neutrophil count decreased	
Grade 1 or 2 >1000/mm^3–LLN	• Continue atezolizumab and tocilizumab.
Grade 3 <1000–500/mm^3	• Continue atezolizumab. • Hold tocilizumab until ANC>1000/mm^3; resume at 4 mg/kg and increase to 8 mg/kg as clinically appropriate.
Grade 4 <500/mm^3	• Permanently discontinue tocilizumab. • Atezolizumab may continue at the discretion of the investigator per medical judgment.
Platelet count decreased	
Grade 1 or 2 <LLN–50,000/mm^3	• Continue atezolizumab. • Hold tocilizumab until platelet count is >100,000/mm^3, resume at 4 mg/kg and increase to 8 mg/kg as clinically appropriate.
Grade 3 or 4 <50,000/mm^3	• Permanently discontinue tocilizumab. • Atezolizumab may be continued at the discretion of the investigator per medical judgment.
Tocilizumab-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab and tocilizumab.
Grade 3	• For the first occurrence of an adverse event, withhold tocilizumab until toxicity is Grade ≤2; tocilizumab may be resumed at the discretion of the investigator per medical judgment. • For the second occurrence of an adverse event, withhold tocilizumab until toxicity if Grade ≤1; tocilizumab may be resumed at the discretion of the investigator per medical judgment. • Continue atezolizumab.
Grade 4	• For the first occurrence of an adverse event, withhold atezolizumab and tocilizumab until toxicity is Grade ≤2 or discontinue at the discretion of the investigator. • For the second occurrence of an adverse event, withhold atezolizumab and tocilizumab until toxicity is Grade ≤2 or discontinue at the discretion of the investigator.

Atezo = atezolizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; LFT = liver function test; LLN = lower limit of normal; NCI CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; TCZ = tocilizumab; ULN = upper limit of normal.

Table A14-4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo+TCZ Arm (cont.)

Event	Action to Be Taken
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue tocilizumab.
Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Continue tocilizumab.
Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • If atezolizumab is discontinued, tocilizumab should also be discontinued.

Atezo = atezolizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; LFT = liver function test; LLN = lower limit of normal; NCI CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; TCZ = tocilizumab; ULN = upper limit of normal.

A14–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO+TCZ ARM (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 in the protocol body for reporting instructions). Adverse events of special interest for the Atezo+TCZ arm 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 in the protocol body)
- 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.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10 \times$ upper limit of normal
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis

- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, HLH, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, and optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade $\geq$2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Serious and/or medically significant infections
- Myocardial infarction/acute coronary syndrome
- GI perforations
- Malignancies
- Demyelinating disorders
- Stroke
- Serious and/or medically significant bleeding events
- Serious and/or medically significant hepatic events
- Myelitis
- Facial paresis

A14–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+TCZ ARM

A14–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of study treatment. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study 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 when updated information on the course and outcome of the pregnancy becomes available.

A14–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 60 days after the last dose of tocilizumab. 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. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to enfortumab vedotin. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A14–5.3.3 Abortions

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

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.

A14–5.3.4 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 in the protocol body).

A14–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+TCZ ARM

Table A14-5 Schedule of Activities for Atezo+TCZ Arm

	Stage 1 Screen [a] Day –28 to –1	Treatment Cycles (28-day cycles)				Stage 2 Screen [c] (see Appendix 7) or Treat Discon [d]	Follow-Up Q3M (±7 D)
		Cycle 1 [b]		Cycles ≥2			
		Day 1	Day 15 (±3 D)	Day 1 (±3 D)	Day 15 (±3 D)		
Informed consent	See Appendix 7.					x [e, f]	
Molecular profile of urothelial carcinoma (if available)		Whenever updated information becomes available					
Vital signs [g]		x	x	x	x	x	
Weight [h]		x		x		x	
Complete physical examination [i]						x	
Limited physical examination [j, h]		x	x	x	x		
ECOG Performance Status [h]		x		x		x	
ECG [k, h]		Perform as clinically indicated.				x [f]	
Hematology [l]		x [m]	x	x [m]	x	x [n]	
Chemistry [o]		x [m]	x	x [m]	x	x	
Coagulation (PT/INR and aPTT)						x [f, n]	
TSH, free T3 (or total T3), free T4 [p]		x [m, n]				x [n]	
HIV, HBV, and HCV testing						x [f, n]	
C-reactive protein		x		x		x [f, n]	
LDH						x [f, n]	
Pregnancy test [q]		x		x		x [n]	x [q]

Table A14-5 Schedule of Activities for Atezo+TCZ Arm (cont.)

	Stage 1 Screen [a] Day −28 to −1	Treatment Cycles (28-day cycles)				Stage 2 Screen [c] (see Appendix 7) or Treat Discon [d]	Follow-Up Q3M (±7 D)
		Cycle 1 [b]		Cycles ≥2			
		Day 1	Day 15 (±3 D)	Day 1 (±3 D)	Day 15 (±3 D)		
Urinalysis [r]	See Appendix 7.	x		x		x [f, l]	
Serum autoantibody sample [s]		Perform if a patient experiences a suspected immune-mediated adverse event.					
PK samples		Refer to Table A14-6.					
ADA samples		Refer to Table A14-6.					
Biomarker samples		Refer to Table A14-6.					
Blood sample for RBR (optional) [t]		x					
Tumor biopsy		x [u]					
Tumor biopsy (optional)		x [v]					
Tumor response assessments		x [w, x, y]					
Concomitant medications [z]		x	x	x	x	x	
Adverse events [aa]		x	x	x	x	x	x
Atezolizumab administration [bb, cc]		x	x	x	x		
Tocilizumab administration [cc, dd]		x		x			
Survival follow-up and anti-cancer treatment							x [ee]

ADA = anti-drug antibody; Atezo=atezolizumab; CT = computed tomography; D = day; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EV = enfortumab vedotin; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; PK = pharmacokinetic; Q3M = every 3 months; Q4W = every 4 weeks; RBR = Research Biosample Repository; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; TB = tuberculosis; TCZ = tocilizumab; Treat = treatment; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Patients who fail their first screening for study eligibility (Stage 1) may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the initiation of study treatment may be used; such tests do not need to be repeated for screening or re-screening.

[b] Treatment must be initiated no later than 7 days after treatment assignment.

Table A14-5 Schedule of Activities for Atezo+TCZ Arm (cont.)

[c] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 in protocol body for details) or unacceptable toxicity may be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.2 in protocol body) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[d] Patients will return to clinic for a Stage 2 screening or treatment discontinuation visit <30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of Stage 2 entry status. Patients who do not enter Stage 2 or who have discontinued Stage 2 treatment will then undergo follow-up assessments.

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[f] Assessments to be performed only for patients undergoing Stage 2 screening.

[g] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, 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. 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.

[h] Assessment may be performed within 24 hours prior to dosing during the treatment period.

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

[j] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] ECG recordings will be obtained during screening. It is recommended that patients 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, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[m] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

[n] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

Table A14-5 Schedule of Activities for Atezo+TCZ Arm (cont.)

[o] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide (if considered standard of care in the region), *serum troponin (at baseline, if considered standard of care/required per local clinical practice, and as clinically indicated during the study),* glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. For U.K. patients, amylase and lipase must be included on Day 1 of each treatment cycle.

[p] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[q] All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum 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. During follow-up, pregnancy tests will be performed at 3 and 6 months. If a pregnancy test was performed within 96 hours prior to Day 1 of Cycle 1, it does not have to be repeated.

[r] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[s] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody.

[t] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[u] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 in protocol body for tissue sample requirements.

[v] Consenting patients may undergo optional tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[w] Patients will undergo tumor assessments at baseline, every 9 weeks (±1 week) for the first 54 weeks following treatment initiation, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until loss of clinical benefit as determined by the investigator (see Section 3.1.1 in protocol body for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new, non–protocol-specified anti-cancer therapy.

[x] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[y] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

Table A14-5 Schedule of Activities for Atezo+TCZ Arm (cont.)

[z] Includes 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 study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[aa] 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.

[bb] Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle. The initial infusion of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[cc] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details).

[dd] Tocilizumab will be administered by IV infusion at a dose of 8 mg/kg Q4W on Day 1 of each 28-day cycle. Each patient will receive 8 mg/kg tocilizumab (or 4 mg/kg in certain circumstances, described in Section A14–5.1.4.3), with a maximum dose of 800 mg tocilizumab (for patients weighing >100 kg).

[ee] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a 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. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table A14-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+TCZ Arm: Preliminary and Expansion Phases

Visit	Time	Sample
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tocilizumab PK (serum) • Tocilizumab ADA (serum) • IL-6 (serum) • sIL-6R (serum) • Biomarker (plasma, serum, and PBMC)
	30 (± 10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
	End of tocilizumab infusion	• Tocilizumab PK (serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tocilizumab PK (serum) • Tocilizumab ADA (serum) • IL-6 (serum) • sIL-6R (serum) • Biomarker (plasma, serum, and PBMC)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tocilizumab PK (serum) • Tocilizumab ADA (serum) • IL-6 (serum) • sIL-6R (serum) • Biomarker (plasma and serum)
Day 1 of Cycle 6	Prior to study treatment	• Tocilizumab PK (serum) • Tocilizumab ADA and sIL-6R (serum)
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tocilizumab PK (serum) • Tocilizumab ADA (serum) • IL-6 (serum) • sIL-6R (serum) • Biomarker (plasma and serum)

ADA = anti-drug antibody; Atezo = atezolizumab; PBMC = peripheral blood mononuclear cell; IL-6 = interleukin 6; PK = pharmacokinetic; sIL-6R = soluble interleukin 6 receptor; TCZ = tocilizumab.

Table A14-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+TCZ Arm: Preliminary and Expansion Phases (cont.)

Visit	Time	Sample
Day 1 of Cycle 10	Prior to study treatment	• Tocilizumab PK (serum) • Tocilizumab ADA (serum) • sIL-6R (serum)
Day 1 of Cycles 12, 14, 16 and every fourth cycle after Cycle 16	Prior to study treatment	• Atezolizumab PK (serum) (Cycles 12 and 16 Atezolizumab PK (serum) (Cycles 12 and 16 only) • Atezolizumab ADA (serum) (Cycles 12 and 16 only) • Tocilizumab PK (serum) • Tocilizumab ADA (serum) • IL-6 (serum) (Cycles 12 and 16 only) • sIL-6R (serum)
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tocilizumab PK (serum) • Tocilizumab ADA (serum) • sIL-6R (serum) • Biomarker (plasma and serum)
Event driven: for cases of anaphylaxis, serious hypersensitivity, or withdrawal due to anaphylaxis or serious hypersensitivity	At time of event and at least 8 weeks after the event	• Tocilizumab PK (serum) • Tocilizumab ADA (serum) • sIL-6R (serum)

ADA = anti-drug antibody; Atezo = atezolizumab; IL-6 = interleukin 6; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; sIL-6R = soluble interleukin 6 receptor; TCZ = tocilizumab.

Note: On the basis of emerging safety 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. On the basis of emerging biomarker data, the number of biomarker samples may be reduced, or sample collection may cease altogether.

A14–7 REFERENCES

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.

Butte MJ, Keir ME, Phamduy TB, et al. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Chang Q, Daly L, Bromberg J. The IL-6 feed-forward loop: A driver of tumorigenesis. Semin Immunol 2014;26:48–53.

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.

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.

De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC Study 30986. J Clin Oncol 2012;30:191–9.

Dijkgraaf EM, Santegoets SJ, Reyners AK, et al. A phase 1 trial combining carboplatin/doxorubicin with tocilizumab, an anti-IL-6R monoclonal antibody, and interferon-$\alpha 2\beta$ in patients with recurrent epithelial ovarian cancer. Ann Oncol 2015;26:2141–9.

Fehrenbacher L, Spira A, Ballinger M, et al. 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.

Fisher DT, Appenheimer MM, Evans SS, et al. The two faces of IL-6 in the tumor microenvironment. Semin Immunol 2014;26:38–47.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.

Mace TA, Shakya R, Pitarresi JR, et al. IL-6 and PD-L1 antibody blockade combination therapy reduces tumor progression in murine model of pancreatic cancer. Gut 2016; epub ahead of print: doi: 10.1136/gutjnl-2016-311585.

Rose-John S, Scheller J, Elson G, et al. Interleukin-6 biology is coordinated by membrane-bound and soluble receptors. J Leukoc Biol 2006;80:227–36.

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.

Scheller J, Chalaris A, Schmidt-Arras D, et al.. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta 2011;1813:878–88.

Tecentriq® (atezolizumab) Summary of Product Characteristics, Genentech.

Tecentriq® (atezolizumab) U.S. Package Insert, Genentech.

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.

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 15
Study Details Specific to Atezo+RO7122290 (FAP-4-1BBL) Arm

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A15–1 BACKGROUND ON ATEZO+RO7122290 ARM

A15–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (Atezo) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that targets programmed death-ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed death-1 (PD-1) and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. 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 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 cancer patients 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 (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, hypophysitis, myocarditis, and myasthenia gravis, have been observed (see Appendix 6). To date, these events have been manageable with treatment.

Atezolizumab (Tecentriq®) is approved for the treatment of urothelial carcinoma (UC), non–small-cell lung cancer (NSCLC), 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.

A15–1.2 BACKGROUND ON RO7122290

RO7122290 is a fibroblast activation protein-α-targeted split 4-1BBL-ligand bispecific antibody-like fusion protein (FAP-4-1BBL). FAP is found on cancer associated stroma cells in >90% of epithelial malignancies, whereas 4-1BB is a co-stimulatory receptor (signal 2) expressed on T cells activated by prior T-cell receptor (TCR) engagement (signal 1) within T-cell inflamed tumors. As a consequence, the anti-tumor activity of RO7122290 will likely be restricted to FAP+ and T-cell inflamed tumor types, such as NSCLC, head and neck squamous cell carcinoma (HNSCC), urinary bladder cancer (uBC), renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), colorectal cancer microsatellite instability-high (CRC-MSI^{high}), triple-negative breast cancer (TNBC), and advanced thymoma/thymus cancer.

In nonclinical studies, RO7122290 was shown to induce potent co-stimulation of T cells or tumor-infiltrating T cells, which was dependent on cross-linking by FAP-expressing

cells/fibroblasts. In vivo, when combined with PD-L1 checkpoint blockade, a murine-specific FAP-4–1BB agonistic surrogate antibody mediated superior efficacy compared to the respective monotherapies in a syngeneic mouse model.

By providing co-stimulation to activated immune cells only in the FAP-positive tumor microenvironment, RO7122290 can improve anti-tumor immune cell function, durability, and longevity without causing immune pathology, which may translate into increased clinical benefit for patients.

RO7122290 is currently being evaluated as monotherapy and in combination with atezolizumab in patients with solid tumors including TNBC, mesothelioma, and thymoma/thymus cancer.

A15–2 RATIONALE FOR ATEZO+RO7122290 ARM

A15–2.1 THE PD-L1 PATHWAY

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).

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.

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 NSCLC, urothelial carcinoma (UC), RCC, melanoma, colorectal cancer, HNSCC, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors, have made a significant impact on the treatment of patients with UC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A15–2.2 TARGETING FAP AND 4-1BB

4-1BB (CD137) is a co-stimulatory receptor expressed on a variety of cells of the immune system, particularly on CD8+ T and natural killer (NK) cells. Signaling through 4-1BB enhances survival, proliferation and effector functions. 4-1BB stimulation is only enabled after FAP-mediated cross-linking of RO7122290. To date, 4-1BB (CD137) agonist monoclonal antibodies, such as urelumab or utomilumab, have entered clinical development but have demonstrated only limited clinical activity when used as single agent. Objective responses (OR) have been observed in limited tumor types such as malignant melanoma and non-Hodgkin's lymphoma. Additionally, urelumab is associated with dose-limiting toxicity ([DLT] hepatotoxicity) that is likely a consequence of FcγR binding (Segal et al. 2017).

FAP, also known as separase, is a dimeric Type II transmembrane glycoprotein with proteolytic activity and has been identified as a promising target for tumor treatment (Hamson et al. 2014). FAP is found on cancer-associated stroma cells in $>$ 90% of human epithelial malignancies, particularly on the cell surface of tumor stromal fibroblasts and activated cancer-associated fibroblasts and pericytes. Immunohistochemical analyses confirmed high FAP expression in the stroma of various tumors, including major tumor entities such as breast, colorectal, lung, pancreatic, gastric, head and neck, kidney cancer and mesothelioma (RO7122290 Investigator's Brochure) and urothelial cancer (Mezheyeuski et al. 2020).

A15–2.3 BENEFIT-RISK ASSESSMENT

Immunotherapy in metastatic UC (mUC) has shown significant promise. Results from the pivotal multicenter Phase II Study GO29293 (IMvigor210) and Phase III Study GO29294 (IMvigor211) showed that durable responses were achieved in second-line post-platinum patients with mUC who received atezolizumab monotherapy (Rosenberg et al. 2016; Powles et al. 2018). In IMvigor210 Cohort 2, the objective response rate (ORR) in all patients was 15%, and responses were seen in all PD-L1 immunochemistry subgroups and the median survival in all patients was 7.9 months. Importantly, atezolizumab was well tolerated, with a low rate of treatment-related Grade 3 or 4 adverse events and discontinuations due to adverse events (Rosenberg et al. 2016). In IMvigor211, as of 13 March 2017, a median overall survival of 8.6 months, an ORR of 13.4% (10.5, 16.9), and a median duration of response (DOR) of 21.7 months was observed in the intent-to-treat (ITT) population. Atezolizumab continued to be well tolerated with a lower rate of treatment-related Grade 3 or 4 adverse events and fewer discontinuations due to adverse events than chemotherapy.

Despite the promise of single-agent checkpoint inhibition, only a small percentage of patients experience benefit, highlighting the need for combinations. One potential mechanism for converting otherwise resistant cancers is manipulation of the phagocytosis checkpoint system via anti-CD47 antibodies, resulting in macrophage mediated phagocytosis and cross-presentation of tumor antigens to T cells with subsequent proliferation of CD8 cells.

Benefit from CIT with checkpoint inhibitor (CPI) monoclonal antibodies such as anti-PD-1/PD-L1 (atezolizumab) is predominantly observed in a subset of patients with inflamed tumor phenotypes. To broaden the response rate (RR) of CPI therapy, especially in non-inflamed tumors, agonistic and direct immune cell-activating compounds are needed to generate a pro-inflammatory environment and sustain immune responses. In this consideration, RO7122290, an antibody fusion protein carrying a trimeric 4-1BBL and a FAP binding site, is designed with a main objective to co-stimulate T cells.

In addition to its stimulatory effects on immune effector cells at the site of disease, RO7122290 may broaden and further enhance the quality, depth, and duration of anti-PD-1/PD-L1 antibody effects specifically in tumor infiltrating lymphocytes. Those immune-stimulatory effects of RO7122290 are expected to occur in all patients independent of the type of prior treatment. Combinations of 4-1BB agonists with PD-1/PD-L1 blockade (with atezolizumab) aim to provide complementary effects in terms of anti-tumor immune responses. Indeed, co-stimulation of T cells by 4-1BB may increase the expression of PD-1 while treatment with anti-PD-1 antibodies may be insufficient to maximize T-cell-mediated anti-tumor responses. Nonclinical models have shown to produce additive or synergistic anti-tumor activity in solid tumor models, as suggested by the PD-1 and 4-1BB co-expression and functional interaction demonstrated in human tumor-infiltrating lymphocytes and mouse models (Chen et al. 2015; Wei et al. 2014; Ascierto et al. 2010; Gros et al. 2014; Palazón et al. 2012; Azpilikueta et al. 2016; Pérez-Ruiz et al. 2017).

Based on currently available nonclinical and preliminary clinical data for RO7122290 ($n = 147$) and the mechanism of action (MoA) from clinical data from other untargeted 4-1BB agonists, RO7122290 is not anticipated to trigger a severe systemic immune response as single agent because it requires target-dependent cross-linking for activity and has abrogated FcγR-binding. In addition, the FAP binding moiety of RO7122290 is expected to result in accumulation/retention of the compound in the tumor microenvironment. Thus, the abrogated FcγR-binding along with the FAP-targeted technology of RO7122290 is expected to minimize the risk for systemic or off-tumor-on-target stimulation of immune effector cells and to contribute to accumulation in the local tumor microenvironment compared with untargeted 4-1BB agonists.

In Study BP40087, the safety and toxicity profile of RO7122290 is being established in patients with solids tumors, with escalating doses of RO7122290 tested alone or in combination with atezolizumab. Results from this study were used to select the recommended dose for this study. Based on the available clinical data from Study BP40087 Part A (single agent) and Part B (combination with atezolizumab), the preliminary safety profile of RO7122290 alone and in combination with atezolizumab is considered acceptable, and manageable, including Grade 3 or 4 immune-mediated adverse events consistent with the MoA (RO7122290 Investigator's Brochure).

More detailed information about expected benefits in relation to potential risks and adverse events of RO7122290 treatment is provided in the RO7122290 Investigator's Brochure.

Considering the high therapeutic need in the second-line setting for patients with mUC for tolerable and effective treatment, and the compelling nonclinical data and anticipated safety profile for the combination of atezolizumab and RO7122290, the benefit–risk assessment favors moving forward with the evaluation of the combination in patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen.

For more information on the benefit–risk assessment, please refer to Section 1.4.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.5.

A15–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+RO7122290 ARM

A15–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W; 1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert; Tecentriq Summary of Product Characteristics). Anti-tumor activity has been observed across doses ranging from 1 to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no DLTs 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 pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A15–3.2 RATIONALE FOR RO7122290 DOSE AND SCHEDULE

In Study BP40087, 147 patients have been exposed to RO7122290 as single agent or in combination with atezolizumab, across a dose range of 5 to 2000 mg QW without identification of maximum tolerated dose (MTD). Clinical effect parameters collected from the dose-escalation phase of the study including 115 patients, in conjunction with preclinical considerations have been employed to determine the biologically efficacious dose (BED) of RO7122290 as the recommended dose in combination with atezolizumab. Since the 4-1BB co-stimulation of RO7122290 is strictly dependent on FAP crosslinking, the BED dose aims around the maximum "trimer" concentration, built up by the formation of FAP/RO7122290/4-1BB complexes.







A15–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+RO7122290 ARM

A15–4.1 TREATMENT IN ATEZO+RO7122290 ARM

A15–4.1.1 Formulation, Packaging, and Handling

A15–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

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

A15–4.1.1.2 RO7122290

[redacted]

For information on the formulation and handling of RO7122290, see the pharmacy manual and the RO7122290 Investigator's Brochure.

A15–4.1.2 Dosage, Administration, and Compliance

Treatment in the Atezo+RO7122290 arm will be administered as outlined in Table A15-1.

Patients in the Atezo+RO7122290 arm will receive treatment until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 in the protocol body for details). Treatment must be initiated no later than 7 days after treatment assignment.

Table A15-1 Treatment Regimen for Atezo+RO7122290 Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • RO7122290 [redacted]

Atezo = atezolizumab.

Note: Atezolizumab will be administered [redacted]. RO7122290 will be administered [redacted]. For subsequent administrations of atezolizumab, the patient should be observed for at least one hour [redacted].

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab or RO7122290 are available.

A15–4.1.2.1 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle [redacted].

Administration of atezolizumab 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A15-2.

Table A15-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during the infusion and 30 (±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, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

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

Guidelines for medical management of infusion-reaction responses (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A15-5.1.4. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

A15–4.1.2.2 RO7122290 Administration

RO7122290 will be administered as described in the pharmacy manual. [redacted] The patient should be observed for at least 2 hours after the first administration of atezolizumab [redacted]



During infusion, vital signs (including, if possible, supine diastolic and systolic blood pressure, pulse rate, and temperature) must be monitored as described in Table A15-6. Vital signs during the infusion are not required to be captured in the eCRF, unless abnormalities are observed.

At the end of the first infusion, the IV line should remain in place for 2 hours. If no infusion-related symptoms occur during this time, the infusion line may be removed. For subsequent infusions and if no IRR has been reported, the IV line should remain in place for 30 minutes from the end of the infusion. If no adverse events occur during the 30 minutes, the infusion line may be removed. If feasible, the line for drawing blood for PK samples (opposite extremity to the one with the infusion line) will remain in place until the 24-hour sample is taken.

A15–4.1.3 Stage 2 Treatment

Patients in the mUC Cohort who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1 in the protocol body) may be given the option of receiving a different treatment combination during Stage 2, as outlined in Table A15-3, provided they meet eligibility criteria (see Section 4.1 in the protocol body). Patients who

experience unacceptable toxicity related to RO7122290 may also be eligible to receive treatment during Stage 2, provided they meet eligibility criteria.

Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A15-3 Stage 2 Treatment Regimens Available for the Atezo+RO712290 Arm

Study Treatment	Appendix
Atezo + SG	Appendix 13

Atezo = atezolizumab; SG = sacituzumab govitecan.

Refer to Appendix 13 for details specific to the Atezo+SG arm.

A15–4.2 CONCOMITANT THERAPY FOR ATEZO+RO7122290 ARM

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 study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A15–4.2.1 Cautionary Therapy for Atezo+RO7122290 Arm

A15–4.2.1.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor-alpha (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α 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 (see Appendix 6 for details) or injection-site or systemic reactions associated with RO7122290 (see Table A15-4).

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 A15-4.2.3) may be used during the study at the discretion of the investigator.

A15–4.2.1.2 Non-Live Vaccines

Non-live vaccines are allowed during the course of the study. The efficacy and safety of inactivated vaccines in patients receiving treatment with RO7122290 alone and in combination with atezolizumab is unknown. Ultimately, for each patient, the decision to receive a non-live vaccine will be a benefit–risk discussion between the participant and the treating physician. This decision will depend on a number of factors, such as the type of non-live vaccine, the potential risk of infection, the underlying disease, and age of the participant.

There are no data on potential interactions of non-live vaccines with RO7122290 alone and/or in combination with atezolizumab. In the absence of evidence-based recommendations, it would be advisable to allow enough time between the administration of the non-live vaccine and that of study drug(s) in order to minimize the potential confounding effect of the non-live vaccine. In particular, vaccination should be avoided on the day of study drug administration, and on days close to study drug administration. In addition, it is recommended that the non-live vaccine not be administered during the first cycle for fixed dose regimens. Adverse events that may overlap with any potential vaccine-related toxicities should have resolved before patients receive non-live vaccines. The timing of administration of a non-live vaccine during the course of the study should be documented if it occurs. The Medical Monitor is available to advise as needed.

A15–4.2.2 Prohibited Therapy for Atezo+RO7122290 Arm

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, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2 in the protocol body), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances outlined in Section A15–4.2.3.

- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the final dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin 2) are prohibited within 4 weeks or 5 half-lives of the drug, 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.
- Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs, due to its potential for causing agranulocytosis.

A15–4.2.3 Permitted Therapy for Atezo+RO7122290 Arm

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

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin at a stable dose)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section A15–4.2.2)
- 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
- Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  After 2 cycles of treatment, palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy.
- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed.

Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator. See Appendix 6 for further information.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections A15–4.2.1 and A15–4.2.2) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-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 5).

A15–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO+RO7122290 ARM

Contraception requirements for women and men in the Atezo+RO7122290 arm are outlined below:

- Women of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use contraception, 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 and 2 months after the final dose of RO7122290. Given that patients will be taking atezo+RO7122290 concurrently, 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 treatments.

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

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

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

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 2 months after the final dose of RO7122290 to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

A15–5 ASSESSMENT OF SAFETY FOR ATEZO+RO7122290 ARM

A15–5.1 SAFETY PLAN FOR ATEZO+RO7122290 ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and RO7122290 in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A15-5.1.1, A15-5.1.2, and A15-5.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A15-5.1.4.

Administration of study treatment 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. Adverse events will be reported as described in Sections 5.2–5.6 in the protocol body.

A15–5.1.1 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, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). See Appendix 6

and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A15–5.1.2 Risks Associated with RO7122290

The clinical experience of RO7122290 is limited. The following are classified as potential risks for RO7122290: IRRs, cytokine release syndrome (CRS), anaphylaxis, immune-mediated adverse events, immunogenicity, hepatotoxicity, tissue inflammation, disruption of vulnerable atherosclerotic plaques, impaired wound healing, cytopenias and infections, skin and subcutaneous tissue disorders, and tumor inflammation and associated adverse events.

A15–5.1.2.1 Potential Risk of Disruption of Vulnerable Atherosclerotic

There is a potential risk that RO7122290 may promote the disruption of vulnerable atherosclerotic plaques. Several lines of evidence suggest that T cells are activated in atherosclerosis, and that 4-1BB/4-1BBL signals have pro-atherogenic roles. Indeed, atherosclerotic arteries express significantly more 4-1BB than normal arteries, and serum levels of soluble 4-1BB are increased in acute coronary syndrome patients (Olofsson et al. 2008; Antunes et al. 2012). Experiments in a mouse model of atherosclerosis showed that treatment with an agonistic anti-4-1BB monoclonal antibody increased the development of atherosclerosis, with high levels of infiltrating T cells and inflammatory cytokines detected in atherosclerotic plaques (Olofsson et al. 2008). FAP has been shown to associate with human thin-cap fiboratheroma and to contribute to type I collagen breakdown in fibrous caps (Brokopp et al. 2011).

To date, no vascular adverse events have been associated with the use of RO7122290 in Study BP40087.

Patients who developed a clinically significant cardiovascular or cerebrovascular disease within six months patients prior to study treatment initiation will be excluded from the study, and patients will be closely monitored throughout the study for the potential development of vascular adverse events. ECGs will be performed at screening, on day 1 of each treatment cycle, and at treatment discontinuation, in addition to a close monitoring of vital signs throughout the study.

A15–5.1.2.2 Potential Risk of Impaired Wound Healing

RO7122290 may potentially impair wound healing. Indeed, FAP expression has been observed in the activated fibroblast compartment of healing wounds (Garin-Chesa et al. 1990). However, clinical studies with sibrotuzumab have not disclosed evidence for delayed wound healing (Scott et al. 2003; Virmani et al. 2006). The FAP binding moiety 4B9 does not inhibit FAP protease activity, and so far there has been no evidence of issues with wound healing in pre-clinical experiments and clinical trials across the Roche FAP platform.

After a major surgical procedure, patients should wait until wounds are fully healed before initiating treatment with RO7122290 and not undergo elective major surgical procedures during significant exposure to RO7122290.

A15–5.1.2.3 Tumor Inflammation and Associated Adverse Events

There is a potential risk that administration of RO7122290 in combination with atezolizumab induces tumor inflammation and flare. Indeed, co-stimulation of activated T-cells through 4-1BB signaling may exacerbate tumor inflammation when present, and significantly strengthen the immune activation by atezolizumab when co-administered, potentially resulting in tumor enlargement and associated adverse events. Depending on tumor anatomic location, events associated with tumor enlargement may potentially result in mass effects on vital structures, including airways, major blood vessels, and/or major organs. Further medical and/or surgical management may be necessary (e.g., anti-inflammatory agents, airway management, decompression, prolonged hospitalization). Patients with tumors involving critical anatomic locations should be closely monitored for tumor inflammation, and prospective consideration for preventive or interventional measures may need to be considered or planned prior to dosing.

To date, two serious and two non-serious treatement-related events of tumor inflammation have been reported in patients treated with RO7122290 in Study BP40087.

Guidelines for the management of tumor inflammation will be provided in the protocol.

For the complete safety information associated with RO7122290. Please refer to RO7122290 Investigator's Brochure.

A15–5.1.3 Risks Associated with Combination Use of Atezolizumab and RO7122290

IRRs/CRS, exaggerated immune cell activation (leading to immune-mediated adverse events associated with atezolizumab [see Section A15–5.1.1], including but not limited to pneumonitis, colitis, and immune-mediated hepatitis), hepatotoxicity, thrombocytopenia, skin disorders, and tumor inflammation and associated adverse events represent the main potential overlapping toxicities when RO7122290 is combined with atezolizumab. Refer to the RO7122290 Investigator's Brochure for a detailed description of the potential risks for RO7122290.

A15–5.1.4 Management of Patients Who Experience Adverse Events in Atezo+RO7122290 Arm

A15–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab in this study. The dose of RO7122290 may be decreased to [redacted] at the investigator's discretion if considered in the best interest of the participant. The Medical Monitor is available to advise as needed (see Section A15-4.1.2.2).

A15–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table A15-4). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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.

RO7122290 may be temporarily suspended in patients who experience toxicity considered to be related to study drug. Treatment may be resumed at the investigator's discretion. The Medical Monitor is available to advise as needed. RO7122290 may be suspended for reasons other than toxicity (e.g., surgical procedures).

If, in the judgment of the investigator, the participant is likely to derive clinical benefit from RO7122290 after a hold of more than 2 cycles (42 days), RO7122290 may be re-started. The Medical Monitor is available to advise as needed. If atezolizumab is discontinued, RO7122290 should also be discontinued and vice versa.

Refer to Section A15-4.1.2 for information on dose interruptions for reasons other than toxicity.

A15–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience adverse events associated with RO7122290 are provided below. For the management of adverse events associated with atezolizumab, see Appendix 6 and the Atezolizumab Investigator's Brochure. Due to their mode of action, both RO7122290 and atezolizumab may trigger the occurrence of immune-mediated adverse events; therefore, management guidelines for immune-mediated adverse events associated with atezolizumab (Appendix 6), are also recommended for the combination of RO7122290 with atezolizumab.
For anaphylaxis precautions, see Appendix 5. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases. For cases in which management guidelines are not covered in this protocol, in the Atezolizumab Investigator's Brochure, or the RO7122290 Investigator's Brochure, patients should be managed as deemed appropriate by the investigator according to best medical judgment and local practice.

A15–5.1.4.4 Infusion-Related Reactions/Cytokine Release Syndrome

Given that IRRs may be indistinguishable from CRS based on symptomatology, single-treatment management guidelines are being recommended for both IRRs and CRS occurring during or after infusion of RO7122290. The approach to have single-treatment management guidelines for IRRs and CRS will continue to be reviewed as additional safety data accumulate. Guidelines for the management of IRRs and CRS considered related to RO7122290 are provided in Table A15-4.

Table A15-4 Management of IRR and CRS Related to RO7122290

CRS Grade [a]	Guidance
Grade 1 Fever [b] ≥ 38°C	• If RO7122290 infusion is ongoing, slow infusion to ≤ 50% or interrupt infusion. • Symptomatic treatment and supportive care. • Monitor fluid balance and administer IV fluids as clinically indicated. • At next cycle administer pre-medications that may include antihistamine, antipyretics/NSAIDS, antiemetic, and corticosteroids.
Grade 2 Fever [b] ≥ 38°C with hypotension not requiring vasopressors and/or [c] hypoxia requiring low-flow oxygen by nasal cannula or blow by	• Follow all Grade 1 recommendations. • Hold further RO7122290 treatment until symptoms completely resolved. • At the restart of the infusion, slow down the rate of infusion to 25% of original rate. • If event occurred during infusion, and symptoms recur with the same or greater severity following interruption of RO7122290 infusion, the infusion must be stopped immediately. Consider managing as a Grade 3 event. No further RO7122290 will be administered for the cycle. • Monitor cardiac and other organ functions closely. • Hemodynamic support as indicated and oxygen for hypoxia. • Admit to ICU as appropriate. • Consider administering a single dose of tocilizumab IV 8 mg/kg. [c] If no improvement within 24 hours: • Notify Medical Monitor. • Administer IV corticosteroids (e.g., methylprednisolone [2 mg/kg/day] or dexamethasone 10 mg if neurologic symptoms are present). Additional monitoring and evaluation: • Consider 24-hour hospitalization. • Work up for organ functions (e.g., liver, cardiac) based on clinical assessment of the investigator. • May receive RO7122290 in next cycle if symptoms resolve to Grade ≤ 1 upon consultation with the Medical Monitor including considerations for dose reduction and/or reduction of infusion rate at the next administration. • At next cycle administer pre-medications that may include antihistamine, antipyretics/NSAIDS, antiemetic, and corticosteroids.

Table A15-4 Management of IRR and CRS Related to RO7122290 (cont.)

CRS Grade [a]	Guidance
Grade 3 Fever [b] ≥38°C Fever [b] ≥38°C with hypotension requiring a vasopressor (with or without) vasopressin) and/or [c] hypoxia [d] requiring high flow oxygen by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• If RO7122290 infusion is ongoing, stop infusion immediately • No further RO7122290 will be administered for the cycle • Cardiopulmonary and organ function monitoring in ICU • Closely monitor and maintain fluid balance; and other supportive care as clinically indicated • Vasopressor support for hypotension with high and repeated doses if required • Notify Medical Monitor • Initiate IV corticosteroids (e.g., methylprednisolone [2 mg/kg/day] or dexamethasone 10 mg if neurologic symptoms are present) • Administer tocilizumab 8 mg/kg IV • If no clinical improvement within 24 hours: repeat dose of tocilizumab 8 mg/kg • Additional monitoring and evaluation: • Hospitalize patient for 24 hours • Work up for organ functions (e.g., liver, cardiac) based on clinical assessment of the investigator • At next cycle administer pre-medications that may include antihistamine, antipyretics/NSAIDS, antiemetic, and corticosteroids; consider a lower infusion rate.
Grade 4 Fever [b] ≥38°C with hypotension requiring multiple vasopressors (excluding vasopressin) and/or [c] hypoxia requiring oxygen by positive pressure ventilation (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Follow all Grade 3 guidelines. • Permanently discontinue RO7122290.

Table A15-4 Management of IRR and CRS Related to RO7122290 (cont.)

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; ICU = intensive care unit; IRR = infusion-related reaction; NSAID = non-steroidal anti-inflammatory drug.

[a] Grading per ASTCT consensus grading (Lee et al. 2019).

[b] Fever is defined as temperature ≥ 38°C, not attributable to any other cause. In patients who develop CRS and then receive antipyretic or anti-cytokine therapy (e.g., tocilizumab or steroids), fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[c] CRS grade is determined by the more severe event: hypotension or hypoxia, not attributable to any other cause. Isolated hypoxia (without hemodynamic instability) requiring oxygen support in a patient with tumor (primary or metastatic) in the lung should be managed as per management guidelines for pulmonary events, including pneumonitis; refer to Appendix 6 for details.

[d] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute, and may include blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

[e] For the schedule of activities for tocilizumab, refer to Appendix 14; doses exceeding 800 mg per infusion are not recommended.

A15–5.1.4.5 Tumor Inflammation and Associated Adverse Events

For information regarding the potential risk of tumor inflammation and associated adverse events, refer to the RO7122290 Investigator's Brochure.

Guidelines for the management of suspected tumor inflammation are provided in Table A15-5.

If corticosteroids are administered, taper before restarting treatment. In case of concurrent respiratory and other organ toxicities, follow the management recommendations for respiratory toxicities.

Table A15-5 Management of Suspected Tumor Inflammation

Event	Initial Management Recommendation	Action to be Taken with RO7122290
Respiratory toxicities Supportive measures, e.g., oxygen support and intubation, as indicated.		
Grade 1	Monitor participant closely.	Continue treatment.
Grade 2	Monitor participant closely. If no resolution to Grade ≤ 1 within 48 hours, administer 1 mg/kg/day of IV methylprednisolone or equivalent followed by tapering with oral steroids until Grade ≤ 1.	Hold until resolution to Grade ≤ 1.
Grade 3/4	Administer 2 mg/kg/day of IV methylprednisolone or equivalent followed by tapering with oral steroids until resolution to Grade 1 or baseline. Ensure participant access to an intensive care unit is available	Hold until resolution to Grade ≤ 1. Consider permanent discontinuation.
Toxicities in other organs systems		
Grade 1 or 2	Monitor participant closely	Continue if Grade 1 event (for Grade 2 events, hold until resolution to Grade 1).
Grade 3	Administer 1 mg/kg/day of IV methylprednisolone or equivalent followed by tapering with oral steroids until Grade 1 or baseline (consider escalating next day to 2 mg/kg/day if no improvement, or escalate to 2 mg/kg directly if event occurs during prophylactic treatment with steroids). Ensure participant access to an intensive care unit is available.	Hold until resolution to Grade ≤ 1. For Grade ≥ 3 toxicity and duration ≥ 5 days permanent discontinuation (including liver enzyme elevations). Exceptions may be warranted depending on the specific benefit–risk profile of the participant. The Medical Monitor is available to advise as needed.
Grade 4	Administer 2 mg/kg/day of IV methylprednisolone or equivalent until Grade 1 or better. Ensure participant access to an intensive care unit is available.	

A15–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO+RO7122290 ARM (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 in the protocol body for reporting instructions). Adverse events of special interest for the Atezo+RO7122290 arm 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 in the protocol body)
- 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.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ upper limit of normal
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, HLH, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, and optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

- Grade ≥ 2 tumor inflammation/flare (e.g., manifestation of signs/symptoms associated with an increase in size of known nodal or extranodal lesions by clinical or radiographic assessment).
- Cardiovascular adverse events
- Myelitis
- Facial paresis

A15–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+RO7122290 ARM

A15–5.3.1 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 atezolizumab and 2 months after the final dose of RO7122290. Given that patients will be taking atezo+RO7122290 concurrently, 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 treatments. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study 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 when updated information on the course and outcome of the pregnancy becomes available.

A15–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 2 months after the final dose of RO7122290. 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. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to RO7122290. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional

information on the pregnancy partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A15–5.3.3 Abortions

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

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.

A15–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male 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 in the protocol body).

A15–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+RO7122290 ARM

Table A15-6 Schedule of Activities for Atezo+RO7122290 Arm (mUC Cohort)

	Stage 1 Screen [a]	Treatment Period (21-day cycles) [b]						Stage 2 Screen [c] (see Appendix 7) or Treat Discon [d]	Follow-Up Q3M (±7 days)
		Cycle 1			Cycle ≥2				
Day (±days)	Day −28 to −1	Day 1	Day 8 (±1)	Day 15 (±1)	Day 1 (±3)	Day 8 (±1)	Day 15 (±1)		
Informed consent	See Appendix 7.							x [e, f]	
Vital signs [g]		x	x	x	x	x	x	x	
Molecular profile of urothelial carcinoma (if available)		Whenever updated information becomes available							
Weight [h]		x			x			x	
Complete physical examination [i]								x	
Limited physical examination [j, h]		x	x	x	x	x	x		
ECOG Performance Status [h]		x	x	x	x	x	x		
ECG [k, h]		Perform as clinically indicated.						x	
Hematology [l]		x [m]	x	x	x [m]	x	x	x [n]	
Chemistry [o]		x [m]	x	x	x [m]	x	x	x [n]	
Coagulation (PT/INR and aPTT)								x [f, n]	
TSH, free T3 (or total T3), free T4 [p]		x [m, n]						x [n]	
HIV, HBV, and HCV testing								x [f, n]	
C-reactive protein		x			x			x [f, n]	
LDH		x			x			x [f, n]	
Pregnancy test [q]		x			x			x [n]	x [q]
Urinalysis [r]		x			x			x [f, n]	

Table A15-6 Schedule of Activities for Atezo+RO7122290 (mUC Cohort) (cont.)

Day (±days)	Stage 1 Screen [a]	Treatment Period (21-day cycles) [b]						Stage 2 Screen [c] (see Appendix 7) or Treat Discon [d]	Follow-Up Q3M (±7 days)
		Cycle 1			Cycle ≥2				
	Day −28 to −1	Day 1	Day 8 (±1)	Day 15 (±1)	Day 1 (±3)	Day 8 (±1)	Day 15 (±1)		
Serum autoantibody sample [s]	See Appendix 7.	Perform if a patient experiences a suspected immune-mediated adverse event							
PK samples		Refer to Table A15-7.							
ADA samples		Refer to Table A15-7.							
Biomarker samples		Refer to Table A15-7.							
Blood sample for RBR (optional) [t]		x							
Tumor biopsy		x [u]							
Tumor biopsy (optional)		x [v]							
Tumor response assessments		x [w, x, y]							
Concomitant medications [z]		x	x	x	x	x	x	x	
Adverse events [aa]		x	x	x	x	x	x	x	x
Atezolizumab administration [bb, cc]		x			x				
[redacted] [cc, dd]		[redacted]							
Survival follow-up and anti-cancer treatment									x [ee]

ADA = anti-drug antibody; Atezo = atezolizumab; CT = computed tomography; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBV = hepatitis B virus; HCV = hepatitis C virus; PK = pharmacokinetic; Q3M = every 3 months; RBR = Research Biosample Repository; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; TCZ = tocilizumab; Treat = treatment; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Table A15-6 Schedule of Activities for Atezo+RO7122290 (mUC Cohort) (cont.)

[a] Patients who fail their first screening for study eligibility (Stage 1) may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the initiation of study treatment may be used; such tests do not need to be repeated for screening or re-screening.

[b] Treatment must be initiated no later than 7 days after treatment assignment.

[c] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details) or unacceptable toxicity may be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.2 in the protocol body) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the final dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 or patients who have discontinued Stage 2 treatment will then undergo follow-up assessments.

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[f] Assessments to be performed only for patients undergoing Stage 2 screening.

[g] Vital signs include respiratory rate, pulse rate, pulse oximetry, and systolic and diastolic blood pressure while the patient is in a seated position, 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 For the first infusion, vital signs should be measured within 60 minutes prior to 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.

[h] Assessment may be performed within 24 hours prior to dosing during the treatment period.

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

[j] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

Table A15-6 Schedule of Activities for Atezo+RO7122290 (mUC Cohort) (cont.)

[l] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[m] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

[n] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[o] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide (if considered standard of care in the region), *serum troponin (at baseline, if considered standard of care/required per local clinical practice, and as clinically indicated during the study),* glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. For U.K. patients, amylase and lipase must be included on Day 1 of each treatment cycle.

[p] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1, and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[q] All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum 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. During follow-up, pregnancy tests will be performed at 3 and 6 months. If a pregnancy test was performed within 96 hours prior to Day 1 of Cycle 1, it does not have to be repeated.

[r] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[s] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody.

[t] 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.

[u] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by investigator (see Section 3.1.1 in the protocol body for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 in the protocol body for tissue sample requirements.

[v] Consenting patients may undergo optional tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[w] Patients will undergo tumor assessments at baseline, every 9 weeks (± 1 week) for the first 54 weeks following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays until loss of clinical benefit as determined by the investigator (see Section 3.1.1 in the protocol body for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new, non–protocol-specified anti-cancer therapy.

[x] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Table A15-6 Schedule of Activities for Atezo+RO7122290 (mUC Cohort) (cont.)

[y] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

[z] Includes 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 study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[aa] 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.

[bb] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Starting with Day 1 of Cycle 2, atezolizumab should be given within ± 3 days of scheduled date (i.e., Day 1 of each 21-day cycle).

[cc] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by investigator (see Section 3.1.1 in the protocol body for details).

[dd] 

[ee] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and clinic visits approximately every 3 months until death (unless patient withdraws consent or Sponsor terminates study). If a patient requests to be withdrawn from follow-up, this request must be documented in source documents and signed by investigator. If the patient withdraws from study, study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table A15-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+RO7122290 Arm: Preliminary and Expansion Phases (mUC Cohort)

Visit	Time	Sample Type
Day 1 of Cycle 1	[redacted]	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • RO7122290 PK (serum) • RO7122290 ADA (serum) • Biomarker (plasma, serum, and PBMC)
		• Atezolizumab PK (serum)
		• RO7122290 PK (serum)
Day 8 of Cycle 1		• RO7122290 PK (serum) • RO7122290 ADA (serum)
		• RO7122290 PK (serum)
Day 15 of Cycle 1		• RO7122290 PK (serum) • RO7122290 ADA (serum) • Biomarker (plasma and serum)
		• RO7122290 PK (serum)
Day 1 of Cycle 2		• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • RO7122290 PK (serum) • RO7122290 ADA (serum) • Biomarker (plasma, serum, and PBMC)
		• RO7122290 PK (serum)
Day 8 of Cycle 2		• RO7122290 PK (serum)
Day 1 of Cycle 3		• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • RO7122290 PK (serum) • RO7122290 ADA (serum) • Biomarker (plasma, serum)
		• RO7122290 PK (serum)

ADA = anti-drug antibody; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety 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. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

Table A15-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+ RO7122290 Arm: Preliminary and Expansion Phases (mUC Cohort) (cont.)

Visit	Time	Sample Type
Day 8 of Cycle 3	[redacted]	• RO7122290 PK (serum)
Day 1 of Cycles 4 and 8		• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • RO7122290 PK (serum) • RO7122290 ADA (serum) • Biomarker (plasma and serum)
		• RO7122290 PK (serum)
Day 1 of Cycles 12 and 16		• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • RO7122290 PK (serum) • RO7122290 ADA (serum)
Treatment discontinuation visit (≤ 30 days after final dose)		• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • RO7122290 PK (serum) • RO7122290 ADA (serum) • Biomarker (plasma and serum)

ADA = anti-drug antibody; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety 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. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether

A15–7 REFERENCES

Antunes RF, Kaski JC, Dimitriu IE. The role of costimulatory receptors of the tumour necrosis factor receptor family in atherosclerosis. J Biomed Biotechnol 2012;2012:1–16.

Ascierto PA, Simeone E, Sznol M, et al. Clinical experiences with anti-CD137 and anti-PD1 therapeutic antibodies. Semin Oncol 2010;37:508–16.

Azpilikueta A, Agorreta J, Labiano S, et al. Successful immunotherapy against transplantable mouse squamous lung carcinoma with anti-PD-1 and anti-CD137 monoclonal antibodies. J Thorac Oncol 2016;11:524–36.

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;54:307–314.

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;56:739–745.

Brokopp CE, Schoenauer R, Richards P, et al. Fibroblast activation protein is induced by inflammation and degrades type I collagen in thin-cap fibroatheromata. Eur Heart J 2011;32:2713–22.

Butte MJ, Keir ME, Phamduy TB, et al. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–122.

Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–6587.

Chen S, Lee LF, Fisher TS, et al. Combination of 4-1BB agonist and PD-1 antagonist promotes antitumor effector/memory CD8 T cells in a poorly immunogenic tumor model. Cancer Immunol Res 2015;3:149–60.

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.

Fehrenbacher L, Spira A, Ballinger M, et al. 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;387:1837–1846.

Garin-Chesa P, Old LJ, Rettig WJ. Cell surface glycoprotein of reactive stromal fibroblasts as a potential antibody target in human epithelial cancers. Proc Natl Acad Sci USA 1990;87:7235–9.

Gros A, Robbins PF, Yao X, et al. PD-1 identifies the patient-specific $CD8^+$ tumor-reactive repertoire infiltrating human tumors. J Clin Invest 2014;124:2246–59.

Hamson EJ, Kean FM, Tholen S, et al. Understanding fibroblast activation protein (FAP): substrates, activities, expression and targeting for cancer therapy. Proteomics Clin Appl 2014;8:454–63.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–723.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–422.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625–38.

Mezheyeuski A, Segersten U, Leiss LW, et al. Fibroblasts in urothelial bladder cancer define stroma phenotypes that are associated with clinical outcome. Sci Rep 2020;10:281.

Olofsson PS, Söderström LÅ, Wågsäter D, et al. CD137 is expressed in human atherosclerosis and promotes development of plaque inflammation in hypercholesterolemic mice. Circulation 2008;117:1292–301.

Pérez-Ruiz E, Etxeberria I, Rodriguez-Ruiz M, et al. anti-CD37 and PD-1/PD-L1 antibodies en route toward clinical synergy. Clin Cancer Res 2017;23:5326–28.

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;387:1909–1920.

Scott AM, Wiseman G, Welt S, et al. A Phase I dose-escalation study of sibrotuzumab in patients with advanced or metastatic fibroblast activation protein-positive cancer. Clin Cancer Res 2003;9:1639–47.

Segal NH, Logan TF, Hodi FS, et al. Results from an integrated safety analysis of urelumab, an agonist anti-CD137 monoclonal antibody. Clin Cancer Res 2017;23:1929–36.

Tecentriq® (atezolizumab) Summary of Product Characteristics, Genentech.

Tecentriq® (atezolizumab) U.S. Package Insert, Genentech.

Virmani R, Burke AP, Farb A, et al. Pathology of the vulnerable plaque. J Am Coll Cardiol 2006;47(8 Suppl): C13–8.

Wei H, Zhao L, Hellstrom I, et al. Dual targeting of CD137 costimulatory and PD-1 co-inhibitory molecules for ovarian cancer immunotherapy. Oncoimmunology 2014;3:e28248

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;187:1113–1119.

Appendix 16
Study Details Specific to Atezo+Cis+Gem Arm (Comparator)

Note: This appendix is not applicable to France.

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A16–1 BACKGROUND ON ATEZO+CIS+GEM ARM

A16–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin (IgG1) monoclonal antibody that targets programmed death-ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed death-1 (PD-1) and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. 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 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 cancer patients 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 has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, myocarditis, and nephritis, have been observed (see Appendix 6). To date, these events have been manageable with treatment.

Atezolizumab (Tecentriq®) is approved for the treatment of urothelial carcinoma (UC), non–small cell lung cancer (NSCLC), 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.

A16–1.2 THE PD-L1 PATHWAY

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).

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.

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 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).

A16–2 RATIONALE FOR THE CLINICAL STUDY OF THE COMBINATION OF ATEZOLIZUMAB IN COMBINATION WITH CISPLATIN AND GEMCITABINE

A16–2.1 NONCLINICAL DATA SUPPORTING THE COMBINED INHIBITION OF THE PD-L1/PD-1 PATHWAY WITH CHEMOTHERAPY

In nonclinical immune competent mouse tumor models, chemotherapy treatment with multiple classes of chemotherapeutic agents resulted in activation or increase of tumor infiltrating CD8+ T cells, whereas there was a depletion of peripheral immune cells, including CD8+ T cells (Belvin et al. 2016). Combination of anti–PD-L1 with several chemotherapeutic agents showed combination efficacy, correlating with the increased activation of tumor infiltrating CD8+ T cells (Belvin et al. 2016). Depending on the immune context of the nonclinical model tested, chemotherapeutic agents showed different mechanisms of activating CD8+ T cells, including increased interferon (IFN)-γ production, increased Granzyme B levels, and decreased markers of exhaustion (Belvin et al. 2016). Tumor cell killing by cytotoxic chemotherapy may expose the immune system to high levels of tumor antigens, and invigorating tumor specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007), and this may reasonably occur in tumors regardless of PD-L1 expression.

In addition, in nonclinical models, oxaliplatin has been shown to enhance immune responses by decreasing T-regulatory cells and myeloid-derived suppressor cells in tumor microenvironment (Sato et al. 2005; Gonzalez-Aparicio et al. 2011), suggesting potential synergy with immunotherapy induced by PD-L1 blockade.

Based on this nonclinical data, these regimens may enhance the efficacy of atezolizumab in patients with urothelial cancer.

A16–2.2 CLINICAL DATA SUPPORTING THE COMBINED INHIBITION OF THE PD-L1/PD-1 PATHWAY WITH CHEMOTHERAPY

The addition of PD-L1 and PD-1 checkpoint inhibitors to standard platinum-based chemotherapy demonstrated encouraging anti-tumor activity and acceptable safety in early Phase I and II studies (Giaccone et al. 2015; Langer et al. 2016; Rizvi et al. 2016).

In multiple large Phase III clinical trials, the addition of PD-L1 and PD-1 checkpoint inhibitors to standard chemotherapy led to significantly longer overall survival (OS) and progression-free survival for patients compared with chemotherapy alone (Gandhi et al. 2018; Paz-Ares et al. 2018; Horn et al. 2018; Schmid et al. 2018). As a result, combinations of PD-L1/PD-1 checkpoint inhibitors with chemotherapies have been approved for patients with different advanced cancers. Several single-arm studies have evaluated combinations of checkpoint inhibitors with chemotherapy in the neoadjuvant setting for patients with muscle invasive bladder cancer (MIBC) (Gupta et al. 2020, Funt et al. 2021). In the BLASST-1 trial, 41 patients with MIBC received gemcitabine plus cisplatin plus nivolumab for 4 cycles before radical cystectomy, with 27 out of 41 (65.8%) patients experiencing a pathological downstaging less than pT1 at the time of cystectomy (Gupta et al. 2020). The frequency of PD-L1+ and PD-L1− patients in the BLASST-1 trial was not reported. In a separate study evaluating the combination of gemcitabine plus cisplatin plus atezolizumab in patients with MIBC, 27 out of 39 patients showed a pathologic response less than pT2, with 17 out of 39 (44%) patients showing pathological complete response (pCR). Notably, 90% of patients had PD-L1− tumor, of which 4 out of 4 patients with PD-L1+ tumors, achieved a tumor downstaging less than pT2; 11 out of 11 patients who did not respond had PD-L1− tumors, and 23 out of 27 (85%) patients who responded had PD-L1− tumors. These results contrast with those of the ABACUS study, where patients with PD-L1− disease had fewer pCR than patients with PD-L1+ disease (24.5% vs 37.1%; Powles et al. 2021). This also contrasts with the results from the PURE-01 study where patients with PD-L1+ disease also showed a higher pCR rate than patients with PD-L1− disease (54.3% vs 13.3%; Necchi et al. 2018). Further investigations are needed to better assess the impact of adding PD-L1 and PD-1 checkpoint inhibitors to cisplatin-based chemotherapy in patients with MIBC, in particular in those with PD-L1− disease.

Historically, only patients who achieve a pCR after neoadjuvant chemotherapy can expect to derive a durable benefit with improved OS (Rosenblatt et al. 2012; Petrelli et al. 2014). The results presented above suggest that the addition of PD-L1 and PD-1 checkpoint inhibitors to chemotherapy could also confer a durable benefit to patients who experience a pathological downstaging (Funt et al. 2021). The duration of recurrence-free survival in patients who experienced an incomplete pathological

downstaging following neoadjuvant treatment with gemcitabine plus cisplatin plus atezolizumab will require longer follow up.

The IMvigor130 study is an ongoing Phase III study comparing atezolizumab monotherapy with chemotherapy and the combination of atezolizumab plus platinum-based chemotherapy in patients with untreated locally advanced or metastatic UC. Patients received either cisplatin or carboplatin in combination with gemcitabine as their chemotherapy. Exploratory analyses suggest improved OS with the addition of atezolizumab to cisplatin-based chemotherapy but not for patients who received carboplatin-based chemotherapy. Patients treated with gemcitabine plus cisplatin plus atezolizumab showed an improved OS when compared to patients treated with gemcitabine plus carboplatin plus atezolizumab, or gemcitabine plus cisplatin plus placebo or gemcitabine plus carboplatin plus placebo (Table A16-1).

Table A16-1 Efficacy Outcomes in Patients Treated with Atezolizumab Plus Chemotherapy in IMvigor 130

IMvigor130: treatment subgroups	IC0/1		IC2/3		HR (95% CI)
	n	Median OS (months)	n	Median OS (months)	
Arm A (atezo + cis/gem)	102	19.5	35	Not reached	0.46 (0.25, 0.83)
Arm A (atezo + carbo/gem)	241	13.9	73	16.6	0.85 (0.61, 1.17)
Arm C (placebo + cis/gem)	102	12.8	34	27.9	0.51 (0.30, 0.86)
Arm C (placebo + carbo/gem)	207	13.0	57	14.0	1.00 (0.71, 1.42)

Atezo = atezolizumab; carbo = carboplatin; cis = cisplatin; gem = gemcitabine; HR = hazard ratio; IC0/1 = presence of programmed death-ligand 1 (PD-L1)–expressing immune cells on < 5% of the tumor area; IC2/3 = presence of PD-L1–expressing immune cells on ≥ 5% of the tumor area; OS = overall survival.

Note: PD-L1 expression on tumor-infiltrating immune cells assessed from archival pretreatment tumor samples (VENTANA SP142 assay).

In the IMvigor130 study, single-cell RNA sequencing (scRNA-seq) was performed on peripheral blood mononuclear cells (PBMCs) obtained at Day 1 of Cycles 1 and 3 from 70 patients receiving atezolizumab plus platinum (cisplatin or carboplatin) and gemcitabine (Arm A) or placebo plus platinum (cisplatin or carboplatin) and gemcitabine (Arm C) in order to assess for differences in the immune profiles of patients treated with cisplatin versus carboplatin. When comparing patients treated with cisplatin versus carboplatin, on-treatment enrichment of hallmark tumor necrosis factor (TNF)–α signaling via NF-κB and inflammatory response gene sets was observed across all immune cell clusters and the trends were even more pronounced in patients treated with the combination of cisplatin plus gemcitabine plus atezolizumab. Among the top-ranked genes enriched in PBMCs in patients treated with cisplatin versus carboplatin following chemotherapy was NINJ1, which mediates plasma membrane rupture during lytic cell

death, releasing damage-associated molecular patterns such as HMGB1, a key player driving immunogenicity in cell death (Apetoh et al. 2007, Galsky et al. 2021).

The results from the IMvigor130 study, as well as ongoing studies evaluating immunotherapy with and without chemotherapy in MIBC, suggest that cisplatin/gemcitabine induces immunogenic cell death and enhances anti-tumor immunity when combined with atezolizumab, even in patients with PD-L1– disease.

A16–2.3 BENEFIT–RISK ASSESSMENT

Taking into account the potentially synergistic mechanisms of action for cisplatin-based chemotherapy and atezolizumab, as well as the preliminary efficacy data and manageable safety profiles for this combination described in Section A16–2.2, treatment with atezolizumab plus chemotherapy (cisplatin and gemcitabine) may have promising therapeutic potential for patients with cisplatin-eligible MIBC. Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in patients receiving atezolizumab in combination with chemotherapy. Patients with severe infection within 4 weeks prior to initiation of study treatment will be excluded. Patients experience adverse events will be managed according to the management guidelines.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.5.

A16–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+CIS+GEM ARM

A16–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert; Tecentriq Summary of Product Characteristics). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached, and no dose-limiting toxicities (DLTs) 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 pharmacokinetic (PK), efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A16–3.2 RATIONALE FOR CISPLATIN AND GEMCITABINE DOSE AND SCHEDULE

In this study, cisplatin at a dose of 70 mg/m^2 will be administered by IV infusion on Day 1 of each 21-day cycle. This is the current recommended cisplatin dosage in the National Comprehensive Cancer Network (NCCN) guidelines for the neoadjuvant treatment of MIBC (NCCN Guidelines, Version 3.2021).

In this study, gemcitabine at a dose of 1000 mg/m^2 will be administered by IV infusion on Days 1 and 8 of each 21-day cycle. This is the current recommended gemcitabine dosage in the NCCN guidelines for the neoadjuvant treatment of MIBC (NCCN Guidelines, Version 3.2021).

A16–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+CIS+GEM ARM

A16–4.1 TREATMENT IN ATEZO+CIS+GEM ARM

A16–4.1.1 Formulation, Packaging, and Handling

A16–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

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

A16–4.1.1.2 Cisplatin

For information on the formulation, packaging, and handling of cisplatin, refer to the local prescribing information.

A16–4.1.1.3 Gemcitabine

For information on the formulation, packaging, and handling of gemcitabine, refer to the local prescribing information.

A16–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus cisplatin plus gemcitabine (Atezo + Cis + Gem) arm will receive treatment as outlined in Table A16-2. Patients will undergo surgery after Cycle 3; treatment in Cycle 4 should be reinitiated 4–6 weeks after surgery, but can be reinitiated up to 12 weeks after surgery if surgical complications arise (see Table A16-2). Treatment will continue until Cycle 17. It is recommended that treatment be initiated as soon as possible and no later than 7 days after randomization.

Table A16-2 Treatment Regimen for Atezo + Cis + Gem Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
Cycles 1–3 Before Surgery 21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Gemcitabine 1000 mg/m^2 IV on Days 1 and 8 of each cycle • Cisplatin 70 mg/m^2 IV on Day 1 of each cycle
Cycles 4–17 After Surgery 21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle

Atezo = atezolizumab; Cis = cisplatin; Gem = gemcitabine.
Note: On Day 1 of each cycle, chemotherapy will be administered after completion of the atezolizumab infusion.

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

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab are available.

A16–4.1.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle for all 17 cycles.

Administration of atezolizumab 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A16-3.

Table A16-3 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • After the infusion of atezolizumab, the patient begins a 30-minute observation period. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during the infusion and at 30 (±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, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A16–5.1.5.3. Atezolizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

A16–4.1.2.2 Cisplatin and Gemcitabine

Cisplatin and gemcitabine will be administered according to the local prescribing information. Cisplatin will be administered by IV infusion at a dose of 70 mg/m^2 on Day 1 of each 21-day cycle for the first 3 cycles only. Gemcitabine will be administered by IV infusion at a dose of 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle for the first 3 cycles only.

Prior to treatment with cisplatin, patients must receive appropriate pretreatment hydration. Premedication with steroids should be limited when clinically feasible, because of their immunosuppressant effects. Prophylactic anti-emetics (e.g., 5-HT3

receptor antagonists) may be administered per local practice. All medications must be recorded on the appropriate Concomitant Medications eCRF.

Cisplatin and gemcitabine will be administered in the first 3 cycles only, unless unacceptable toxicity occurs or the patient is withdrawn from study treatment for any reason.

Guidelines for cisplatin and gemcitabine dose modification, treatment interruption, and discontinuation because of toxicities are provided in Section A16–5.1.5.

Cisplatin and gemcitabine treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with cisplatin and gemcitabine should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

A16–4.2 CONCOMITANT THERAPY FOR ATEZO+CIS+GEM ARM

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 study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A16–4.2.1 Permitted Therapy for Atezo+Cis+Gem Arm

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

- Oral contraceptives with a failure rate of $< 1\%$ per year (see Section A16–4.3)
- 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 A16–4.2.3).
- 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

- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy. Chemotherapy should be interrupted as per institutional standard of care.

- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

Premedication with antihistamines, antipyretics, 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 therapies other than those defined as cautionary or prohibited therapies (see Sections A16–4.2.2 and A16–4.2.3) 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 β2-adrenergic agonists; see Appendix 5).

A16–4.2.2 Cautionary Therapy for Atezo + Cis + Gem Arm

A16–4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α 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 6 for details).

A16–4.2.2.2 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 A16–4.2.3) may be used during the study at the discretion of the investigator.

A16–4.2.2.3 Cautionary Therapy Related to Cisplatin

Caution should be used when co-administering nephrotoxic (e.g., cephalosporins, aminoglycosides, or amphotericin B or contrast media) or ototoxic (e.g., aminoglycosides, loop diuretics) medicinal products that will potentiate the toxic effect of cisplatin on the kidneys and auditory function. Starting a new anti-convulsant treatment with phenytoin is strictly contraindicated during cisplatin therapy.

A16–4.2.3 Prohibited Therapy for Atezo + Cis + Gem Arm

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 4.1.4 in the protocol body), and during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined above in Section A16–4.1.2.
- Investigational therapy (other than protocol-mandated study treatment) 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 treatment with atezolizumab, and for 5 months after the final dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug (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.

A16–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO+CIS+GEM ARM

Contraception requirements for men and women in the Atezo + Cis + Gem arm are outlined below:

- 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 and for 6 months after the final dose of cisplatin and gemcitabine. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and 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 acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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

  With a female partner of childbearing potential who is not pregnant, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 6 months after the final dose of cisplatin and gemcitabine. Men must refrain from donating sperm during this same period.

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of cisplatin and gemcitabine to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

A16–5 ASSESSMENT OF SAFETY FOR ATEZO+CIS+GEM ARM

A16–5.1 SAFETY PLAN FOR ATEZO+CIS+GEM ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab, cisplatin, and gemcitabine in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A16–5.1.1, A16–5.1.2, A16–5.1.3, and A16–5.1.4). Guidelines for management of patients who experience specific adverse events are provided in Section A16–5.1.5.

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, cisplatin, and gemcitabine 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. Adverse events will be reported as described in Sections 5.2–5.6. An Internal Monitoring Committee and Scientific Oversight Committee will review safety data throughout the study as described in Section 3.1.6 in the protocol body.

A16–5.1.1 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, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A16–5.1.2 Risks Associated with Cisplatin

The most common adverse events (> 10%) with cisplatin are hematological (leukopenia, thrombocytopenia and anemia), gastrointestinal (GI) (anorexia, nausea, vomiting and diarrhea), ear disorders (hearing impairment), renal disorders (renal failure, nephrotoxicity, hyperuricemia) and fever.

For more details regarding the safety profile of cisplatin, see the prescribing information for cisplatin.

A16–5.1.3 Risks Associated with Gemcitabine

The most common adverse events (> 10%) with gemcitabine are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased alkaline phosphatase, proteinuria, influenza-like symptoms, hematuria, allergic skin rash, thrombocytopenia, alopecia, dyspnea, and peripheral edema.

For more details regarding the safety profile of gemcitabine, refer to the gemcitabine prescribing information.

A16–5.1.4 Risks Associated with Combination Use of Atezolizumab, Cisplatin, and Gemcitabine

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab plus cisplatin plus gemcitabine: GI toxicities, hepatotoxicity, hematologic toxicity, renal toxicity, cardiac toxicities, pulmonary toxicities, neurologic toxicities, and skin toxicities.

A16–5.1.5 Management of Patients Who Experience Specific Adverse Events in the Atezo + Cis + Gem Arm

A16–5.1.5.1 Dose Modifications

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

Dose modifications of chemotherapy are based on the previous cycle. Dose re-escalations are only permitted for the Day 8 gemcitabine dose adjustment for hematologic parameters (see Table A16-4). For management of drug-related toxicities, the dose of cisplatin may be reduced by 10 mg/m^2 (i.e., one dose level) up to two times and the dose of gemcitabine may be reduced by 100 mg/m^2 (i.e., one dose level) up to two times, as outlined in Table A16-5.

Guidelines for gemcitabine and cisplatin dose modifications are shown in Table A16-4.

Table A16-4 Dose-Modification Levels

	Starting Dose	Dose Level −1	Dose Level −2
Atezolizumab	1200 mg fixed dose	Dose reductions not permitted	Dose reductions not permitted
Cisplatin [a]	70 mg/m^2	60 mg/m^2	50 mg/m^2
Gemcitabine [b]	1000 mg/m^2	900 mg/m^2	800 mg/m^2

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

[b] Dose re-escalations of gemcitabine are only permitted after an adjustment of the Day 8 gemcitabine dose (refer to Table A16-5 for hematologic toxicities). The maximum re-escalation permitted is to the previous Day 1 dose administered. The Day 8 dose reduction only applies to Day 8 and does not count towards the allowed number of dose reductions per patient.

Treatment with filgrastim or pegfilgrastim may be used if needed. Treatment with sargramostim is not allowed.

A16–5.1.5.2 Treatment Interruption for Toxicities

Atezolizumab may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before study treatment can be resumed. If study treatment is withheld for > 12 weeks, the patient will be discontinued from study treatment. However, study treatment may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Study treatment can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Cisplatin and/or gemcitabine treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table A16-5).

In the absence of disease recurrence, cisplatin and gemcitabine together may be discontinued for toxicity independent of atezolizumab. Additionally, in the absence of disease recurrence, atezolizumab may be discontinued for toxicity independent of cisplatin and gemcitabine. Chemotherapy alone or atezolizumab alone may be continued as therapy until completion of the 3 cycles pre-surgery if the patient is likely to derive clinical benefit.

Refer to Section A16–4.1.2 for information on dose interruptions for reasons other than toxicity.

A16–5.1.5.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Table A16-5. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

The investigator may use discretion in adhering to the guidelines for cisplatin and gemcitabine described below, taking into account the severity of the event and benefit versus risk for the patient, with the goal of maximizing patient compliance and access to supportive care. Additionally, the prescribing information, as well as local hospital or clinical practice, must be followed.

Patients who discontinue cisplatin permanently (e.g., for adverse events) will also discontinue gemcitabine permanently. Dosing with atezolizumab should continue until completion of the 3 cycles pre-surgery as long as patients are experiencing clinical benefit in the opinion of the investigator.

Table A16-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cis + Gem Arm

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reactions	• Guidelines for management of IRRs and CRS for atezolizumab are provided in Appendix 6. • Guidelines for management of IRRs for cisplatin and gemcitabine should be consistent with local clinical practice. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue the causative agent.
Gastrointestinal toxicity	
Diarrhea or colitis, Grade 1	• Follow guidelines for atezolizumab in Appendix 6. • Continue cisplatin and gemcitabine.
Diarrhea or colitis, Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. [a] • First occurrence: If event resolves to Grade 1 or better while withholding gemcitabine and cisplatin, resume gemcitabine and cisplatin with full dose with prophylaxis (if possible). If not, permanently discontinue gemcitabine and cisplatin. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level with prophylaxis (if possible). [d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin and gemcitabine reduced by one dose level with prophylaxis (if possible). [d] If not, permanently discontinue cisplatin and gemcitabine.
Diarrhea or colitis, Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. [a] • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level with prophylaxis (if possible). [d] If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level with prophylaxis (if possible). [d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: Permanently discontinue cisplatin and gemcitabine
Diarrhea or colitis, Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue cisplatin and gemcitabine and contact the Medical Monitor. [c, e]

Table A16-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Nausea or vomiting, Grade 3	• Continue atezolizumab. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. • Administer 5-HT3 serotonin receptor antagonist, olanzapine 10 mg orally on Days 1–4 chemotherapy, and aprepitant for prophylaxis for future cycles of chemotherapy. • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: Permanently discontinue cisplatin and gemcitabine.
Nausea or vomiting, Grade 4	• Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. • Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Administer 5-HT3 serotonin receptor antagonist, olanzapine 10 mg orally on Days 1–4 chemotherapy, and aprepitant for prophylaxis for future cycles of chemotherapy. • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: Permanently discontinue cisplatin and gemcitabine.
Stomatitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset and withhold cisplatin and gemcitabine for up to 6 weeks after event onset. • If event resolves to Grade 1 or better while withholding atezolizumab, resume atezolizumab. If not, permanently discontinue atezolizumab and contact the Medical Monitor. • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level with prophylaxis (if possible). [d] If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level with prophylaxis (if possible). [d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: Permanently discontinue cisplatin and gemcitabine.

Table A16-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Stomatitis, Grade 4	• Withhold atezolizumab for up to 12 weeks after event onset. Permanently discontinue cisplatin and gemcitabine. [e] • If event resolves to Grade 1 or better while withholding atezolizumab, resume atezolizumab. If not, permanently discontinue atezolizumab and contact the Medical Monitor.
Hepatic events	
Hepatic event, Grade 1	• Continue atezolizumab, cisplatin, and gemcitabine. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	• Continue atezolizumab, cisplatin, and gemcitabine. • Monitor LFTs more frequently until return to baseline values. Events of > 5 days' duration: • Withhold atezolizumab for up to 12 weeks after event onset and withhold cisplatin and gemcitabine for up to 6 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better while withholding atezolizumab, resume atezolizumab. [b] If not, permanently discontinue atezolizumab and contact the Medical Monitor. [c] • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine at full dose level. If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine.

Table A16-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Hepatic event, Grade 3	• Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: Permanently discontinue cisplatin and gemcitabine.
Hepatic event, Grade 4	• Permanently discontinue atezolizumab, cisplatin, and gemcitabine and contact the Medical Monitor. [c, e] • Manage as per Grade 3 guidelines.
Hematologic toxicity (excluding febrile neutropenia)	
Day 1 of any cycle	
ANC ≥ 1.5×10^9/L (1500/μL) and platelet count to ≥ 100×10^9/L (100,000/μL)	• Continue cisplatin, gemcitabine, and atezolizumab.
ANC ≥ 1.5×10^9/L (1500/μL) and platelet count to < 100×10^9/L (100,000/μL)	• Continue atezolizumab. • Withhold cisplatin and gemcitabine and assess ANC and platelet counts weekly. • If ANC ≥ 1.5×10^9/L (1500/μL) and platelet count improves to ≥ 100×10^9/L (100,000/μL) ≤ 6 weeks after event onset, resume cisplatin and gemcitabine at full dose level. If not, permanently discontinue cisplatin and gemcitabine.
ANC < 1.5×10^9/L (1000/μL) and platelet count to ≥ 100×10^9/L (100,000/μL)	• Continue atezolizumab. • Withhold cisplatin and gemcitabine and assess ANC and platelet counts weekly. • If ANC improves to ≥ 1.5×10^9/L (1500/μL) and platelet count ≥ 100×10^9/L (100,000/μL) ≤ 6 weeks after event onset, resume cisplatin and gemcitabine at full dose level. If not, permanently discontinue gemcitabine and cisplatin.

Table A16-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cis + Gem Arm (cont.)

Event	Action to Be Taken
ANC $< 1.5 \times 10^9$/L (1500/μL) and/or platelet count to $< 100 \times 10^9$/L (100,000/μL)	• Continue atezolizumab. • Withhold cisplatin and gemcitabine and assess ANC and platelet counts weekly. • If ANC improves to $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count $\geq 100 \times 10^9$/L (100,000/μL) ≤ 6 weeks after event onset, resume cisplatin and gemcitabine at full dose level. If not, permanently discontinue gemcitabine and cisplatin.
Day 8	
ANC $\geq 1.0 \times 10^9$/L (1000/μL) and/or platelet count to $\geq 75 \times 10^9$/L (75,000/μL)	• Continue gemcitabine with no dose reduction.
ANC $< 1.0 \times 10^9$/L (1000/μL) and/or platelet count to $< 75 \times 10^9$/L (75,000/μL)	• Continue gemcitabine at 500 mg/m^2.
ANC $< 0.5 \times 10^9$/L (500/μL) and/or platelet count to $< 50 \times 10^9$/L (50,000/μL)	• Withhold gemcitabine.
Hematologic toxicity (life-threatening)	
Febrile neutropenia, Grade 3	• Withhold cisplatin, gemcitabine, and atezolizumab. • If fever resolves and ANC improves to $\geq 1.0 \times 10^9$/L (1000/μL) ≤ 6 weeks after event onset, resume cisplatin and gemcitabine reduced by one dose level and provide GCSF support.[d] If not, permanently discontinue cisplatin and gemcitabine. • If fever resolves and ANC improves to $\geq 1.0 \times 10^9$/L (1000/μL) ≤ 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab.

Table A16-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Febrile neutropenia, Grade 4	• Withhold cisplatin, gemcitabine, and atezolizumab. • If fever resolves and ANC improves to $\geq 1.0 \times 10^9$/L (1000/μL) $\leq$ 6 weeks after event onset, resume cisplatin and gemcitabine reduced by two dose levels and provide GCSF support. [d] If not, permanently discontinue cisplatin and gemcitabine. • If fever resolves and ANC improves to $\geq 1.0 \times 10^9$/L (1000/μL) $\leq$ 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab.
Immune-mediated myocarditis	
Immune-mediated myocarditis, Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue cisplatin and gemcitabine
Immune-mediated myocarditis, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue cisplatin, and gemcitabine. [e]
Dermatologic events	
Dermatologic event, Grade 1	• Follow guidelines for atezolizumab in Appendix 6. • Continue cisplatin and gemcitabine.
Dermatologic event, Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue cisplatin and gemcitabine.
Dermatologic event, Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. • First occurrence: If event resolves to Grade 1 or better while withholding gemcitabine and cisplatin, resume gemcitabine and cisplatin reduced by one dose level. [d] If not, permanently discontinue gemcitabine and cisplatin. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level [d]. If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: Permanently discontinue cisplatin and gemcitabine.
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab, cisplatin, and gemcitabine. [c, e]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Follow guidelines for atezolizumab in Appendix 6. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue cisplatin and gemcitabine.

Table A16-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Neurologic disorders	
Immune-mediated neuropathy, Grade 1	• Follow guidelines for atezolizumab in Appendix 6. • Continue cisplatin and gemcitabine.
Immune-mediated neuropathy, Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue cisplatin and gemcitabine. • Initiate treatment as per institutional guidelines.
Immune-mediated neuropathy, Grade 3-4	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue cisplatin and gemcitabine and contact the Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Cisplatin-related neurotoxicity, Grade 2	• Continue atezolizumab. • Permanently discontinue cisplatin and gemcitabine.
Cisplatin-related neurotoxicity, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. • Permanently discontinue cisplatin and gemcitabine. • If event resolves to Grade 2 or better while withholding atezolizumab, resume atezolizumab. If not, permanently discontinue atezolizumab and contact the Medical Monitor.
Cisplatin-related ototoxicity	• Hold atezolizumab, cisplatin, and gemcitabine. • Refer to audiology to perform hearing assessment. For loss of greater than 25 decibels in two consecutive hearing frequencies, repeat audiometry assessment 1 week later. • If hearing loss is resolved, then the patient will be re-treated with a cisplatin dose that is one level lower than the prior cycle [d] and continue atezolizumab and gemcitabine. • If hearing loss persists, continue atezolizumab and permanently discontinue cisplatin and gemcitabine.

Table A16-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Renal events	
Renal event, Grade 1	• Continue atezolizumab and gemcitabine. If CrCl ≥ 50 mL/min (calculated according to estimated GFR), continue cisplatin at full dose. If CrCL < 50 mL/min, withhold cisplatin for 1 week and recheck creatinine and estimated GFR. If CrCl is recovered to ≥ 50 mL/min, resume cisplatin reduced by one dose level. Repeat courses of cisplatin should not be given unless levels of serum creatinine are below 1.5 mg/100mL (130 µmol /L) or blood urea below 55 mg/100 mL (9mmol/L), and circulating blood levels are at an acceptable level. Measurement of BUN, serum creatinine or GFR should be performed prior to initiating therapy and prior to each subsequent course. [d] • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. • If event resolves to Grade 1 or better and CrCl ≥ 50 mL/min while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. Repeat courses of cisplatin should not be given unless levels of serum creatinine are below 1.5 mg/100mL (130 µmol /L) or blood urea below 55 mg/100 mL (9mmol/L), and circulating blood levels are at an acceptable level. Measurement of BUN, serum creatinine or GFR should be performed prior to initiating therapy and prior to each subsequent course. [d] If event does not resolve while withholding cisplatin and gemcitabine, permanently discontinue cisplatin and gemcitabine.
Renal event, Grades 3 and 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold gemcitabine and cisplatin for up to 6 weeks after event onset. • If event resolves to Grade 1 or better and CrCl ≥ 50 mL/min while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. Repeat courses of cisplatin should not be given unless levels of serum creatinine are below 1.5 mg/100mL (130 µmol /L) or blood urea below 55 mg/100 mL (9mmol/L), and circulating blood levels are at an acceptable level. Measurement of BUN, serum creatinine or GFR should be performed prior to initiating therapy and prior to each subsequent course. [d] If event does not resolve while withholding cisplatin and gemcitabine, permanently discontinue cisplatin and gemcitabine.

Table A16-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Pulmonary events	
Pulmonary event, Grade 1	• Follow guidelines for atezolizumab in Appendix 6. • Continue cisplatin and gemcitabine
Pulmonary event, Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • For recurrent events, treat as a Grade 3 or 4 event. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. If event resolves to Grade 1 or better, resume cisplatin and gemcitabine reduced by one dose level. [d] If event does not resolve while withholding cisplatin and gemcitabine, permanently discontinue cisplatin and gemcitabine • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue gemcitabine and cisplatin.
Endocrine events	
Hypothyroidism, Grade 1	• Follow guidelines for atezolizumab in Appendix 6. • Continue cisplatin and gemcitabine.
Hypothyroidism, Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • Consider withholding cisplatin and gemcitabine. • Resume cisplatin and gemcitabine when symptoms are controlled and thyroid function is improving.
Hypothyroidism, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. • Resume cisplatin and gemcitabine at same dose level when symptoms are controlled and thyroid function is improving.
Hyperthyroidism, Grade 1	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Follow guidelines for atezolizumab in Appendix 6. • Continue cisplatin and gemcitabine **TSH < 0.1 mU/L:** • Follow guidelines for Grade 2 hyperthyroidism. • Consider patient referral to endocrinologist

Table A16-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Hyperthyroidism, Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • Consider withholding cisplatin and gemcitabine. • Resume cisplatin and gemcitabine when symptoms are controlled and thyroid function is improving.
Hyperthyroidism, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. • Resume cisplatin and gemcitabine at same dose level when symptoms are controlled and thyroid function is improving.
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue cisplatin and gemcitabine.
Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Withhold gemcitabine and cisplatin for up to 6 weeks after event onset. • First occurrence: If event resolves to Grade 1 or better while withholding gemcitabine and cisplatin, resume gemcitabine and cisplatin reduced by one dose level. [d] If not, permanently discontinue gemcitabine and cisplatin. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: Permanently discontinue cisplatin and gemcitabine.
Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold gemcitabine and cisplatin for up to 6 weeks after event onset. • First occurrence: If event resolves to Grade 1 or better while withholding gemcitabine and cisplatin, resume gemcitabine and cisplatin reduced by one dose level. [d] If not, permanently discontinue gemcitabine and cisplatin. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue gemcitabine and cisplatin. • Third occurrence: Permanently discontinue gemcitabine and cisplatin.

Table A16-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Chemotherapy-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab, cisplatin, and gemcitabine.
Grade 3	• Continue atezolizumab. Withhold gemcitabine and cisplatin for up to 6 weeks after event onset. • First occurrence: If event resolves to Grade 1 or better while withholding gemcitabine and cisplatin, resume gemcitabine and cisplatin reduced by one dose level.[d] If not, permanently discontinue gemcitabine and cisplatin. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level.[d] If not, permanently discontinue gemcitabine and cisplatin. • Third occurrence: Permanently discontinue gemcitabine and cisplatin.
Grade 4	• Withhold atezolizumab, gemcitabine, and cisplatin. • If event resolves to Grade 1 or better while withholding atezolizumab, consider resuming atezolizumab. The Medical Monitor is available to advise as needed. If not, permanently discontinue atezolizumab. • First occurrence: If event resolves to Grade 1 or better while withholding gemcitabine and cisplatin, resume gemcitabine and cisplatin reduced by one dose level.[d] If not, permanently discontinue gemcitabine and cisplatin. • Second occurrence: If event resolves to Grade 1 or better while withholding gemcitabine and cisplatin, resume gemcitabine and cisplatin reduced by one dose level.[d] If not, permanently discontinue gemcitabine and cisplatin. • Third occurrence: Permanently discontinue gemcitabine and cisplatin.
Hemolytic uremic syndrome	• Withhold atezolizumab. • If event resolves to Grade 1 or better while withholding atezolizumab, consider resuming atezolizumab. The Medical Monitor is available to advise as needed. If not, permanently discontinue atezolizumab. • Permanently discontinue gemcitabine and cisplatin.

Table A16-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cis + Gem Arm (cont.)

CrCl = creatinine clearance; CRS = cytokine release syndrome; ECMO = extracorporeal membrane oxygenation; GFR = glomerular filtration rate; GI = gastrointestinal; IRR = infusion-related reaction; MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone; VAD = ventricular assist device.

[a] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the assessment of benefit-risk by the investigator and in alignment with the protocol requirements for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

[d] All dose reductions for cisplatin and gemcitabine are permanent. If further dose reduction is indicated for cisplatin and/or gemcitabine after two dose reductions, both drugs should be discontinued, but the patient may continue atezolizumab at the investigator's discretion.

[e] At first occurrence of Grade 4 event, cisplatin and gemcitabine may be withheld for 6 weeks. If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, consider retreating at a reduced dose of two levels below original dose with prophylaxis (if possible). The Medical Monitor is available to advise as needed. If not, permanently discontinue cisplatin and gemcitabine. At second occurrence of Grade 4 event, permanently discontinue cisplatin and gemcitabine.

A16–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR THE ATEZO+CIS+GEM ARM (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 the Atezo + Cis + Gem arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either 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.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ upper limit of normal
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, HLH, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, or toxic epidermal necrolysis)

- Myelitis
- Facial paresis

A16–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN THE ATEZO+CIS+GEM ARM

A16–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab, within 6 months after the final dose of cisplatin, or within 6 months after the final dose of gemcitabine. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail 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 when updated information on the course and outcome of the pregnancy becomes available.

A16–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the final dose of cisplatin, and 6 months after the final dose of gemcitabine. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A16–5.3.3 Abortions

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

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

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

A16–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male 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).

A16–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+CIS+GEM ARM

Table A16-6 Schedule of Activities for Atezo+Cis+Gem Arm (MIBC Cohorts)

		Treatment Cycles (21-Day Cycles)/Surgery						Treat Discon [e]	Follow-Up Q3M (± 7 D) [f]
	Screening [a]	Cycle 1 [b]		Cycles 2–3		Surgery [c]	Cycles 4–17 [d]		
Assessment/Procedure	Days –28 to –1	Day 1	Day 8 (–1 to +3 D)[g]	Day 1 (±3 D)	Day 8 (–1 to +3 D)[g]		Day 1 (±3 D)		
Molecular profile of urothelial carcinoma (if available)	See Appendix 7.	Whenever updated information becomes available							
Vital signs [h]		x		x			x	x	
Weight [i]		x		x			x	x	
Complete physical examination [j]								x	
Limited physical examination [k, i]		x		x			x		
ECOG Performance Status [i]		x		x			x	x	
ECG [l, i]		Perform as clinically indicated.							
Hematology [m]		x [n]	x	x [n]	x		x [n]	x	
Chemistry [o]		x [n]		x [n]			x [n]	x	
TSH, free T3 (or total T3), and free T4 [p]		x [n]						x	
C-reactive protein		x		x			x	x	
Pregnancy test [q]		x		x			x	x	x [q]
Urinalysis [r]		x		x			x		
Serum autoantibody sample [s]		Perform if a patient experiences a suspected immune-related adverse event							
PK samples		Refer to Table A16-7.							

Table A16-6 Schedule of Activities for Atezo + Cis + Gem Arm (MIBC Cohorts) (cont.)

Assessment/Procedure	Screening [a]	Treatment Cycles (21-Day Cycles)/Surgery						Treat Discon [e]	Follow-Up Q3M (± 7 D) [f]
		Cycle 1 [b]		Cycles 2–3		Surgery [c]	Cycles 4–17 [d]		
	Days –28 to –1	Day 1	Day 8 (–1 to +3 D)[g]	Day 1 (±3 D)	Day 8 (–1 to +3 D)[g]		Day 1 (±3 D)		
ADA samples	See Appendix 7.	Refer to Table A16-7.							
Biomarker samples		Refer to Table A16-7.							
Blood sample for RBR (optional) [t]		x							
Stool sample (optional) [u]		x [u]							
Tumor biopsy		x [v]					x [v]		
Tumor response assessments							x [w, x]		
Concomitant medications [y]		x		x			x	x	
Adverse events [z]		x	x	x	x		x	x	x
Atezolizumab administration [aa, bb]		x		x			x		
Cisplatin administration [cc]		x		x					
Gemcitabine administration [dd]		x	x	x	x				
Cystectomy						x [ee]			
Lymph node dissection						x [ee]			
Survival follow-up and anti-cancer treatment									x [ff]

ADA = anti-drug antibody; CT = computed tomography; D = day; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MIBC = muscle invasive bladder cancer; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q3M = every 3 months; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; Treat = treatment; TSH = thyroid-stimulating hormone.

Table A16-6 Schedule of Activities for Atezo + Cis + Gem Arm (MIBC Cohorts) (cont.)

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Patients who fail their first screening for study eligibility may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the initiation of study treatment may be used; such tests do not need to be repeated for screening or re-screening.

[b] Treatment must be initiated no later than 7 days after treatment assignment.

[c] A minimum of 7 days between time of last infusion and surgery is required.

[d] Treatment in Cycle 4 should be reinitiated 4–6 weeks after surgery, but can be reinitiated up to 12 weeks after surgery if surgical complications arise.

[e] Patients will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients.

[f] Patients should return for follow-up visits every 3 months until 24 months after the treatment discontinuation visit. Patients may then continue with standard-of-care treatment with their doctor.

[g] Day 8 dose of gemcitabine may be given no earlier than Day 7 but may be given up to Day 11 (−1 to + 3) of a cycle. Blood counts for gemcitabine dosing should be obtained within 1 day prior to Day 1 and Day 8 of each cycle of therapy if possible.

[h] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, 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. 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 the infusion and at 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 the infusion and at 30 (± 10) minutes after the infusion.

[i] Assessment may be performed within 24 hours prior to dosing during the treatment period.

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

[k] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

Table A16-6 Schedule of Activities for Atezo + Cis + Gem Arm (MIBC Cohorts) (cont.)

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[n] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

[o] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. For U.K. patients, amylase and lipase must be included on Day 1 of each treatment cycle.

[p] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[q] All women of childbearing potential will have a serum pregnancy test at screening. Urine or serum 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. During follow-up, pregnancy tests will be performed at 3 and 6 months. If a pregnancy test was performed within 96 hours prior to Day 1 of Cycle 1, it does not have to be repeated.

[r] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[s] Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[t] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[u] Stool samples will be collected before surgery for cystectomy and lymph node dissection, preferably after Day 1 of Cycle 3. Patients who consent to providing optional stool samples will receive the collection device on or before Day 1 of Cycle 3.

[v] During the study (i.e., up to 24 months after the treatment discontinuation visit), patients will undergo tumor biopsy sample collection at the time of disease recurrence as determined by the investigator (see Section 4.5.7 in the protocol body for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or disease recurrence, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 in protocol body for tissue sample requirements.

[w] Patients will undergo tumor assessments at baseline, within 4 weeks prior to resuming systemic therapy following surgery, and then every 12 weeks (±2 weeks) while on treatment and until 24 months (104 weeks) after the treatment discontinuation visit, regardless of dose delays, or until disease recurrence, whichever occurs first (see Section 3.1.3 in the protocol body for details). Tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease recurrence.

[x] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[y] Includes 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 study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

Table A16-6 Schedule of Activities for Atezo + Cis + Gem Arm (MIBC Cohorts) (cont.)

[z] 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] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[bb] Treatment will continue until unacceptable toxicity or disease recurrence (as defined in Section 4.5.7) or until completion of 14 cycles post-surgery, whichever comes first.

[cc] Cisplatin will be administered by IV infusion at a dose of 70 mg/m^2 on Day 1 of each 21-day cycle for the first 3 cycles. Weight will be measured for dose calculation (baseline weight should be used to calculate dose unless there is a greater than 5% weight change).

[dd] Gemcitabine will be administered by IV infusion at a dose of 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle for the first 3 cycles. Weight will be measured for dose calculation (baseline weight should be used to calculate dose unless there is a greater than 5% weight change). Day 8 gemcitabine should not be administered any earlier than Day 7, but can be administered up to Day 11.

[ee] A specimen from surgical resection (i.e., radical cystectomy) along with an associated pathology report and tissue from lymph node dissection must be submitted. See Section 4.5.8 in protocol body for tissue sample requirements.

[ff] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months for 24 months after the treatment discontinuation visit (unless the patient withdraws consent or the Sponsor terminates the study). If a 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. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table A16-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+Cis+Gem Arm: Preliminary and Expansion Phases (MIBC Cohorts)

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (blood, PBMC, plasma, serum, and urine)
	30 (± 10) minutes after the end of atezolizumab infusion	• Atezolizumab PK (serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (PBMC, plasma and serum)
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (blood and urine)
Surgery for cystectomy	Prior to surgery	• Biomarker (blood, PBMC and urine)
Day 1 of Cycles 4 and 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum in Cycles 4 and 8) • Biomarker (blood and urine, Cycle 4)

ADA = anti-drug antibody; Atezo = atezolizumab; Cis = cisplatin; Gem = gemcitabine; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety 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. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

Table A16-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+Cis+Gem Arm: Preliminary and Expansion Phases (MIBC Cohorts) (cont.)

Visit	Time	Sample Type
Day 1 of Cycle 6 (~3 months post-cystectomy)	At visit	• Biomarker (blood and urine) [a]
Day 1 of Cycle 12	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum) [a]

ADA = anti-drug antibody; Atezo = atezolizumab; Cis = cisplatin; Gem = gemcitabine; PK = pharmacokinetic.

Note: On the basis of emerging safety 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. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Biomarker collections are applicable only after approval from local regulatory authorities.

A16–7 REFERENCES

Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med 2007;13:1050–9.

Belvin MP, Luoh SM, Cheung J, et al. Effects of chemotherapeutic agents on the tumor immune microenvironment [abstract]. American Association of Cancer Research (AACR) 2016;76 (14_suppl).

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.

Butte MJ, Keir ME, Phamduy TB, et al. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

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.

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.

Fehrenbacher L, Spira A, Ballinger M, et al. 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.

Funt AS, Lattanzi M, Whiting K, et al. Neoadjuvant atezolizumab (A) with gemcitabine and cisplatin (GC) in patients (pts) with muscle-invasive bladder cancer (MIBC): A multicenter, single-arm, phase 2 trial. J Clin Oncol 2021;39(15 suppl):4517.

Galsky MD, Guan X, Banchereau R, et al. Cisplatin (cis)-related immunomodulation and efficacy with atezolizumab (atezo) + cis- vs carboplatin (carbo)-based chemotherapy (chemo) in metastatic urothelial cancer (mUC) [abstract]. European Society for Medical Oncology (ESMO) Congress 2021.

Gandhi L, Rodriguez-Abreu D, Gadgeel S, et. al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078–92.

Giaccone G, Camidge DR, Liu SV, et al. Safety, activity and biomarkers of atezolizumab (MPDL3280A) with platinum-based chemotherapy (chemo) in non-small cell lung cancer (NSCLC): A Phase Ib study [abstract 513]. European Society For Medical Oncology at Eur Cancer Congress 2015 (ECC 2105): Sep 25–29 [cited Jan 2017]; Vienna, Austria. Available from: http://www.eccocongress.org/Vienna2015/Scientific-Programme/Abstract-search#.

Gonzalez-Aparicio M, Alzuguren P, Mauleon I, et al. Oxaliplatin in combination with liver-specific expression of interleukin 12 reduces the immunosuppressive microenvironment of tumours and eradicates metastatic colorectal cancer in mice. Gut 2011;60:341–9.

Gupta S, Sonpavde G, Weight CJ, et al. Results from BLASST-1 (Bladder Cancer Signal Seeking Trial) of nivolumab, gemcitabine, and cisplatin in muscle invasive bladder cancer (MIBC) undergoing cystectomy. J Clin Oncol 2020;38(6 suppl):439.

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.

Horn L, Mansfield AS, Szczesna A, et. al. First Line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018;379:2220-9.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.

Langer CJ, Gadgeel SM, Borghael H, et al., Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17:1497–508.

Merritt RE, Mahtabifard A, Yamada RE, et al. Cisplatin augments cytotoxic T-lymphocyte-mediated antitumor immunity in poorly immunogenic murine lung cancer. J Thorac Cardiovasc Surg 2003;126:1609–17.

[NCCN] National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: bladder cancer [resource on the Internet]. 3.2021 [cited 15 July 2021]. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx.

Necchi A, Anichini A, Raggi D, et al. Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): an open-label, single-arm, phase II study. Int J Clin Oncol 2018;36:3353–60.

Paz-Ares L, Luft A, Vincente D, et. al. Pembrolizumab plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer. N Engl J Med 2018;379:2040–51.

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.

Powles T, Kockx M, Rodriguez-Vida A, et al. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. Nat Med 2019;25:1706–1714.

Rizvi NA, Hellmann MD, Brahmer JR, et al. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non–small-cell lung cancer. J Clin Oncol 2016;34:2969–79.

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 2011;61:1229–38.

Sato E, Olson SH, Ahn J, et al. Intraepithelial CD8+ tumor-infiltrating lymphocytes and high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. Proc Natl Acad Sci USA 2005;102:18538–43.

Schmid P, Adams S, Rugo HS, et. al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 2018;379:2108–21.

Tecentriq® (atezolizumab) U.S. Package Insert, Genentech.

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 17
Study Details Specific to Atezo+Tira+Cis+Gem Arm

Note: This appendix is not applicable to France.

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A17–1 BACKGROUND ON ATEZO+TIRA+CIS+GEM ARM

A17–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin (IgG1) monoclonal antibody that targets programmed death-ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed death-1 (PD-1) and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. 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 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 cancer patients 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 has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, myocarditis, and nephritis, have been observed (see the Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab (Tecentriq®) is approved for the treatment of urothelial carcinoma (UC), non-small cell lung cancer (NSCLC), 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.

A17–1.2 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/kappa mAb derived in Open Monoclonal Technology (OMT) rats that binds T-cell Immunoreceptor with Immunoglobulin and Immunoreceptor Tyrosine-Based Inhibition Motif [ITIM] domains (TIGIT) and prevents its interaction with the poliovirus receptor (PVR). The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and consists of two heavy chains (456 amino acid residues each) and two light chains (220 amino acid residues each).

The inhibitory immunoreceptor TIGIT has been shown to limit the effector function of tumor-associated lymphocytes. TIGIT is an immunoglobulin (Ig) super family member expressed on subsets of activated T cells and natural killer (NK) cells, and found highly expressed in tumor tissue and in tumor-infiltrating immune cells in many human cancers, including, but not limited to NSCLC, breast cancer, multiple myeloma (MM), and non-Hodgkin lymphoma (NHL). In multiple tumor types, TIGIT is coordinately expressed with PD-1 (Yu et al. 2009; Johnston et al. 2014; Manieri et al. 2017). Genetic ablation or antibody blockade of TIGIT has been shown to enhance NK cell killing, CD4+ and CD8+ T-cell activation, and effector function in vitro and in vivo in nonclinical models (Yu et al. 2009; Johnston et al. 2014; Stanietsky et al. 2009; Joller et al. 2011). In the nonclinical tumor models, TIGIT interacted with high affinity to CD155 (also known as PVR), which also has an activating counter-receptor CD226. Activation of TIGIT on T cells and NK cells was demonstrated to limit proliferation, effector cytokine production, and killing of target tumor cells (Yu et al. 2009; Stanietsky et al. 2009; Johnston et al. 2014).

Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of the tumor-specific T-cell responses, which may result in improved meaningful anti-tumor activity when tiragolumab is used in combination with other cancer immunotherapies and administered with chemotherapy. The available nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in cancer patients.

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

A17–2 RATIONALE FOR ATEZO+TIRA+CIS+GEM ARM

A17–2.1 THE PD-L1 PATHWAY

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).

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.

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 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).

A17–2.2 THE TIGIT PATHWAY

TIGIT is an immune inhibitory receptor that is a member of the immunoglobulin super family (Yu et al. 2009). TIGIT is expressed on the surface of activated T cell and NK cell subsets and interacts with high affinity with CD155 (also known as PVR) (Yu et al. 2009). Genetic ablation of TIGIT in T cells in mice results in exacerbated T-cell responses in nonclinical models of autoimmune and viral infections, demonstrating the role of TIGIT in inhibiting T-cell responses (Joller et al. 2011; Johnston et al. 2014). TIGIT expression is elevated in the tumor microenvironment in many human tumors, is concordantly expressed with other checkpoint immune-receptors such as PD-1 on the surface of T cells, and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014; Manieri et al. 2017). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014; Wang et al. 2015; Manieri et al. 2017).

TIGIT is expressed in a wide variety of human tumors, including most solid tumors, such as NSCLC, breast cancer and melanoma, and hematological tumors, such as MM and NHL, and fluorescence activated cell sorting (FACS) analysis of T cells isolated from fresh tumor samples revealed that TIGIT and PD-1 are also co-expressed on tumor infiltrating T cells (Johnston et al. 2014; Yadav et al. 2016; Yang 2016; Guillerey at al. 2018). TIGIT expression ranged from 30%–80% and 50%–80% on tumor-infiltrating CD4+ and CD8+ T cells, respectively (Johnston et al. 2014).

Therefore, TIGIT is a potential target for therapeutic intervention, aimed at restoring the immune response against the tumor. Agents that inhibit TIGIT's interaction with PVR may inhibit an important source of tumor-associated immune suppression and therefore may enhance the activity of other immune-based therapies. Nonclinical studies using genetically deficient mice and blocking antibodies have revealed a key role for TIGIT in

regulating T-cell responses in cancer. Together these data support the hypothesis that anti-TIGIT may reactivate anti-tumor immunity and provide clinical benefits to patients with cancer.

A17–2.3 NONCLINICAL DATA SUPPORTING THE COMBINED INHIBITION OF THE PD-L1/PD-1 PATHWAY WITH CHEMOTHERAPY

In nonclinical immune competent mouse tumor models, chemotherapy treatment with multiple classes of chemotherapeutic agents resulted in activation or increase of tumor infiltrating CD8+ T cells, whereas there was a depletion of peripheral immune cells, including CD8+ T cells (Belvin et al. 2016). Combination of anti–PD-L1 with several chemotherapeutic agents showed combination efficacy, correlating with the increased activation of tumor infiltrating CD8+ T cells (Belvin et al. 2016). Depending on the immune context of the nonclinical model tested, chemotherapeutic agents showed different mechanisms of activating CD8+ T cells, including increased interferon (IFN)-γ production, increased Granzyme B levels, and decreased markers of exhaustion (Belvin et al. 2016). Tumor cell killing by cytotoxic chemotherapy may expose the immune system to high levels of tumor antigens, and invigorating tumor specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007), and this may reasonably occur in tumors regardless of PD-L1 expression.

In addition, in nonclinical models, oxaliplatin has been shown to enhance immune responses by decreasing T-regulatory cells and myeloid-derived suppressor cells in tumor microenvironment (Sato et al. 2005; Gonzalez-Aparicio et al. 2011), suggesting potential synergy with immunotherapy induced by PD-L1 blockade.

Based on this nonclinical data, these regimens may enhance the efficacy of atezolizumab in patients with urothelial cancer.

A17–2.4 CLINICAL DATA SUPPORTING THE COMBINED INHIBITION OF THE PD-L1/PD-1 PATHWAY WITH CHEMOTHERAPY

The addition of PD-L1 and PD-1 checkpoint inhibitors to standard platinum-based chemotherapy demonstrated encouraging anti-tumor activity and acceptable safety in early Phase I and II studies (Giaccone et al. 2015; Langer et al. 2016; Rizvi et al. 2016).

In multiple large Phase III clinical trials, the addition of PD-L1 and PD-1 checkpoint inhibitors to standard chemotherapy led to significantly longer overall survival (OS) and progression-free survival for patients compared with chemotherapy alone (Gandhi et al. 2018; Paz-Ares et al. 2018; Horn et al. 2018; Schmid P et al. 2018). As a result, combinations of PD-1/PD-L1 checkpoint inhibitors with chemotherapies have been

approved for patients with different advanced cancers. Several single-arm studies have evaluated combinations of checkpoint inhibitors with chemotherapy in the neoadjuvant setting for patients with muscle invasive bladder cancer (MIBC) (Gupta et al. 2020, Funt et al. 2021). In the BLASST-1 trial, 41 patients with MIBC received gemcitabine plus cisplatin plus nivolumab for 4 cycles before radical cystectomy with 27 out of 41 (65.8%) patients experiencing a pathological downstaging less than pT1 at the time of cystectomy (Gupta et al. 2020). The frequency of PD-L1+ and PD-L1− patients in the BLASST-1 trial was not reported. In a separate study evaluating the combination of gemcitabine plus cisplatin plus atezolizumab in patients with MIBC, 27 out of 39 patients showed a pathologic response less than pT2, with 17 out of 39 (44%) patients showing pathological complete response (pCR). Notably, 90% of patients had PD-L1− tumor, of which 4 out of 4 patients with PD-L1+ tumors, achieved a tumor downstaging less than pT2; 11 out of 11 patients who did not respond had PD-L1− tumors, and 23 out of 27 (85%) patients who responded had PD-L1− tumors. These results contrast with those of the ABACUS study, where patients with PD-L1− disease had fewer pCR than patients with PD-L1+ disease (24.5% vs 37.1%; Powles et al. 2021). This also contrasts with the results from the PURE-01 study where patients with PD-L1+ disease also showed a higher pCR rate than patients with PD-L1− disease (54.3% vs 13.3%; Necchi et al. 2018). Further investigations are needed to better assess the impact of adding PD-L1 and PD-1 checkpoint inhibitors to cisplatin-based chemotherapy in patients with MIBC, in particular in those with PD-L1− disease.

Historically, only patients who achieve a pCR after neoadjuvant chemotherapy can expect to derive a durable benefit with improved OS (Rosenblatt et al. 2012; Petrelli et al. 2014). The results presented above suggest that the addition of PD-L1 and PD-1 checkpoint inhibitors to chemotherapy could also confer a durable benefit to patients who experience a pathological downstaging (Funt et al. 2021). The duration of recurrence-free survival in patients who experienced an incomplete pathological downstaging following neoadjuvant treatment with gemcitabine plus cisplatin plus atezolizumab will require longer follow up.

The IMvigor130 study is an ongoing Phase III study comparing atezolizumab monotherapy with chemotherapy and the combination of atezolizumab plus platinum-based chemotherapy, in patients with untreated locally advanced or metastatic UC. Patients received either cisplatin or carboplatin in combination with gemcitabine as their chemotherapy. Exploratory analyses suggest improved OS with the addition of atezolizumab to cisplatin-based chemotherapy but not for patients who received carboplatin-based chemotherapy. Patients treated with gemcitabine plus cisplatin plus atezolizumab showed an improved OS when compared to patients treated with gemcitabine plus carboplatin plus atezolizumab, or gemcitabine plus cisplatin plus placebo or gemcitabine plus carboplatin plus placebo (Table A17-1).

Table A17-1 Efficacy Outcomes in Patients Treated with Atezolizumab Plus Chemotherapy in IMvigor 130

IMvigor130: treatment subgroups	IC0/1		IC2/3		HR (95% CI)
	n	Median OS (months)	n	Median OS (months)	
Arm A (atezo + cis/gem)	102	19.5	35	Not reached	0.46 (0.25, 0.83)
Arm A (atezo + carbo/gem)	241	13.9	73	16.6	0.85 (0.61, 1.17)
Arm C (placebo + cis/gem)	102	12.8	34	27.9	0.51 (0.30, 0.86)
Arm C (placebo + carbo/gem)	207	13.0	57	14.0	1.00 (0.71, 1.42)

Atezo = atezolizumab; carbo = carboplatin; cis = cisplatin; gem = gemcitabine; HR = hazard ratio; IC0/1 = presence of programmed death-ligand 1 (PD-L1)–expressing immune cells on < 5% of the tumor area; IC2/3 = presence of PD-L1–expressing immune cells on ≥ 5% of the tumor area; OS = overall survival.

Note: PD-L1 expression on tumour-infiltrating immune cells assessed from archival pretreatment tumor samples (VENTANA SP142 assay).

In the IMvigor130 study, single-cell RNA sequencing (scRNA-seq) was performed on peripheral blood mononuclear cells (PBMCs) obtained at Day 1 of Cycles 1 and 3 from 70 patients receiving atezolizumab plus platinum (cisplatin or carboplatin) and gemcitabine (Arm A) or placebo plus platinum (cisplatin or carboplatin) and gemcitabine (Arm C) in order to assess for differences in the immune profiles of patients treated with cisplatin vs carboplatin. When comparing patients treated with cisplatin versus carboplatin, on-treatment enrichment of hallmark tumor necrosis factor (TNF)–α signaling via NF-κB and inflammatory response gene sets was observed across all immune cell clusters and the trends were even more pronounced in patients treated with the combination of cisplatin plus gemcitabine plus atezolizumab. Among the top-ranked genes enriched in PBMCs in patients treated with cisplatin versus carboplatin following chemotherapy was NINJ1, which mediates plasma membrane rupture during lytic cell death, releasing damage-associated molecular patterns such as HMGB1, a key player driving immunogenicity in cell death (Apetoh et al. 2007; Galsky et al. 2021).

The results from the IMvigor130 study, as well as ongoing studies evaluating immunotherapy with and without chemotherapy in MIBC, suggest that cisplatin/gemcitabine induces immunogenic cell death and enhances anti-tumor immunity when combined with atezolizumab, even in patients with PD-L1– disease.

A17–2.5 COMBINED INHIBITION OF THE PD-L1/PD-1 AND TIGIT PATHWAYS

Durable clinical benefit is limited to a minority of patients treated with single-agent PD-L1/PD-1 inhibitors. Therapies targeting the mechanisms of resistance to anti-PD-L1/PD-1 therapies are needed to improve outcomes in patients with solid

cancers. Resistance to PD-L1/PD-1 blockade may result in the expression of multiple co-inhibitory receptors on the surface of effector T cells. Nonclinical tumor models have shown that TIGIT selectively suppressed the effector function of chronically stimulated CD8+ T cells, and that inhibiting both TIGIT and PD-L1/PD-1 resulted in superior efficacy compared with single-agent treatments (Johnston et al. 2014). Hence, respectively targeting both TIGIT and PD-L1 with tiragolumab and atezolizumab in patients may enhance the efficacy of PD-L1/PD-1 blockade across different cancer types.

A17–2.6 COMBINED INHIBITION OF THE PD-L1/PD-1 AND TIGIT PATHWAYS WITH CHEMOTHERAPY

Because of the established benefit to patients of adding PD-L1 and PD-1 checkpoint inhibitors to chemotherapy in many solid tumors, and the nonclinical finding that concomitant blockade of both TIGIT and PD-L1/PD-1 pathways demonstrated superior efficacy over single-agent PD-L1/PD-1 blockade, it is hypothesized that the combination of TIGIT and PD-L1/PD-1 blockade with chemotherapy may result in even deeper and more durable responses compared with standard chemotherapy alone or even single agent PD-L1/PD-1 blockade and chemotherapy. Evaluating the safety and efficacy of tiragolumab and atezolizumab with chemotherapy in patients with MIBC in this study will enable future tests of this hypothesis.

A17–2.7 CLINICAL STUDIES OF TIRAGOLUMAB

Tiragolumab is currently under investigation in two ongoing clinical studies in patients with solid tumors (Studies GO30103 and GO40290) and one ongoing clinical study in patients with hematological malignancies (Study GO40136).

A17–2.7.1 Clinical Study of Tiragolumab as a Single Agent or in Combination with Atezolizumab

Study GO30103 is a first-in-human, open-label, multicenter, global, dose-escalation/dose-expansion Phase I study designed to evaluate the safety, tolerability, and pharmacokinetics of tiragolumab as a single agent (Phase Ia) and in combination with atezolizumab (Phase Ib) in patients with locally advanced, recurrent, or metastatic incurable tumors.

As of the data cutoff date of 3 December 2018, 42 patients have been enrolled in the Phase Ia portion of the study of tiragolumab monotherapy evaluating dose levels from 2 mg to 1200 mg, and 164 patients have been enrolled in Phase Ib portion evaluating dose levels of tiragolumab from 2 mg to 600 mg, in combination with 1200 mg atezolizumab. Twenty-three patients crossed over from the Phase Ia portion of the study to the Phase Ib portion. One patient in the Phase Ib portion was enrolled in the study at the tiragolumab dose level of 30 mg but was not treated with study drug(s) (tiragolumab and/or atezolizumab) as of the clinical cutoff date.

As of 3 December 2018, the best observed response in the Phase Ia portion of the study was prolonged stable disease in 8 of 42 patients with some patients experiencing a decrease in tumor size with single-agent tiragolumab. In the Phase Ib portion of the study of tiragolumab in combination with atezolizumab, a complete response was observed in 3 of 164 patients (400 mg [n = 2] and 600 mg [n = 1]), a partial response in 22 out of 164 patients (30 mg [n = 2], 400 mg [n = 7], and 600 mg [n = 13]), and stable disease was observed in 38 out of 164 patients (2 mg [n = 1], 8 mg [n = 3], 30 mg [n = 2], 100 mg [n = 3], 400 mg [n = 12], 600 mg [n = 16], and 1200 mg [n = 1]). This included patients with multiple solid tumor types, including urothelial cancer, renal cell cancer, NSCLC, HNSCC, esophageal cancer, and triple-negative breast cancer.

Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence or severity of adverse events in the Phase Ia or Phase Ib portions of Study GO30103 in solid tumors have been determined for tiragolumab as a single agent and in combination with atezolizumab. A fatal case of hepatic toxicity culminating in fulminant liver failure occurred in a patient with metastatic head and neck cancer enrolled in the Phase Ia expansion cohort of Study GO30103 at the highest dose of tiragolumab (1200 mg) that had cleared in dose escalation. The dose of tiragolumab in Study WO39613 will be 600 mg.

Overall, tiragolumab as a single agent or in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile is observed to be consistent across different solid tumor indications.

A17–2.7.2 Clinical Study of Tiragolumab in Combination with Atezolizumab in PD-L1–Selected Patients with NSCLC

Study GO40290 is a global, multicenter, randomized, blinded, placebo-controlled Phase II study designed to evaluate the safety and efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated, locally advanced unresectable, or metastatic PD-L1–selected NSCLC.

As of the primary clinical cutoff date of 30 June 2019, a total of 135 patients with a PD-L1 TPS ≥ 1% were included in the intent-to-treat (ITT) population and were randomly assigned to receive tiragolumab plus atezolizumab (n = 67) or placebo plus atezolizumab (n = 68). Of the enrolled patients, 43.0% of patients had a TPS ≥ 50% relative to 57.0% of patients with a TPS 1%–49%, 59.3% had non-squamous histology compared with 40.7% of patients who had squamous histology, and 10.4% of patients were never-smokers versus 89.6% who had smoked. These three stratification factors were well balanced between treatment groups. Demographics were also generally well balanced between treatment groups, with a median age of 68 years in both the tiragolumab plus atezolizumab and placebo plus atezolizumab arms. There were more

females (41.8% vs. 29.4%) and more White patients (62.7% vs. 58.8%) in the tiragolumab plus atezolizumab arm compared with the placebo plus atezolizumab arm.

In the ITT population, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (31.3%) than in the placebo plus atezolizumab arm (16.2%). In the subgroup of patients with TPS ≥50%, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (n=29; 55.2% [95% CI: 35.4%, 75.0%]) than the placebo plus atezolizumab arm (n=29; 17.2% [95% CI: 1.8%, 32.7%]). Of note, responders in the tiragolumab plus atezolizumab arm included patients with both squamous and non-squamous histology.



To date, most adverse events have been Grade 1 or Grade 2. Serious adverse events, Grade 3–5 adverse events, adverse events leading to discontinuation, and adverse events leading to death have been balanced between the two treatment arms. Serious and high-grade treatment-related adverse events have also been balanced between the two treatment arms. Immune-mediated adverse events were balanced between the two treatment arms, with the exception of a higher frequency of infusion-related reaction (IRR) and rash reported in the atezolizumab plus tiragolumab arm. Discontinuation due to adverse events was low (approximately 6% in both arms). A fatal case of Epstein-Barr virus (EBV) reactivation and possible secondary hemophagocytic lymphohistiocytosis (HLH) was reported in Study GO40290 in a [redacted]year-old male in [redacted] with metastatic lymphoepithelioma-like carcinoma subtype of NSCLC (PD-L1 positive), which can be associated with EBV infection in [redacted] patients.

Overall, tiragolumab in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile seems to be consistent as reported across different solid tumor indications.

Refer to the Tiragolumab Investigator's Brochure for additional details on all ongoing and planned clinical studies.

A17–2.8 BENEFIT-RISK ASSESSMENT

Taking into account the potentially synergistic mechanisms of action for tiragolumab and atezolizumab, as well as the preliminary efficacy data and manageable safety profiles for each of the combinations described in Sections A17–2.7 and A17–2.4, treatment with atezolizumab plus tiragolumab plus chemotherapy (cisplatin and gemcitabine) may have promising therapeutic potential for patients with cisplatin-eligible MIBC.

Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in patients receiving atezolizumab in combination with chemotherapy. Patients with severe infection within 4 weeks prior to initiation of study treatment will be excluded. Patients experience adverse events will be managed according to the management guidelines.

The majority of immune-mediated adverse events reported in this arm of the study (as of CCOD 8 February 2023) have been low grade and manageable, however two severe myositis cases were reported, including one case with a fatal outcome, which led to a clinical hold from the U.S. Food and Drug Administration (FDA) on the enrollment for MIBC Cohort 3. A further investigation of immune-mediated adverse events in the tiragolumab development program did not reveal a significant increase of reported immune-mediated adverse events when tiragolumab was added to the atezolizumab-containing regimens. However, the addition of certain chemotherapies, for example, cisplatin and gemcitabine, might lead to the development of severe myositis, or myositis with overlapping toxicities, such as with myocarditis and myasthenia gravis.

Additional safety measures, including exploratory troponin and CPK surveillance at each cycle for all patients enrolled in this arm and updated guidelines for management (Appendix 6) have been added to this study to protect patient safety.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of atezolizumab, tiragolumab, cisplatin, and gemcitabine may be found in the Tiragolumab and Atezolizumab Investigator's Brochures and cisplatin and gemcitabine prescribing information.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit-risk assessment, please refer to Section 1.5.

A17–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+TIRA+CIS+GEM ARM

A17–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for

atezolizumab (Tecentriq® U.S. Package Insert; Tecentriq SmPC). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached, and no dose-limiting toxicities (DLTs) 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 pharmacokinetic (PK), efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A17–3.2 RATIONALE FOR TIRAGOLUMAB DOSE AND SCHEDULE

Tiragolumab will be administered at a fixed dose of 600 mg IV Q3W (600 mg on Day 1 of each 21-day cycle). The fixed dose of 600 mg IV Q3W was selected based on available clinical PK, efficacy, and safety data from the combined Phase Ia/Phase Ib Study GO30103, with single-agent tiragolumab or tiragolumab in combination with atezolizumab. In the Phase Ia portion of the study with tiragolumab as a single agent, the MTD was not reached, and no DLTs were observed in dose-escalation. [redacted] Prolonged stable disease was observed in patients in the Phase Ia portion of the study at tiragolumab doses beginning at 400 mg. In the Phase Ib portion of the study with tiragolumab plus atezolizumab, the MTD was not reached. Anti-tumor activity, as measured by radiographic partial responses, was observed across doses for tiragolumab beginning at 30 mg and ranging up to 600 mg in combination with 1200 mg atezolizumab.

Refer to the Tiragolumab Investigator's Brochure for additional details.

A17–3.3 RATIONALE FOR CISPLATIN AND GEMCITABINE DOSE AND SCHEDULE

In this study, cisplatin at a dose of 70 mg/m^2 will be administered by IV infusion on Day 1 of each 21-day cycle. This is the current recommended cisplatin dosage in the National Comprehensive Cancer Network (NCCN) guidelines for the neoadjuvant treatment of MIBC (NCCN Guidelines, Version 3.2021).

In this study, gemcitabine at a dose of 1000 mg/m^2 will be administered by IV infusion on Days 1 and 8 of each 21-day cycle. This is the current recommended gemcitabine dosage in the NCCN guidelines for the neoadjuvant treatment of MIBC (NCCN Guidelines, Version 3.2021).

A17–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+TIRA+CIS+GEM ARM

A17–4.1 SAFETY EVALUATION IN ATEZO+TIRA+CIS+GEM ARM

Because of the potential for overlapping toxicities (immune mediated toxicities, gastrointestinal [GI] toxicities, hepatotoxicity, hematologic toxicity, renal toxicity, cardiac toxicities, pulmonary toxicities, neurologic toxicities, and skin toxicities), special caution will be taken by performing a planned safety evaluation (see Section 3.1.4.2 in protocol body). Randomization to the Atezo+Tira+Cis+Gem arm will be paused after the enrollment of 6 patients until all of the patients in that arm have completed a safety evaluation of at least one cycle (21 days) of treatment. Patients who withdraw prior to 21 days will not be replaced, and the safety evaluation will be based on the available data at the time all remaining patients have a follow-up of 21 days. If the combination is sufficiently safe, randomization will be resumed.

A17–4.2 TREATMENT IN ATEZO+TIRA+CIS+GEM ARM

A17–4.2.1 Formulation, Packaging, and Handling

A17–4.2.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

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

A17–4.2.1.2 Tiragolumab

The tiragolumab drug product will be supplied in single-use, 15-mL glass vials. The vials contain 10 mL of tiragolumab drug product and are buffered in histidine solution containing polysorbate 20, sucrose, L-methionine, and WFI. The approximate concentration of tiragolumab antibody in the vials is 60 mg/mL.

For information on the formulation and handling of tiragolumab, see the pharmacy manual and the Tiragolumab Investigator's Brochure.

A17–4.2.1.3 Cisplatin

For information on the formulation, packaging, and handling of cisplatin, refer to the local prescribing information.

A17–4.2.1.4 Gemcitabine

For information on the formulation, packaging, and handling of gemcitabine, refer to the local prescribing information.

A17–4.2.2 Dosage, Administration, and Compliance

Patients in the Atezo + Tira + Cis + Gem arm will receive treatment as outlined in Table A17-2. Patients will undergo surgery after Cycle 3; treatment in Cycle 4 should be reinitiated 4–6 weeks after surgery, but can be reinitiated up to 12 weeks after surgery if surgical complications arise (see Table A17-2). Treatment will continue until Cycle 17. It is recommended that treatment be initiated as soon as possible and no later than 7 days after randomization.

Table A17-2 Treatment Regimen for Atezo + Tira + Cis + Gem Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
Cycles 1–3 Before Surgery 21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Tiragolumab 600 mg IV on Day 1 of each cycle • Gemcitabine 1000 mg/m^2 IV on Days 1 and 8 of each cycle • Cisplatin 70 mg/m^2 IV on Day 1 of each cycle
Cycles 4–17 After Surgery 21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Tiragolumab 600 mg IV on Day 1 of each cycle

Atezo = atezolizumab; Cis = cisplatin; Gem = gemcitabine; Tira = tiragolumab.
Note: On Day 1 of each cycle, chemotherapy will be administered after completion of the atezolizumab and tiragolumab infusions.

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

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab or tiragolumab are available.

A17–4.2.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle for all 17 cycles.

Administration of atezolizumab 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A17-3.

Table A17-3 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • After the infusion of atezolizumab, the patient begins a 30-minute observation period. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during the infusion and at 30 (±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, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Guidelines for medical management of IRRs for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A17–5.1.6.3. Atezolizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

A17–4.2.2.2 Tiragolumab

Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle (for all 17 cycles) with a post-infusion observation period as described in Table A17-4.

Administration of tiragolumab 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 5. Tiragolumab infusions will be administered per the instructions outlined in Table A17-4.

Table A17-4 Administration of First and Subsequent Tiragolumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the tiragolumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Tiragolumab should be infused over 60 (±10) minutes. • After the infusion of tiragolumab, the patient begins a 60-minute observation period. • Record vital signs every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. • Patients will be informed about the possibility of delayed post-infusion symptoms and will be 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, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Tiragolumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±10) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient tolerated the previous infusion of tiragolumab well without infusion-associated adverse events, the observation period may be reduced to 30 minutes. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 15 (±10) minutes after the infusion.

Guidelines for medical management of IRRs for tiragolumab are provided in Appendix 6.

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A17–5.1.6.3. Tiragolumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with tiragolumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

A17–4.2.2.3 Cisplatin and Gemcitabine

Cisplatin and gemcitabine will be administered according to the local prescribing information. Cisplatin will be administered by IV infusion at a dose of 70 mg/m^2 on Day 1 of each 21-day cycle for the first 3 cycles only. Gemcitabine will be administered by IV

infusion at a dose of 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle for the first 3 cycles only.

Prior to treatment with cisplatin, patients must receive appropriate pretreatment hydration. Premedication with steroids should be limited when clinically feasible, because of their immunosuppressant effects. Prophylactic anti-emetics (e.g., 5-HT3 receptor antagonists) may be administered per local practice. All medications must be recorded on the appropriate Concomitant Medications eCRF.

Cisplatin and gemcitabine will be administered in the first 3 cycles only, unless unacceptable toxicity occurs or the patient is withdrawn from study treatment for any reason.

Guidelines for cisplatin and gemcitabine dose modification, treatment interruption, and discontinuation because of toxicities are provided in Section A17–5.1.6.

Cisplatin and gemcitabine treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

A17–4.3 CONCOMITANT THERAPY FOR ATEZO+TIRA+CIS+GEM ARM

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 study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A17–4.3.1 Permitted Therapy for Atezo + Tira + Cis + Gem Arm

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

- Oral contraceptives with a failure rate of < 1% per year (see Section A17–4.4)
- 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 A17–4.3.3).
- 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
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab and tiragolumab may be continued during palliative radiotherapy. Chemotherapy should be interrupted as per institutional standard of care.
- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

Premedication with antihistamines, antipyretics, 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 therapies other than those defined as cautionary or prohibited therapies (see Sections A17–4.3.2 and A17–4.3.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-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 5).

A17–4.3.2 Cautionary Therapy for Atezo + Tira + Cis + Gem Arm

A17–4.3.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab and tiragolumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not

feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α 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 and tiragolumab therapy (refer to Appendix 6 for details).

A17–4.3.2.2 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 A17–4.3.3) may be used during the study at the discretion of the investigator.

A17–4.3.2.3 Cautionary Therapy Related to Cisplatin

Caution should be used when co-administering nephrotoxic (e.g., cephalosporins, aminoglycosides, or amphotericin B or contrast media) or ototoxic (e.g., aminoglycosides, loop diuretics) medicinal products that will potentiate the toxic effect of cisplatin on the kidneys and auditory function. Starting a new anti-convulsant treatment with phenytoin is strictly contraindicated during cisplatin therapy.

A17–4.3.3 Prohibited Therapy for Atezo + Tira + Cis + Gem Arm

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 4.1.4 in the protocol body), and during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined above in Section A17–4.3.1.
- Investigational therapy (other than protocol-mandated study treatment) 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 treatment with atezolizumab and tiragolumab, and for 5 months after the final dose of atezolizumab and for 90 days after the final dose of tiragolumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug (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 and/or tiragolumab.

A17–4.4 CONTRACEPTION REQUIREMENTS FOR ATEZO+TIRA+CIS+GEM ARM

Contraception requirements for men and women in the Atezo + Tira + Cis + Gem arm are outlined below:

- 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, for 90 days after the final dose of tiragolumab, for 6 months after the final dose of cisplatin, and for 6 months after the final dose of gemcitabine. Women must refrain from donating eggs during this same period

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and 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 acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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

  With a female partner of childbearing potential who is not pregnant, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for 90 days after the final dose of tiragolumab, for 6 months after the final dose of cisplatin, and for 6 months after the final dose of gemcitabine. Men must refrain from donating sperm during this same period.

With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of cisplatin and gemcitabine to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

A17–5 ASSESSMENT OF SAFETY FOR ATEZO+TIRA+CIS+GEM ARM

A17–5.1 SAFETY PLAN FOR ATEZO+TIRA+CIS+GEM ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab, tiragolumab, cisplatin, and gemcitabine in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A17–5.1.1, A17–5.1.2, A17–5.1.3, A17–5.1.4, and A17–5.1.5). Guidelines for management of patients who experience specific adverse events are provided in Section A17–5.1.6.

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. Because of the potential for overlapping toxicities (immune-mediated toxicities, GI toxicities, hepatotoxicity, hematologic toxicity, renal toxicity, cardiac toxicities, pulmonary toxicities, neurologic toxicities, and skin toxicities) identified for atezolizumab in combination with tiragolumab, cisplatin, and gemcitabine, special caution will be taken with a planned safety evaluation of the first 6 patients randomized to Atezo+Tira+Cis+Gem arm. Randomization to the Atezo+Tira+Cis+Gem arm will be paused after the enrollment of 6 patients until all of the patients in that arm have completed a safety evaluation of 21 days. If the combination is sufficiently safe, randomization will be resumed.

In addition the following events will trigger a permanent halt in enrollment:

- Any event of Grade 4 or Grade 5 myositis or any Grade 5 adverse event of special interest

The following events will result in a halt in enrollment and Internal Monitoring Committee review:

- A Grade 4 adverse event of special interest occurring in either the pre or post surgical period
- If >20% of patients have a treatment-related adverse event causing a >4 week delay in surgery (from the planned surgery date)

Administration of atezolizumab, tiragolumab, cisplatin, and gemcitabine 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. Adverse events will be reported as described in Sections 5.2–5.6. An Internal Monitoring Committee and Scientific Oversight Committee will review safety data throughout the study as described in Section 3.1.6.

A17–5.1.1 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, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to HLH. Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A17–5.1.2 Risks Associated with Tiragolumab

IRRs and immune-mediated hepatitis are identified risks of tiragolumab. Lymphopenia is an identified risk of tiragolumab when used in combination with atezolizumab and chemotherapies.

Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events).

Refer to Appendix 6 of the protocol and Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of anticipated safety risks for tiragolumab.

A17–5.1.2.1 Infusion-Related Reactions

Because tiragolumab is a therapeutic monoclonal antibody and targets immune cells, IRRs associated with hypersensitivity reactions and/or target-mediated cytokine release may occur. Clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

IRRs have been reported in patients treated with tiragolumab, with or without atezolizumab. The majority of events were mild to moderate and manageable.

To minimize the risk and sequelae of IRRs, the initial dose of tiragolumab will be administered over 60 minutes followed by a 60-minute observation period. Subsequent

infusions and observation times may be shortened if the preceding infusion was well tolerated. All infusions of tiragolumab will be administered in an appropriate medical setting.

Refer to Section A17–4.2.2.2 for detailed guidance on administration of tiragolumab in this study. Refer to Appendix 5 for guidance on anaphylaxis precautions and Appendix 6 for guidance on management of IRRs.

A17–5.1.2.2 Immune-Mediated Hepatitis

The use of tiragolumab to block the immune inhibitory receptor TIGIT serves to increase a baseline T-cell and NK-cell immune response, especially in combination with other checkpoint inhibitors (i.e., atezolizumab). A disruption in the functioning of immune checkpoint molecules may lead to imbalances in immunologic tolerance that results in an unchecked immune response, including immune-mediated hepatitis.

Refer to Appendix 6 for guidance on the management of immune-mediated hepatitis.

A17–5.1.2.3 Lymphopenia

The IgG1 backbone of tiragolumab with the intact Fc-effector function may lead to antibody-dependent cell-mediated cytotoxicity-mediated reduction in lymphocyte count. Lymphopenia is an identified risk with tiragolumab in combination with atezolizumab and chemotherapies.

Transient decreases in lymphocyte count without clinical sequelae have been observed in patients treated with tiragolumab, with or without atezolizumab. Patients with a lymphocyte count < 500 cells/mL will be excluded from this study (see Section 4.1.3), and CBCs will be monitored regularly during the study (see Section A17–6).

A17–5.1.2.4 Immune-Mediated Adverse Events

Nonclinical models have suggested a role of TIGIT signaling interruption in autoimmunity. In a knockout model (TIGIT–/–), loss of TIGIT signaling resulted in hyperproliferative T-cell responses and exacerbation of experimental autoimmune encephalitis (EAE). TIGIT–/– and wild-type B6 mice were immunized with myelin oligodendrocyte glycoprotein peptide in an EAE using suboptimal doses. In contrast to the wild-type B6 mice, the majority of the TIGIT–/– mice developed severe EAE (Joller et al. 2011).

Clinical experience with therapeutic agents intended to enhance anti-tumor T-cell responses has demonstrated that development of autoimmune inflammatory conditions is a general risk and may therefore be considered a potential risk of tiragolumab. Such immune-mediated adverse events have been described for virtually all organ systems and include, but are not limited to colitis, pneumonitis, endocrinopathies, ocular toxicity,

pancreatic toxicity, neurologic toxicity, cardiac toxicity, nephritis, myositis, and severe cutaneous adverse reactions.

Patients with a history of autoimmune disease will be excluded from this study (see Section 4.1.4.1).

Management guidelines for individual suspected immune-mediated adverse events are provided in A17–5.1.6.

A17–5.1.2.5 Embryofetal Toxicity

Embryofetal toxicity is a potential risk with tiragolumab. Administration of tiragolumab is expected to have adverse effects on pregnancy based on the expression of TIGIT on decidual NK and $CD8^+$ T cells (Powell et al. 2017; van der Zwan et al. 2018; Vento-Tormo et al. 2018), and the expected role of these cells in the recognition and response to foreign fetal, placental, and viral antigens at the maternal-fetal interface as well as maintenance of maternal-fetal tolerance. No reproductive or teratogenicity studies in animals have been conducted with tiragolumab. There are no clinical studies of tiragolumab in pregnant women. Tiragolumab should not be administered to pregnant women.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of embryofetal toxicity.

A17–5.1.3 Risks Associated with Cisplatin

The most common adverse events (> 10%) with cisplatin are hematological (leukopenia, thrombocytopenia and anemia), gastrointestinal (GI) (anorexia, nausea, vomiting and diarrhea), ear disorders (hearing impairment), renal disorders (renal failure, nephrotoxicity, hyperuricemia), and fever.

For more details regarding the safety profile of cisplatin, see the prescribing information for cisplatin.

A17–5.1.4 Risks Associated with Gemcitabine

The most common adverse events (> 10%) with gemcitabine are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased alkaline phosphatase, proteinuria, influenza-like symptoms, hematuria, allergic skin rash, thrombocytopenia, alopecia, dyspnea, and peripheral edema.

For more details regarding the safety profile of gemcitabine, refer to the gemcitabine prescribing information.

A17–5.1.5 Risks Associated with Combination Use of Atezolizumab, Tiragolumab, Cisplatin, and Gemcitabine

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab plus tiragolumab plus cisplatin plus gemcitabine: immune-mediated toxicities, including HLH (see Appendix 6 for complete list), GI toxicities, hepatotoxicity, hematologic toxicity, renal toxicity, cardiac toxicities, pulmonary toxicities, neurologic toxicities, and skin toxicities.

A17–5.1.6 Management of Patients Who Experience Specific Adverse Events in the Atezo + Tira + Cis + Gem Arm

A17–5.1.6.1 Dose Modifications

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

Dose modifications of chemotherapy are based on the previous cycle. Dose re-escalations are only permitted for the Day 8 gemcitabine dose adjustment for hematologic parameters (see Table A17-5). For management of drug-related toxicities, the dose of cisplatin may be reduced by 10 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 100 mg/m^2 (one dose level) up to two times, as outlined in Table A17-5.

Table A17-5 Dose-Modification Levels

	Starting Dose	Dose Level −1	Dose Level −2
Atezolizumab	1200 mg fixed dose	Dose reductions not permitted	Dose reductions not permitted
Tiragolumab	600 mg fixed dose	Dose reductions not permitted	Dose reductions not permitted
Cisplatin [a]	70 mg/m^2	60 mg/m^2	50 mg/m^2
Gemcitabine [b]	1,000 mg/m^2	900 mg/m^2	800 mg/m^2

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

[b] Dose re-escalations of gemcitabine are only permitted after an adjustment of the Day 8 gemcitabine dose (refer to Table A17-5 for hematologic toxicities). The maximum re-escalation permitted is to the previous Day 1 dose administered. The Day 8 dose reduction only applies to Day 8 and does not count towards the allowed number of dose reductions per patient.

Treatment with filgrastim or pegfilgrastim may be used if needed. Treatment with sargramostim is not allowed.

Guidelines for gemcitabine and cisplatin dose modifications are shown in Table A17-6.

A17–5.1.6.2 Treatment Interruption for Toxicities

Atezolizumab and tiragolumab may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before study treatment can be resumed. If study treatment is withheld for > 12 weeks, the patient will be discontinued from study treatment. However, study treatment may be withheld for > 12 weeks to allow patients to taper off corticosteroids prior to resuming treatment. Study treatment can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. Atezolizumab and tiragolumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The decision to re-challenge patients with atezolizumab and tiragolumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Based on the available characterization of mechanism of action, tiragolumab may cause adverse events similar to, but independent of, atezolizumab. Tiragolumab may also exacerbate the frequency or severity of atezolizumab-related adverse events or may have non-overlapping toxicities with atezolizumab. Because these scenarios may not be distinguishable from each other in the clinical setting, immune-mediated adverse events should generally be attributed to both agents, and dose interruptions or treatment discontinuation in response to immune-mediated adverse events should be applied to both tiragolumab and atezolizumab. If atezolizumab is discontinued, tiragolumab should also be discontinued. If tiragolumab is discontinued, atezolizumab should also be discontinued.

Cisplatin and/or gemcitabine treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table A17-6).

In the absence of disease progression, cisplatin and gemcitabine may be discontinued for toxicity independent of atezolizumab and tiragolumab. Additionally, in the absence of disease progression, atezolizumab and tiragolumab may be discontinued together for toxicity independent of cisplatin and gemcitabine. Chemotherapy alone or both tiragolumab and atezolizumab in combination together without chemotherapy may be continued as therapy if the patient is likely to derive clinical benefit.

Refer to Section A17–4.2.2 for information on dose interruptions for reasons other than toxicity.

A17–5.1.6.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Table A17-6. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

The investigator may use discretion in adhering to the guidelines for cisplatin and gemcitabine described below, taking into account the severity of the event and benefit versus risk for the patient, with the goal of maximizing patient compliance and access to supportive care. Additionally, the prescribing information, as well as local hospital or clinical practice, must be followed.

Patients who discontinue cisplatin permanently (e.g., for adverse events) will also discontinue gemcitabine permanently. Dosing with atezolizumab and tiragolumab should continue until completion of the 3 cycles pre-surgery as long as patients are experiencing clinical benefit in the opinion of the investigator.

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tira + Cis + Gem Arm

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reactions	• Guidelines for management of IRRs and CRS for atezolizumab and tiragolumab are provided in Appendix 6. • Guidelines for management of IRRs for cisplatin and gemcitabine should be consistent with local clinical practice. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue the causative agent.
Gastrointestinal toxicity	
Diarrhea or colitis, Grade 1	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Continue cisplatin and gemcitabine.
Diarrhea or colitis, Grade 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. [a] • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine at full dose level with prophylaxis (if possible). If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level with prophylaxis (if possible). [d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level with prophylaxis (if possible). [d] If not, permanently discontinue cisplatin and gemcitabine.
Diarrhea or colitis, Grade 3	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. [a] • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level with prophylaxis (if possible). [d] If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine resume cisplatin and gemcitabine reduced by one dose level with prophylaxis (if possible). [d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: Permanently discontinue cisplatin and gemcitabine.
Diarrhea or colitis, Grade 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Permanently discontinue cisplatin and gemcitabine and contact the Medical Monitor. [c, e]

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tira + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Nausea or vomiting, Grade 3	• Continue atezolizumab and tiragolumab. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. • Administer 5-HT3 serotonin receptor antagonist, olanzapine 10 mg orally on Days 1–4 chemotherapy, and aprepitant for prophylaxis for future cycles of chemotherapy. • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: Permanently discontinue cisplatin and gemcitabine.
Nausea or vomiting, Grade 4	• Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. • Permanently discontinue atezolizumab and tiragolumab and contact the Medical Monitor. [c] • Administer 5-HT3 serotonin receptor antagonist, olanzapine 10 mg orally on Days 1–4 chemotherapy, and aprepitant for prophylaxis for future cycles of chemotherapy. • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: Permanently discontinue cisplatin and gemcitabine.
Stomatitis, Grade 3	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset and withhold cisplatin and gemcitabine for up to 6 weeks after event onset. • If event resolves to Grade 1 or better while withholding atezolizumab and tiragolumab, resume atezolizumab and tiragolumab. If not, permanently discontinue atezolizumab and tiragolumab and contact the Medical Monitor. • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level with prophylaxis (if possible). [d] If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level with prophylaxis (if possible). [d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: Permanently discontinue cisplatin and gemcitabine.

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tira + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Stomatitis, Grade 4	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. Permanently discontinue cisplatin and gemcitabine. [e] • If event resolves to Grade 1 or better while withholding atezolizumab and tiragolumab, resume atezolizumab and tiragolumab. If not, permanently discontinue atezolizumab and tiragolumab and contact the Medical Monitor.
Hepatic events	
Hepatic event, Grade 1	• Continue atezolizumab, tiragolumab, cisplatin, and gemcitabine. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	• Continue atezolizumab, tiragolumab, cisplatin, and gemcitabine. • Monitor LFTs more frequently until return to baseline values. Events of > 5 days' duration: • Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset and withhold cisplatin and gemcitabine for up to 6 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better while withholding atezolizumab and tiragolumab, resume atezolizumab and tiragolumab. [b] If not, permanently discontinue atezolizumab and tiragolumab and contact the Medical Monitor. [c] • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine at full dose level. If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine.

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tira + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Hepatic event, Grade 3	• Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. Permanently discontinue atezolizumab and tiragolumab and contact the Medical Monitor. [c] • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over $\geq$ 1 month. • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: Permanently discontinue cisplatin and gemcitabine.
Hepatic event, Grade 4	• Permanently discontinue atezolizumab, tiragolumab, cisplatin, and gemcitabine and contact the Medical Monitor. [c, e] • Manage as per Grade 3 guidelines.
Hematologic toxicity (excluding febrile neutropenia)	
ANC $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count to $\geq 100 \times 10^9$/L (100,000/μL)	• Continue cisplatin, gemcitabine, atezolizumab, and tiragolumab.
ANC $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count to $< 100 \times 10^9$/L (100,000/μL)	• Continue atezolizumab and tiragolumab. • Withhold cisplatin and gemcitabine and assess ANC and platelet counts weekly. • If ANC $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count improves to $\geq 100 \times 10^9$/L (100,000/μL) $\leq$ 6 weeks after event onset, resume cisplatin and gemcitabine at full dose level. If not, permanently discontinue cisplatin and gemcitabine.
ANC $< 1.5 \times 10^9$/L (1500/μL) and platelet count to $\geq 100 \times 10^9$/L (100,000/μL)	• Continue atezolizumab and tiragolumab. • Withhold cisplatin and gemcitabine and assess ANC and platelet counts weekly. • If ANC improves to $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count $\geq 100 \times 10^9$/L (100,000/μL) $\leq$ 6 weeks after event onset, resume cisplatin and gemcitabine at full dose level. If not, discontinue gemcitabine and cisplatin.

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tira + Cis + Gem Arm (cont.)

Event	Action to Be Taken
ANC $< 1.5 \times 10^9$/L (1500/μL) and/or platelet count to $< 100 \times 10^9$/L (100,000/μL)	• Continue atezolizumab and tiragolumab. • Withhold cisplatin and gemcitabine and assess ANC and platelet counts weekly. • If ANC improves to $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count $\geq 100 \times 10^9$/L (100,000/μL) $\leq$ 6 weeks after event onset, resume cisplatin and gemcitabine at full dose level. If not, permanently discontinue gemcitabine and cisplatin.
Day 8	
ANC $\geq 1.0 \times 10^9$/L (1000/μL) and/or platelet count to $\geq 75 \times 10^9$/L (75,000/μL)	• Continue gemcitabine with no dose reduction.
ANC $< 1.0 \times 10^9$/L (1000/μL) and/or platelet count to $< 75 \times 10^9$/L (75,000/μL)	• Continue gemcitabine at 500 mg/m^2
ANC $< 0.5 \times 10^9$/L (500/μL) and/or platelet count to $< 50 \times 10^9$/L (50,000/μL)	• Withhold gemcitabine.
Hematologic toxicity (life-threatening)	
Febrile neutropenia, Grade 3	• Withhold cisplatin, gemcitabine, atezolizumab, and tiragolumab. • If fever resolves and ANC improves to $\geq 1.0 \times 10^9$/L (1000/μL) $\leq$ 6 weeks after event onset, resume cisplatin and gemcitabine reduced by one dose level and provide GCSF support. [d] If not, permanently discontinue cisplatin and gemcitabine. • If fever resolves and ANC improves to $\geq 1.0 \times 10^9$/L (1000/μL) $\leq$ 12 weeks after event onset, resume atezolizumab and tiragolumab. If not, permanently discontinue atezolizumab and tiragolumab.

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tira + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Febrile neutropenia, Grade 4	• Withhold cisplatin, gemcitabine, atezolizumab, and tiragolumab. • If fever resolves and ANC improves to $\geq 1.0 \times 10^9$/L (1000/μL) ≤ 6 weeks after event onset, resume cisplatin and gemcitabine reduced by two dose levels and provide GCSF support. [d] If not, permanently discontinue cisplatin and gemcitabine. • If fever resolves and ANC improves to $\geq 1.0 \times 10^9$/L (1000/μL) ≤ 12 weeks after event onset, resume atezolizumab and tiragolumab. If not, permanently discontinue atezolizumab and tiragolumab.
Immune-mediated myocarditis	
Immune-mediated myocarditis, Grade 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Permanently discontinue cisplatin and gemcitabine.
Immune-mediated myocarditis, Grade 3 or 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Permanently discontinue cisplatin, and gemcitabine. [e]
Dermatologic events	
Dermatologic event, Grade 1	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Continue cisplatin and gemcitabine.
Dermatologic event, Grade 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Continue cisplatin and gemcitabine.
Dermatologic event, Grade 3	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. [a] • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: Permanently discontinue cisplatin and gemcitabine.
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab, tiragolumab, cisplatin, and gemcitabine. [c, e]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue cisplatin and gemcitabine.

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tira + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Neurologic disorders	
Immune-mediated neuropathy, Grade 1	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Continue cisplatin and gemcitabine.
Immune-mediated neuropathy, Grade 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Permanently discontinue cisplatin and gemcitabine. • Initiate treatment as per institutional guidelines.
Immune-mediated neuropathy, Grade 3–4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Permanently discontinue cisplatin and gemcitabine and contact the Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Cisplatin-related neurotoxicity, Grade 2	• Continue atezolizumab and tiragolumab. • Permanently discontinue cisplatin and gemcitabine.
Cisplatin-related neurotoxicity, Grade 3 or 4	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. • Permanently discontinue cisplatin and gemcitabine. • If event resolves to Grade 2 or better while withholding atezolizumab and tiragolumab, resume atezolizumab and tiragolumab. If not, permanently discontinue atezolizumab and tiragolumab and contact the Medical Monitor.
Cisplatin-related ototoxicity	• Hold atezolizumab, tiragolumab, cisplatin, and gemcitabine. • Refer to audiology to perform hearing assessment. For loss of greater than 25 decibels in two consecutive hearing frequencies, repeat audiometry assessment 1 week later. • If hearing loss is resolved, then the patient will be re-treated with a cisplatin dose that is one level lower than the prior cycle [d] and continue atezolizumab, tiragolumab, and gemcitabine. • If hearing loss persists, continue atezolizumab and tiragolumab and permanently discontinue cisplatin and gemcitabine.

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tira + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Renal events	
Renal event, Grade 1	• Continue atezolizumab, tiragolumab, and gemcitabine. If CrCl ≥ 50 mL/min (calculated according to estimated GFR), continue cisplatin at full dose. If CrCL < 50 mL/min, withhold cisplatin for 1 week and recheck creatinine and estimated GFR. If CrCl is recovered to ≥ 50 mL/min, resume cisplatin reduced by one dose level. Repeat courses of cisplatin should not be given unless levels of serum creatinine are below 1.5 mg/100mL (130 µmol /L) or blood urea below 55 mg/100 mL (9mmol/L), and circulating blood levels are at an acceptable level. Measurement of BUN, serum creatinine or GFR should be performed prior to initiating therapy and prior to each subsequent course. [d] • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. [a] • If event resolves to Grade 1 or better and CrCl ≥ 50 mL/min while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level. Repeat courses of cisplatin should not be given unless levels of serum creatinine are below 1.5 mg/100mL (130 µmol /L) or blood urea below 55 mg/100 mL (9mmol/L), and circulating blood levels are at an acceptable level. Measurement of BUN, serum creatinine or GFR should be performed prior to initiating therapy and prior to each subsequent course. [d] If event does not resolve while withholding cisplatin and gemcitabine, permanently discontinue cisplatin and gemcitabine.
Renal event, Grades 3 and 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. • If event resolves to Grade 1 or better and CrCl ≥ 50 mL/min while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one level. Repeat courses of cisplatin should not be given unless levels of serum creatinine are below 1.5 mg/100mL (130 µmol /L) or blood urea below 55 mg/100 mL (9mmol/L), and circulating blood levels are at an acceptable level. Measurement of BUN, serum creatinine or GFR should be performed prior to initiating therapy and prior to each subsequent course. [d] If event does not resolve while withholding cisplatin and gemcitabine, permanently discontinue cisplatin and gemcitabine.

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tira + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Pulmonary events	
Pulmonary event, Grade 1	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Continue cisplatin and gemcitabine.
Pulmonary event, Grade 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • For recurrent events, treat as a Grade 3 or 4 event. • Withhold cisplatin and gemcitabine. If event resolves to Grade 1 or better, resume cisplatin and gemcitabine reduced by one dose level.[d] If event does not resolve while withholding cisplatin and gemcitabine, permanently discontinue cisplatin and gemcitabine • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Permanently discontinue gemcitabine and cisplatin.
Endocrine events	
Hypothyroidism, Grade 1	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Continue cisplatin and gemcitabine.
Hypothyroidism, Grade 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Consider withholding cisplatin and gemcitabine. • Resume cisplatin and gemcitabine when symptoms are controlled and thyroid function is improving.
Hypothyroidism, Grade 3 or 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. • Resume cisplatin and gemcitabine at same dose level when symptoms are controlled and thyroid function is improving.

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tira + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Hyperthyroidism, Grade 1	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Continue cisplatin and gemcitabine. **TSH < 0.1 mU/L:** • Follow guidelines for Grade 2 hyperthyroidism. • Consider patient referral to endocrinologist.
Hyperthyroidism, Grade 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Consider withholding cisplatin and gemcitabine. • Resume cisplatin and gemcitabine when symptoms are controlled and thyroid function is improving.
Hyperthyroidism, Grade 3 or 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. • Resume cisplatin and gemcitabine at same dose level when symptoms are controlled and thyroid function is improving.
Atezolizumab and tiragolumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Continue cisplatin and gemcitabine.
Grade 3	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • Withhold gemcitabine and cisplatin for up to 6 weeks after event onset. • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level. [d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: Permanently discontinue cisplatin and gemcitabine.

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tira + Cis + Gem Arm (cont.)

Event	Action to Be Taken
Grade 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 6. • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin reduced by one dose level.[d] If not, permanently discontinue cisplatin and gemcitabine. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin and gemcitabine reduced by one dose level.[d] If not, permanently discontinue cisplatin and gemcitabine. • Third occurrence: Permanently discontinue cisplatin and gemcitabine.
Chemotherapy-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab, tiragolumab, cisplatin, and gemcitabine.
Grade 3	• Continue atezolizumab and tiragolumab. Withhold cisplatin and gemcitabine for up to 6 weeks after event onset. • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level.[d] If not, permanently discontinue gemcitabine and cisplatin. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level.[d] If not, permanently discontinue gemcitabine and cisplatin. • Third occurrence: Permanently discontinue cisplatin and gemcitabine.
Grade 4	• Withhold atezolizumab, tiragolumab, cisplatin, and gemcitabine. • If event resolves to Grade 1 or better while withholding atezolizumab and tiragolumab and upon consultation with the Medical Monitor[c] that atezolizumab and tiragolumab should be continued, resume atezolizumab and tiragolumab. If not, permanently discontinue atezolizumab and tiragolumab. • First occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level.[d] If not, permanently discontinue gemcitabine and cisplatin. • Second occurrence: If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, resume cisplatin and gemcitabine reduced by one dose level.[d] If not, permanently discontinue gemcitabine and cisplatin. • Third occurrence: Permanently discontinue cisplatin and gemcitabine.
Hemolytic uremic syndrome	• Withhold atezolizumab and tiragolumab. • If event resolves to Grade 1 or better while withholding atezolizumab and tiragolumab consider resuming atezolizumab. The Medical Monitor is available to advise as needed. If not, permanently discontinue atezolizumab and tiragolumab. • Permanently discontinue gemcitabine and cisplatin.

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tira + Cis + Gem Arm (cont.)

CrCl = creatinine clearance; CRS = cytokine release syndrome; ECMO = extracorporeal membrane oxygenation; GFR = glomerular filtration rate; IRR = infusion-related reaction; MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone; VAD = ventricular assist device.

[a] Atezolizumab and tiragolumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. 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 duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

[d] All dose reductions for cisplatin and gemcitabine are permanent. If further dose reduction is indicated for cisplatin and/or gemcitabine after two dose reductions, both drugs should be discontinued, but the patient may continue atezolizumab and tiragolumab at the investigator's discretion.

[e] At first occurrence of Grade 4 event, cisplatin and gemcitabine may be withheld for 6 weeks. If event resolves to Grade 1 or better while withholding cisplatin and gemcitabine, consider retreating at a reduced dose two levels below original dose with prophylaxis (if possible). The Medical Monitor is available to advise as needed. If not, permanently discontinue cisplatin and gemcitabine. At second occurrence of Grade 4 event, permanently discontinue cisplatin and gemcitabine.

A17–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR THE ATEZO+TIRA+CIS+GEM ARM (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 the Atezo + Tira + Cis + Gem arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either 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.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ upper limit of normal
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, HLH, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, or toxic epidermal necrolysis)

- Myelitis
- Facial paresis

A17–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN THE ATEZO+TIRA+CIS+GEM ARM

A17–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab, within 90 days after the final dose of tiragolumab, within 6 months after the final dose of cisplatin, or within 6 months after the final dose of gemcitabine. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail 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 when updated information on the course and outcome of the pregnancy becomes available.

A17–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 90 days after the last dose of tiragolumab, 6 months after the final dose of cisplatin, and 6 months after the final dose of gemcitabine. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A17–5.3.3 Abortions

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

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

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

A17–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male 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).

A17–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+TIRA+CIS+GEM ARM

Table A17-7 Schedule of Activities for Atezo + Tira + Cis + Gem Arm (MIBC Cohorts)

Assessment/Procedure	Screening [a]	Treatment Cycles (21-Day Cycles)/Surgery						Treat Discon [e]	Follow-Up Q3M (± 7 D) [f]
		Cycle 1 [b]		Cycles 2–3		Surgery [c]	Cycles 4–17 [d]		
	Days –28 to –1	Day 1	Day 8 (–1 to +3 D) [g]	Day 1 (±3 D)	Day 8 (–1 to +3 D) [g]		Day 1 (±3 D)		
Molecular profile of urothelial carcinoma (if available)	See Appendix 7.	Whenever updated information becomes available							
Vital signs [h]		x		x			x	x	
Weight [i]		x		x			x	x	
Complete physical examination [j]								x	
Limited physical examination [k, i]		x		x			x		
ECOG Performance Status [i]		x		x			x	x	
ECG [l, i]		Perform as clinically indicated.							
Hematology [m]		x [n]	x	x [n]	x		x [n]	x	
Chemistry [o]		x [n]		x [n]			x [n]	x	
TSH, free T3 (or total T3), and free T4 [p]		x [n]						x	
C-reactive protein		x		x			x	x	
Pregnancy test [q]		x		x			x	x	x [q]
Urinalysis [r]		x		x			x		

Table A17-7 Schedule of Activities for Atezo + Tira + Cis + Gem Arm (MIBC Cohorts) (cont.)

Assessment/Procedure	Screening [a]	Treatment Cycles (21-Day Cycles)/Surgery						Treat Discon [e]	Follow-Up Q3M (± 7 D) [f]
		Cycle 1 [b]		Cycles 2–3		Surgery [c]	Cycles 4–17 [d]		
	Days –28 to –1	Day 1	Day 8 (–1 to +3 D) [g]	Day 1 (±3 D)	Day 8 (–1 to +3 D) [g]		Day 1 (±3 D)		
Cardiac and muscle enzymes tests (troponin I or T and CPK)		x	x	x	x		x	x	
Serum autoantibody sample [s]		Perform if a patient experiences a suspected immune-related adverse event							
PK samples	See Appendix 7.	Refer to Table A17-8.							
ADA samples		Refer to Table A17-8.							
Biomarker samples		Refer to Table A17-8.							
Blood sample for RBR (optional) [t]		x							
Stool sample (optional) [u]		x [u]							
Tumor biopsy		x [v]					x [v]		
Tumor response assessments							x [w, x]		
Concomitant medications [y]		x		x			x	x	
Adverse events [z]		x	x	x	x		x	x	x
Atezolizumab administration [aa, bb]		x		x			x		
Tiragolumab administration [bb, cc]		x		x			x		
Cisplatin administration [dd]		x		x					
Gemcitabine administration [ee]		x	x	x	x				

Table A17-7 Schedule of Activities for Atezo + Tira + Cis + Gem Arm (MIBC Cohorts) (cont.)

		Treatment Cycles (21-Day Cycles)/Surgery						Treat Discon [e]	Follow-Up Q3M (± 7 D) [f]
	Screening [a]	Cycle 1 [b]		Cycles 2–3		Surgery [c]	Cycles 4–17 [d]		
Assessment/Procedure	Days –28 to –1	Day 1	Day 8 (–1 to +3 D) [g]	Day 1 (±3 D)	Day 8 (–1 to +3 D) [g]		Day 1 (±3 D)		
Cystectomy						x [ff]			
Lymph node dissection						x [ff]			
Survival follow-up and anti-cancer treatment									x [gg]

ADA = anti-drug antibody; CT = computed tomography; D = day; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MIBC = muscle invasive bladder cancer; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q3M = every 3 months; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; Treat = treatment; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Patients who fail their first screening for study eligibility may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the initiation of study treatment may be used; such tests do not need to be repeated for screening or re-screening.

[b] Treatment must be initiated no later than 7 days after treatment assignment.

[c] A minimum of 7 days between time of last infusion and surgery is required.

[d] Treatment in Cycle 4 should be reinitiated 4–6 weeks after surgery, but can be reinitiated up to 12 weeks after surgery if surgical complications arise.

[e] Patients will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients.

[f] Patients should return for follow-up visits every 3 months until 24 months after the treatment discontinuation visit. Patients may then continue with standard-of-care treatment with their doctor

Table A17-7 Schedule of Activities for Atezo + Tira + Cis + Gem Arm (MIBC Cohorts) (cont.)

[g] Day 8 dose of gemcitabine may be given no earlier than Day 7 but may be given up to Day 11 (−1 to + 3) of a cycle. Blood counts for gemcitabine dosing should be obtained within 1 day prior to Day 1 and Day 8 of each cycle of therapy if possible.

[h] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, 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. 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 the infusion and at 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 the infusion and at 30 (± 10) minutes after the infusion.

[i] Assessment may be performed within 24 hours prior to dosing during the treatment period.

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

[k] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[n] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

[o] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. For U.K. patients, amylase and lipase must be included on Day 1 of each treatment cycle.

[p] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[q] All women of childbearing potential will have a serum pregnancy test at screening. Urine or serum 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. During follow-up, pregnancy tests will be performed at 3 and 6 months. If a pregnancy test was performed within 96 hours prior to Day 1 of Cycle 1, it does not have to be repeated.

[r] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[s] Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

Table A17-7 Schedule of Activities for Atezo + Tira + Cis + Gem Arm (MIBC Cohorts) (cont.)

[t] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[u] Stool samples will be collected before surgery for cystectomy and lymph node dissection, preferably after Day 1 of Cycle 3. Patients who consent to providing optional stool samples will receive the collection device on or before Day 1 of Cycle 3.

[v] During the study (i.e., up to 24 months after the treatment discontinuation visit), patients will undergo tumor biopsy sample collection at the time of disease recurrence as determined by the investigator (see Section 4.5.7 in the protocol body for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or disease recurrence, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 in protocol body for tissue sample requirements.

[w] Patients will undergo tumor assessments at baseline, within 4 weeks prior to resuming systemic therapy following surgery, and then every 12 weeks (±2 weeks) while on treatment and until 24 months (104 weeks) after the treatment discontinuation visit, regardless of dose delays, or until disease recurrence, whichever occurs first (see Section 3.1.3 in the protocol body for details. Tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease recurrence.

[x] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[y] Includes 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 study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[z] 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] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[bb] Treatment will continue until unacceptable toxicity or disease recurrence (as defined in Section 4.5.7) or until completion of 14 cycles post-surgery, whichever comes first.

[cc] Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle. The initial dose of tiragolumab will be delivered over 60 (± 10) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 10) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

Table A17-7 Schedule of Activities for Atezo + Tira + Cis + Gem Arm (MIBC Cohorts) (cont.)

[dd] Cisplatin will be administered by IV infusion at a dose of 70 mg/m^2 on Day 1 of each 21-day cycle for the first 3 cycles. Weight will be measured for dose calculation (baseline weight should be used to calculate dose unless there is a greater than 5% weight change).

[ee] Gemcitabine will be administered by IV infusion at a dose of 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle for the first 3 cycles. Weight will be measured for dose calculation (baseline weight should be used to calculate dose unless there is a greater than 5% weight change). Day 8 gemcitabine should not be administered any earlier than Day 7, but can be administered up to Day 11.

[ff] A specimen from surgical resection (i.e., radical cystectomy) along with an associated pathology report and tissue from lymph node dissection must be submitted. See Section 4.5.8 in protocol body for tissue sample requirements.

[gg] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months for 24 months after the treatment discontinuation visit (unless the patient withdraws consent or the Sponsor terminates the study). If a 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. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

Table A17-8 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Tira + Cis + Gem Arm: Preliminary and Expansion Phases (MIBC Cohorts)

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarker (blood, PBMC, plasma, serum, and urine)
	30 (± 10) minutes after the end of atezolizumab infusion	• Atezolizumab PK (serum)
	30 (± 10) minutes after the end of tiragolumab infusion	• Tiragolumab PK (serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarker (PBMC, plasma and serum)
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarker (blood and urine)
Surgery for cystectomy	Prior to surgery	• Biomarker (blood, PBMC, and urine)
Day 1 of Cycles 4 and 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarker (plasma, serum in Cycles 4 and 8) • Biomarker (blood and urine, Cycle 4)

ADA = anti-drug antibody; Atezo = atezolizumab; Cis = cisplatin; Gem = gemcitabine; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety 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. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

Table A17-8 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Tira + Cis + Gem Arm: Preliminary and Expansion Phase (MIBC Cohorts) (cont.)

Visit	Time	Sample Type
Day 1 of Cycle 6 (~3 months post-cystectomy)	At visit	• Biomarker (blood and urine) [a]
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarker (plasma, serum) [a]

ADA = anti-drug antibody; Atezo = atezolizumab; Cis = cisplatin; Gem = gemcitabine; PK = pharmacokinetic.

Note: On the basis of emerging safety 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. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Biomarker collections are applicable only after approval from local regulatory authorities.

A17–7 REFERENCES

Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med 2007;13:1050–9.

Belvin MP, Luoh SM, Cheung J, et al. Effects of chemotherapeutic agents on the tumor immune microenvironment [abstract]. American Association of Cancer Research (AACR) 2016;76 (14_suppl).

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.

Butte MJ, Keir ME, Phamduy TB, et al. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Chen L, Deng H, Lu M, et al. B7-H1 expression associates with tumor invasion and predicts patient's survival in human esophageal cancer. Int J Clin Exp Pathol 2014;7:6015–23.

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.

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.

Dhupar R, Van Der Kraak L, Pennathur A, et al. Targeting immune checkpoints in esophageal cancer: a high mutational load tumor. Ann Thorac Surg 2017;103:1340–49.

Fehrenbacher L, Spira A, Ballinger M, et al. 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.

Funt AS, Lattanzi M, Whiting K, et al. Neoadjuvant atezolizumab (A) with gemcitabine and cisplatin (GC) in patients (pts) with muscle-invasive bladder cancer (MIBC): A multicenter, single-arm, phase 2 trial. J Clin Oncol 2021;39(15 suppl):4517.

Galsky MD, Guan X, Banchereau R, et al. Cisplatin (cis)-related immunomodulation and efficacy with atezolizumab (atezo) + cis- vs carboplatin (carbo)-based chemotherapy (chemo) in metastatic urothelial cancer (mUC) [abstract]. European Society for Medical Oncology (ESMO) Congress 2021.

Gandhi L, Rodriguez-Abreu D, Gadgeel S, et. al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018;378:2078–92.

Giaccone G, Camidge DR, Liu SV, et al. Safety, activity and biomarkers of atezolizumab (MPDL3280A) with platinum-based chemotherapy (chemo) in non-small cell lung cancer (NSCLC): A Phase Ib study [abstract 513]. European Society For Medical Oncology at Eur Cancer Congress 2015 (ECC 2105): Sep 25–29 [cited Jan 2017]; Vienna, Austria. Available from: http://www.eccocongress.org/Vienna2015/Scientific-Programme/Abstract-search#.

Gonzalez-Aparicio M, Alzuguren P, Mauleon I, et al. Oxaliplatin in combination with liver-specific expression of interleukin 12 reduces the immunosuppressive microenvironment of tumours and eradicates metastatic colorectal cancer in mice. Gut 2011;60:341–9.

Guillerey C, Harjunpää H, Carrié N, et al. TIGIT immune checkpoint blockade restores $CD8^+$ T cell immunity against multiple myeloma. Blood 2018;132:1689–94.

Gupta S, Sonpavde G, Weight CJ, et al. Results from BLASST-1 (Bladder Cancer Signal Seeking Trial) of nivolumab, gemcitabine, and cisplatin in muscle invasive bladder cancer (MIBC) undergoing cystectomy. J Clin Oncol 2020;38(6 suppl):439.

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.

Horn L, Mansfield AS, Szczesna A, et. al. First Line Atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018;379:2220–9.

Johnston RJ, Comps-Agrar L, Hackney J, et al. The immunoreceptor TIGIT regulates antitumor and antiviral CD8(+) T cell effector function. Cancer Cell 2014;26:923–37.

Joller N, Hafler JP, Brynedal B, et al. Cutting edge: TIGIT has T cell-intrinsic inhibitory functions. J Immunol 2011;186:1338–42.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.

Langer CJ, Gadgeel SM, Borghael H, et al., Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17:1497–508.

Manieri NA, Chiang EY, and Grogan JL. TIGIT: a key inhibitor of the cancer immunity cycle. Trends Immunol 2017;38:20–8.

Merritt RE, Mahtabifard A, Yamada RE, et al. Cisplatin augments cytotoxic T-lymphocyte-mediated antitumor immunity in poorly immunogenic murine lung cancer. J Thorac Cardiovasc Surg 2003;126:1609–17.

Necchi A, Anichini A, Raggi D, et al. Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): an open-label, single-arm, phase II study. Int J Clin Oncol 2018;36:3353–60.

[NCCN] National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: bladder cancer [resource on the Internet]. 3.2021 [cited 15 July 2021]. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx.

Ohigashi Y, Sho M, Yamada Y, et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. Clin Cancer Res 2005;11:2947–53.

Paz-Ares L, Luft A, Vincente D, et. al. Pembrolizumab plus chemotherapy in squamous non-small-cell lung cancer. N Engl J Med 2018;379:2040-51.

Powell RM, Lissauer D, Tamblyn J, et al. Decidual T cells exhibit a highly differentiated phenotype and demonstrate potential fetal specificity and a strong transcriptional response to IFN. J Immunol 2017;199:3406–17.

Powles T, Kockx M, Rodriguez-Vida A, et al. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. Nat Med 2019;25:1706–1714.

Rizvi NA, Hellmann MD, Brahmer JR, et al. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non–small-cell lung cancer. J Clin Oncol 2016;34:2969–79.

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 2011;61:1229–38.

Sato E, Olson SH, Ahn J, et al. Intraepithelial CD8+ tumor-infiltrating lymphocytes and high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. Proc Natl Acad Sci USA 2005;102:18538–43.

Schmid P, Adams S, Rugo HS, et. al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 2018;379:2108–21.

Stanietsky N, Simic H, Arapovic J, et al. The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity. Proc Natl Acad Sci USA 2009;106:17858–63.

Tecentriq® (atezolizumab) U.S. Package Insert, Genentech.

Vincent J, Mignot G, Chalmin F, et al. 5-fluorouracil selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity. Cancer Res 2010;70:3052–61.

Wang F, Hou H, Wu S, et al. TIGIT expression levels on human NK cells correlate with functional heterogeneity among healthy individuals. Eur J Immunol 2015;45:2886–97.

van der Zwan A, Bi K, Norwitz ER, et al. Mixed signature of activation and dysfunction allows human decidual $CD8^+$ T cells to provide both tolerance and immunity. Proc Natl Acad Sci USA 2018;115:385–90.

Vento-Tormo R, Efremova M, Botting RA, et al. Single-cell reconstruction of the early maternal-fetal interface in humans. Nature 2018;563:347–53.

Yadav M, Green C, Ma C, et al. Tigit, CD226 and PD-L1/PD-1 are highly expressed by marrow-infiltrating T cells in patients with multiple myeloma. Blood 2016;128:2102.

Yang Z. Expression and function of tigit in B-cell non-hodgkin lymphoma. Blood 2016;128:4138.

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.

Yu X, Harden K, Gonzalez LC, et al. The surface protein TIGIT suppresses T cell activation by promoting the generation of mature immunoregulatory dendritic cells. Nat Immunol 2009;10:48–57.

Zhao JJ, Zhou ZQ, Wang P, et al. Orchestration of immune checkpoints in tumor immune contexture and their prognostic significance in esophageal squamous cell carcinoma. Cancer Manag Res 2018;10:6457–68.

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