Official Title: A Phase Ib/II, Open-Label, Multicenter, Randomized Umbrella Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatment Combinations in Patients with Metastatic Pancreatic Ductal Adenocarcinoma (Morpheus–Pancreatic Cancer)

NCT Number: NCT03193190

Document Date: Protocol Amendment Version 16: 04-Oct-2023

PROTOCOL

TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (MORPHEUS–PANCREATIC CANCER)**
PROTOCOL NUMBER:	WO39608
VERSION NUMBER:	*16*
TEST COMPOUNDS:	Atezolizumab (RO5541267), Bevacizumab (RO4876646), Tiragolumab (RO7092284), Tocilizumab (RO4877533)
STUDY PHASE:	Phase Ib/II
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 132,850 EudraCT Number: 2016-004126-42 *EU CT Number: to be determined* Clinical Investigation Identification Number (CIV ID): Not applicable NCT Number: NCT03193190
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.

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocol		
Version	**Date Final**	**Country**	**Version**	**Date Final**
16	*See electronic date stamp on final page of this document.*	—	—	—
15	*14 March 2023*	—	—	—
13	7 December 2022	Japan	14	25 January 2023
11	12 March 2022	Japan	12	12 March 2022
9	21 July 2020	Japan	10	25 August 2020
8	9 April 2020	—	—	—
6	22 November 2019	ex-United States	7	5 December 2019
4	11 May 2018	Germany	5	22 October 2019
1	4 February 2017	Spain	3	28 February 2018
		Germany	2	5 October 2017

PROTOCOL AMENDMENT, VERSION 16: RATIONALE

Protocol WO39608, Version 16 has been updated to remove the atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus AB928 arm, as the treatment arm has met the criteria for closure. In addition, the protocol has been aligned with the Atezolizumab Investigator's Brochure, Version 20. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- A section describing duration of participation has been added to align with Clinical Trials Regulation (CTR) requirements (Section 3.3).
- The study length has been increased to 7–9 years due to expanded study arm enrollment (Section 3.3)
- The section 'Exclusion Criteria for AB928-Containing Arm during Stage 1' (formerly Section 4.1.2.4) has been removed due to closure of the atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus AB928 study arm. Information regarding the Emergency Medical Call Center has been added for completeness (Section 5.4.1).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 20 (Appendix 2).
  - The management guidelines for Grade 1 pulmonary events have been updated to include consideration of resuming treatment.
  - Guidance for the management of immune-mediated cardiac events in high-risk patients has been included.
  - Use of transthoracic echocardiogram has been added to the guidance for evaluation of immune-mediated myocarditis.
  - The dose and duration of initial corticosteroid treatment for the management of Grade 2–4 immune-mediated myocarditis or pericardial disorders has been updated.
  - The potential association of myasthenia with myositis has been clarified, and further guidance for the management of neurologic disorders has been added.
  - Management guidelines for immune-mediated myositis have been updated.
- The atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus AB928 arm has been removed due to meeting the criteria for closure. The content of Appendix 12 [previously entitled "Study Details Specific to Atezo+Chemo+AB928 Arm (Cohort 1)"] has been removed. Appendix 12 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (MORPHEUS–PANCREATIC CANCER)**
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SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

PROTOCOL TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (MORPHEUS–PANCREATIC CANCER)**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 132,850 EudraCT Number: 2016-004126-42 *EU CT Number: to be determined* Clinical Investigation Identification Number (CIV ID): Not applicable NCT Number: NCT03193190

STUDY RATIONALE

The purpose of this study is to evaluate the efficacy, safety, and pharmacokinetics of immunotherapy-based treatment combinations in patients with metastatic pancreatic ductal adenocarcinoma (PDAC). Current treatment options for patients with metastatic PDAC are primarily limited to gemcitabine-based or fluoropyrimidine-based chemotherapies which are associated with significant toxicities that negatively affect quality of life. For patients whose disease has progressed during chemotherapy, there are no approved treatment options. Therefore, there is a high unmet need for improved medical intervention for patients with metastatic PDAC.

OBJECTIVES AND ENDPOINTS

Table 1 Objectives and Corresponding Endpoints for Stage 1

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• Objective response, defined as a complete response or partial response 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 at specific timepoints (e.g., 6 months) • DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • Disease control, defined as stable disease for ≥12 weeks or a complete or partial response, 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 National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results

ADA = anti-drug antibody; DOR = duration of response; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1.

Table 2 Objectives and Corresponding Endpoints for 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 National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results

ADA = anti-drug antibody; DOR = duration of response; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1.

OVERALL DESIGN AND STUDY POPULATION

This is a Phase Ib/II, open-label, multicenter, randomized umbrella study in patients with metastatic PDAC. 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). Two cohorts will be enrolled in parallel in this study: Cohort 1 will consist of patients who have received no prior systemic therapy for metastatic PDAC, and Cohort 2 will consist of patients who have received one line of prior systemic therapy for PDAC. Currently, there are no arms open for enrollment in Cohort 2. In each cohort, eligible patients will initially be randomly assigned to one of several treatment arms (Stage 1). Patients in Cohort 2 who experience disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may be eligible to receive treatment with a different treatment combination (Stage 2)

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

Table 3 Study Design and Study Population

Phase:	Phase Ib/II	**Population Type:**	Adult patients
Control Method:	Standard of care Active comparator	**Population Diagnosis or Condition:**	Metastatic pancreatic ductal adenocarcinoma
Interventional Model:	Parallel	**Population Age:**	≥ 18 years
Test Compounds:	Atezolizumab (RO5541267), Bevacizumab (RO4876646), Tiragolumab (RO7092284), Tocilizumab (RO4877533)	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Gemcitabine, Nab-paclitaxel, 5-Fluororuracil, Leucovorin, Oxaliplatin	**Study Intervention Assignment Method:**	Randomization
Number of Arms:	7	**Number of Participants to Be Enrolled:**	Approximately 290–470

STUDY TREATMENT

Table 4 Stage 1 Study Treatments for Cohort 1

Stage 1 Study Treatments for Cohort 1	
Treatment Group	Administration Method and Schedule
Standard treatment (chemotherapy) (28-day cycles)	• Nab-paclitaxel 125 mg/m^2 IV on Days 1, 8, and 15 of each cycle • Gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 of each cycle
Atezolizumab plus chemotherapy plus bevacizumab (CIT combination) (28-day cycles)	• Atezolizumab: 840 mg IV infusion over 30–60 minutes on Days 1 and 15 of each cycle • Bevacizumab: 10 mg/kg IV infusion over 30–90 minutes on Days 1 and 15 of each cycle • Nab-paclitaxel 125 mg/m^2 IV on Days 1, 8, and 15 of each cycle • Gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 of each cycle
Atezolizumab plus chemotherapy plus tiragolumab (CIT combination) (28-day cycles)	• Atezolizumab: 840 mg IV infusion over 30–60 minutes on Days 1 and 15 of each cycle • Tiragolumab: 420 mg IV infusion over [redacted] minutes on Days 1 and 15 of each cycle • Nab-paclitaxel 125 mg/m^2 IV on Days 1, 8, and 15 of each cycle • Gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 of each cycle
Atezolizumab plus chemotherapy plus tocilizumab (CIT combination) (28-day cycles)	• Tocilizumab: 8 mg/kg IV infusion over 60 minutes on Day 1 of each cycle • Atezolizumab: 1680 mg IV infusion over 30–60 minutes on Day 1 of each cycle • Nab-paclitaxel 125 mg/m^2 IV on Days 1, 8, and 15 of each cycle • Gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 of each cycle

CIT = cancer immunotherapy.

Table 5 Stage 1 Study Treatments for Cohort 2

Stage 1 Study Treatments for Cohort 2	
Treatment Group	Administration Method and Schedule
Standard treatment (chemotherapy) (28-day cycles)	• Nab-paclitaxel 125 mg/m^2 IV on Days 1, 8, and 15 of each cycle • Gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 of each cycle or • Oxaliplatin 85 mg/m^2 IV over 2 hours (± 5 minutes) on Days 1 and 15 of each cycle • Leucovorin 400 mg/m^2 IV over 2 hours (± 15 minutes) on Days 1 and 15 of each cycle • 5-Fluorouracil 400 mg/m^2 IV push on Days 1 and 15 of each cycle • 5-Fluorouracil 2400 mg/m^2 IV continuous infusion over 46 (± 2) hours on Days 1 and 2 and on Days 15 and 16 of each cycle
There are currently no treatments for Cohort 2 Stage 1.	

nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

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

For management of drug-related toxicities, the dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times, the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times, and tocilizumab may be reduced up to one time, as outlined in Table 6.

Table 6 Recommended Dose Reductions for Nab-Paclitaxel, Gemcitabine and Tocilizumab

	Initial Dose	First Dose Reduction	Second Dose Reduction
Nab-paclitaxel	125 mg/m^2	100 mg/m^2	75 mg/m^2
Gemcitabine	1000 mg/m^2	800 mg/m^2	600 mg/m^2
Tocilizumab	8 mg/kg	4 mg/kg	NA

NA = not applicable; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

DURATION OF PARTICIPATION

Treatment will continue until disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1. (RECIST v1.1). The total duration of study, from screening of the first patient to the end of the study, is expected to be approximately $7 - 9$ years if expansion is ungated.

COMMITTEES

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

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-FU	5-fluorouracil
ADA	anti-drug antibody, also known as anti-therapeutic antibody
ASCO	American Society of Clinical Oncology
[redacted]	
Atezo	atezolizumab
BCRP	breast cancer resistance protein
Bev	bevacizumab
Chemo	chemotherapy (nab-paclitaxel and gemcitabine)
CIT	cancer immunotherapy
COVID-19	coronavirus disease 2019
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
[redacted]	
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
ESMO	European Society for Medical Oncology
FFPE	formalin-fixed, paraffin-embedded
FOLFIRINOX	leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin
FOLFOX	5-fluorouracil, leucovorin, and oxaliplatin
GI	gastrointestinal
[redacted]	
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
IFN	interferon
IL	interleukin
IMC	Internal Monitoring Committee
IND	Investigational New Drug (Application)

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (CONT.)

Abbreviation	Definition
IRB	Institutional Review Board
IRR	infusion-related reaction
IxRS	interactive voice or web-based response system
LPLV	last patient, last visit
MRI	magnetic resonance imaging
nab-paclitaxel	nanoparticle albumin–bound paclitaxel
NCCN	National Cancer Comprehensive Network
NCI	National Cancer Institute
NCI CTCAE v4.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
NGS	next-generation sequencing
ORR	objective response rate
OS	overall survival (rate)
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PDAC	pancreatic ductal adenocarcinoma
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PPD	purified protein derivative
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SITC	Society for Immunotherapy of Cancer
SOC	Scientific Oversight Committee
T3	triiodothyronine
T4	thyroxine
TB	tuberculosis
Tira	tiragolumab
TCZ	tocilizumab
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal
VCA	viral capsid antigen
[redacted]	

1. BACKGROUND

1.1 TREATMENT FOR PANCREATIC CANCER

Pancreatic cancer is known for its aggressiveness, and the high incidence and mortality rates have remained unchanged for the last 20 years. It is the fourth leading cause of cancer-related mortality in the United States as well as in the European Union, with increasing world-wide mortality rates that align with the projection of being the second leading cause of cancer death in the United States by 2030 (Malvezzi et al. 2014; American Cancer Society 2016). Presently, surgical resection offers the only therapeutic means of cure. However, only 15%–20% of patients have resectable disease and 80% present with advanced disease at initial diagnosis. Even patients who receive curative surgery will have disease relapses, resulting in 5-year survival rates of 25%–30% and 10% in patients with node-negative and node-positive disease at pancreaticoduodenectomy, respectively (Trede et al. 1990; Geer and Brennan 1993; Tsao et al. 1994; Yeo et al. 1995). Patients who have locally advanced and unresectable disease often receive radiochemotherapy, resulting in a median overall survival (OS) of 9–13 months, but rarely offering long-term survival (Czito et al. 2000). Patients with metastatic disease at initial diagnosis have the worst prognosis, with a median OS of 8.5–11.1 months with first-line treatment with FOLFIRINOX (leucovorin, 5-fluorouracil [5-FU], irinotecan, and oxaliplatin) or with nanoparticle albumin–bound paclitaxel (nab-paclitaxel) plus gemcitabine (Conroy et al. 2011; Von Hoff et al. 2013), with a 5-year OS for metastatic cancer of 2% (Malvezzi et al. 2014; American Cancer Society 2016). Therefore, there is a high unmet need for improved medical intervention.

1.2 FIRST-LINE TREATMENT FOR PANCREATIC CANCER

Two treatment regimens, FOLFIRINOX and combination treatment with nab-paclitaxel plus gemcitabine, have been established as standard of care for the first-line treatment of patients with metastatic pancreatic ductal adenocarcinoma (PDAC) on the basis of two randomized studies comparing combination treatment with gemcitabine alone. The ACCORD-11 study demonstrated statistically significantly improved efficacy ($p < 0.001$) for FOLFIRINOX compared with gemcitabine with respect to OS (median OS, 11.1 vs. 6.8 months), objective response rate (ORR) (31.6% vs. 9.4%), and progression-free survival (PFS) (median PFS, 6.4 vs. 3.3 months) (Conroy et al. 2011). The MPACT study demonstrated statistically significantly improved efficacy ($p < 0.001$) for nab-paclitaxel plus gemcitabine compared with gemcitabine with respect to OS (median OS, 8.5 vs. 6.7 months), ORR (23% vs. 7%), and PFS (median PFS, 5.5 vs. 3.7 months) (Von Hoff et al. 2013).

Given its high toxicity profile, FOLFIRINOX is recommended for patients with a more favorable comorbidity profile, as described in guidelines from the European Society for Medical Oncology (ESMO) (Ducreux et al. 2015), the American Society of Clinical Oncology (ASCO) (Sohal et al. 2016), and the National Cancer Comprehensive Network (NCCN 2017). Nab-paclitaxel plus gemcitabine is recommended for patients with a less favorable comorbidity profile.

Despite the improvements in OS associated with FOLFIRINOX and nab-paclitaxel plus gemcitabine, the 5-year survival rate for advanced pancreatic disease remains poor (Sohal et al. 2016), emphasizing the great need for treatment regimens with improved survival outcomes. Participation in a clinical trial is listed as a preferred option (NCCN 2017).

1.3 SECOND-LINE TREATMENT FOR PANCREATIC CANCER

Second-line treatment for pancreatic cancer depends on the type of first-line therapy and the local standard of care, as described in the ESMO, ASCO, and NCCN guidelines (Ducreux et al. 2015; Sohal et al. 2016; NCCN 2017). When patients receive FOLFIRINOX as first-line therapy, gemcitabine-based therapy is often used as second-line therapy (Portal et al. 2015). Nab-paclitaxel plus gemcitabine demonstrated a median PFS and median OS of 5.1 months and 8.8 months, respectively, and a 17.5% ORR in the second-line setting (Portal et al. 2015; NCCN 2017). In contrast, when nab-paclitaxel plus gemcitabine is utilized for first-line therapy, 5-FU–containing regimens, including FOLFOX (5-FU, leucovorin, and oxaliplatin) (Chiorean et al. 2016) and nanoliposomal irinotecan plus 5-FU plus leucovorin, are recommended by ESMO and NCCN guidelines (Ducreux et al. 2015; NCCN 2017). In two studies of FOLFOX as second-line treatment in patients with pancreatic cancer (FIRGEM and CONKO-003 studies), no objective responses were observed. Median PFS and median OS were 1.7 months and 4.3 months, respectively, in the FIRGEM study (Zaanan et al. 2014) and 2.9 months and 5.9 months, respectively, in the CONKO-003 study (Oettle et al. 2014). In the NAPOLI-1 Phase III study in patients with metastatic pancreatic cancer who progressed after a gemcitabine-based regimen, treatment with nanoliposomal irinotecan plus 5-FU and leucovorin versus treatment with 5-FU and leucovorin alone resulted in statistically significant improvement in median OS (6.1 months vs. 4.2 months; $p = 0.012$) and median PFS (3.1 months vs. 1.5 months; $p = 0.0001$). Nanoliposomal irinotecan monotherapy did not demonstrate a statistically significant improvement in efficacy (Wang-Gillam et al. 2016). Participation in a clinical trial is recommended as the preferred option for second-line therapy (NCCN 2017).

1.4 STUDY RATIONALE

This study will enroll two populations of patients with metastatic PDAC: patients who have received no prior systemic treatment for metastatic PDAC (Cohort 1) and patients who have received one line of prior systemic therapy for PDAC (Cohort 2). Given the relatively poor prognosis and limited treatment options for these patients, these populations are considered appropriate for trials of novel therapeutic candidates.

Recent therapeutic advances for patients with metastatic pancreatic cancer have prolonged OS, but the prognosis still remains poor, with a median OS of approximately 8.5–11 months in the first-line setting (Conroy et al. 2011; Von Hoff et al. 2013). Patients who receive second-line treatment for their disease have an even worse prognosis, with a median OS of approximately 6 months (Oettle et al. 2014; Zaanan et al. 2014; Wang-Gillam et al. 2016). Approved therapies are associated with significant toxicities (e.g., neuropathy, febrile neutropenia, and myelosuppression) that negatively affect quality of life. Currently, no treatment options are available for patients whose disease has progressed during or after gemcitabine-based and fluoropyrimidine-based therapies.

Cancer immunotherapy (CIT) has demonstrated clear clinical efficacy, with significant survival benefits observed across multiple advanced malignancies. Currently, the prevailing CIT approach is to circumvent immune evasion mechanisms and reinvigorate anti-tumor responses by targeting T-cell inhibitory factors such as PD-L1/PD-1. While 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 a continuous 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 an effective anti-cancer immune response will be critical for propagating cancer immunity and advancing the field of CIT, most likely through combined targeted therapy regimens.

This Phase Ib/II umbrella study is designed to accelerate the development of CIT combinations by identifying early signals and establishing proof-of-concept clinical data in patients with PDAC. 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 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 control arm in which patients will receive one of two standard

chemotherapy regimens. Moreover, patients who experience disease progression 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 1. The control and experimental treatment regimens are described in Section 3.1.1 (see Table 4 and Table 6). 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 Appendices 7, 12, 14–16.

Table 1 Target and Proposed Mechanism-of-Action Classification for Experimental Investigational Medicinal Products

Experimental IMP	Target	Proposed Mechanism-of-Action Classification
Atezolizumab	PD-L1	Checkpoint inhibitor
Bevacizumab	VEGF	Angiogenesis inhibitor, recruitment of T cells to the tumor microenvironment [a]
Tiragolumab	TIGIT	TIGIT antagonist, improves activation and effectiveness of T-cell and NK-cell tumor-killing activity [b]
Tocilizumab	IL-6R	IL-6R inhibitor; decreases tumor-associated macrophages, T-regulatory cells, and myeloid-derived suppressor cells [c]

IL-6R = interleukin-6 receptor; IMP = investigational medicinal product; NK = natural killer; TIGIT = T-cell immunoreceptor with Ig and ITIM domains; VEGF = vascular endothelial growth factor.

[a] Wallin et al. 2016.

[b] Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014.

[c] Rose-John et al. 2006; Scheller et al. 2011; Fisher et al. 2014.

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 checkpoint inhibitor therapies (e.g., atezolizumab). At this time, there is insufficient evidence for causal association between immune checkpoint inhibitor 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 checkpoint inhibitor 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 checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving 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

This study will evaluate the efficacy, safety, and pharmacokinetics of immunotherapy-based treatment combinations in patients with metastatic PDAC. Specific objectives and corresponding endpoints for the study are outlined below for Stage 1 (see Table 2) and Stage 2 (see Table 3).

Table 2 Objectives and Corresponding Endpoints for Stage 1

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• Objective response, defined as a complete response or partial response 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 at specific timepoints (e.g., 6 months) • DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • Disease control, defined as stable disease for ≥12 weeks or a complete or partial response, as determined by the investigator according to RECIST v1.1

ADA=anti-drug antibody; DOR=duration of response; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

Table 2 Objectives and Corresponding Endpoints for Stage 1 (cont.)

[redacted]

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 National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results

[redacted]

ADA = anti-drug antibody; DOR = duration of response; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

Table 2 Objectives and Corresponding Endpoints for Stage 1 (cont.)

ADA = anti-drug antibody; DOR = duration of response; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

Table 3 Objectives and Corresponding Endpoints for Stage 2

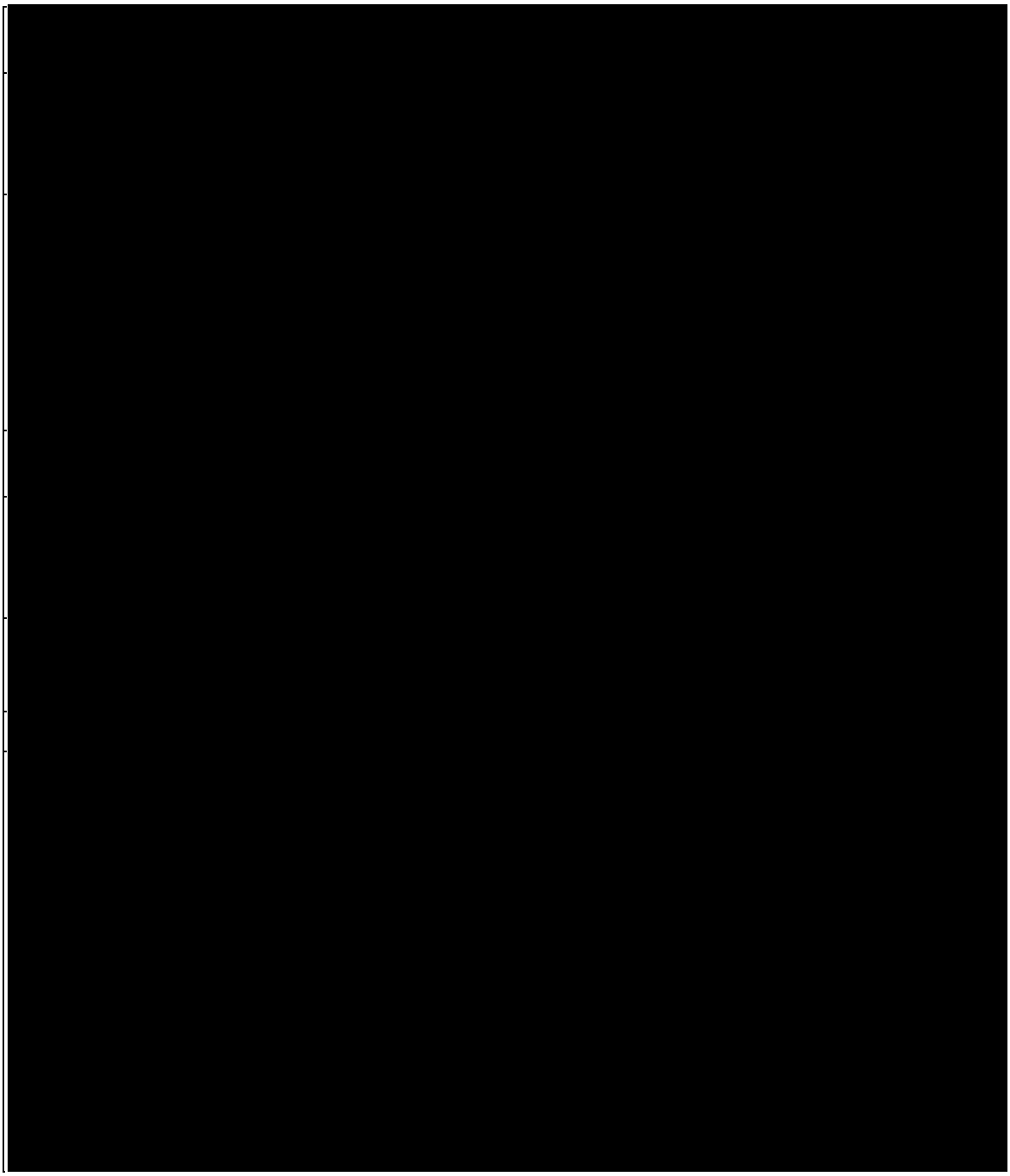
[redacted]

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 National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results

ADA = anti-drug antibody; [redacted]
PK = pharmacokinetic; [redacted].

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

Table 3 Objectives and Corresponding Endpoints for Stage 2 (cont.)



ADA = anti-drug antibody; DOR = duration of response; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

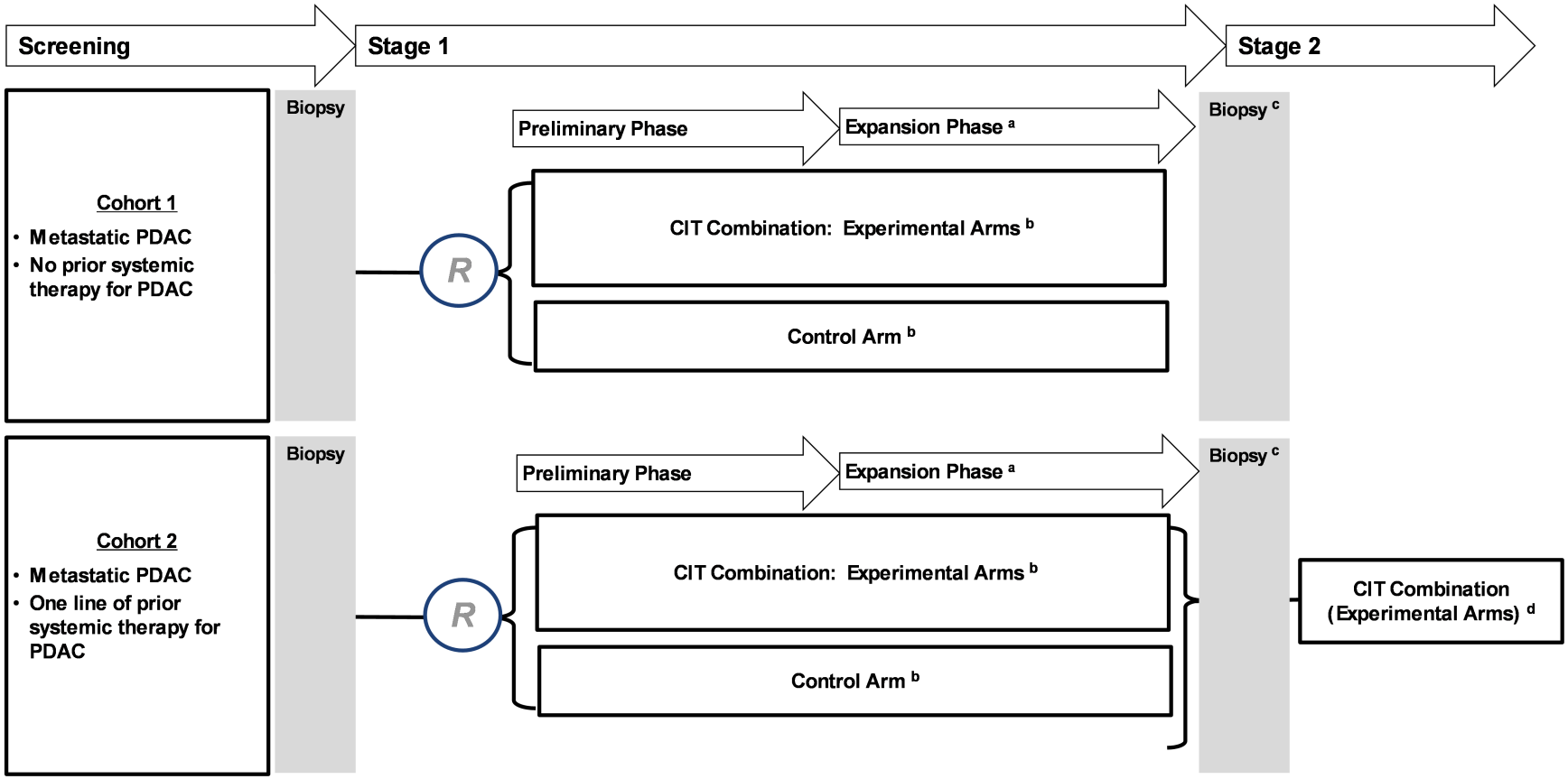
3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase Ib/II, open-label, multicenter, randomized umbrella study in patients with metastatic PDAC. 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). Two cohorts will be enrolled in parallel in this study: Cohort 1 will consist of patients who have received no prior systemic therapy for metastatic PDAC, and Cohort 2 will consist of patients who have received one line of prior systemic therapy for PDAC (see Figure 1). Currently, there are no arms open for enrollment in Cohort 2. In each cohort, eligible patients will initially be randomly assigned to one of several treatment arms (Stage 1; see Section 3.1.2). Patients in Cohort 2 who experience disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may be eligible to receive treatment with a different treatment combination (Stage 2; see Section 3.1.5).

Figure 1 Study Schema



CIT = cancer immunotherapy; PDAC = pancreatic ductal adenocarcinoma; R = randomization; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] If deemed clinically feasible by the investigator, patients enrolled in an experimental arm during the expansion phase will undergo an on-treatment biopsy 4 weeks after initiation of Stage 1 treatment (or 6 weeks after initiation of Stage 1 treatment for patients in the Atezo + Chemo + TCZ arm), unless on-treatment tissue samples have already been collected and determined to be evaluable from a minimum of 15 patients treated with the same CIT combination.

[b] Refer to Table 4 for a summary of available Stage 1 treatment regimens in Cohorts 1 and 2.

[c] If deemed clinically feasible by the investigator, a biopsy will be performed for patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator (see details on tissue sample collection in Section 4.5.7).

[d] Refer to Table 6 for a summary of available Stage 2 treatment regimens.

3.1.2 Stage 1

During Stage 1, patients in Cohort 1 will be randomly assigned to a control arm (chemotherapy) or an experimental arm consisting of atezolizumab and chemotherapy in combination with bevacizumab (Atezo + Chemo + Bev), tiragolumab (Atezo + Chemo + Tira), or tocilizumab (Atezo + Chemo + TCZ), and patients in Cohort 2 will be randomly assigned to a control arm (chemotherapy) or an experimental arm, as outlined in Table 4 (see also Figure 2 and Figure 3). Details on the treatment regimens for Stage 1 are provided in Appendices 7, 12, 14–16, as specified in Table 4. Table 5 lists Stage 1 treatment arms for which enrollment and patient follow-up have been completed.

Approximately 290–470 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. For most arms, approximately 15 patients will be enrolled during the preliminary phase. However, approximately 30 patients will be enrolled in the Atezo + Chemo + TCZ arm during the preliminary phase to ensure a sufficient number of patients with high C-reactive protein to facilitate the evaluation of benefit and risk in this subpopulation. 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. In some arms, randomization will be suspended to allow for a safety evaluation in a minimum of 6 patients (see Section 3.1.3 for details). Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion. Additional patients may be enrolled to ensure balance among treatment arms with respect to demographic and baseline characteristics, including potential predictive biomarkers, to enable further subgroup analyses. New experimental arms may be added during the course of the study by amending the protocol.

Patients in Stage 1 will be randomly assigned to treatment arms, and the randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), [redacted] 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 4 Stage 1 Treatment Regimens

Cohort	Arm Name	Treatment [a]	Number of Patients [b]		Appendix
			Preliminary Phase	Expansion Phase [c]	
1	Control	Nab-paclitaxel and gemcitabine	Variable [b]		Appendix 7
	Atezo + Chemo + Bev	Atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab	15	25	Appendix 15
	Atezo + Chemo + Tira	Atezolizumab, nab-paclitaxel, gemcitabine, and tiragolumab	20 [d]	25	Appendix 14
	Atezo + Chemo + TCZ	Atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab	30 [d,e]	25	Appendix 16
2	Control	One of the following treatment regimens, as determined on the basis of the patient's first-line treatment regimen: • Nab-paclitaxel and gemcitabine • mFOLFOX6	Variable [b]		Appendix 7

Atezo = atezolizumab; Bev = bevacizumab; Chemo = chemotherapy (nab-paclitaxel and gemcitabine); mFOLFOX6 = 5-fluorouracil, leucovorin, and oxaliplatin; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TCZ = tocilizumab; Tira = tiragolumab.

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

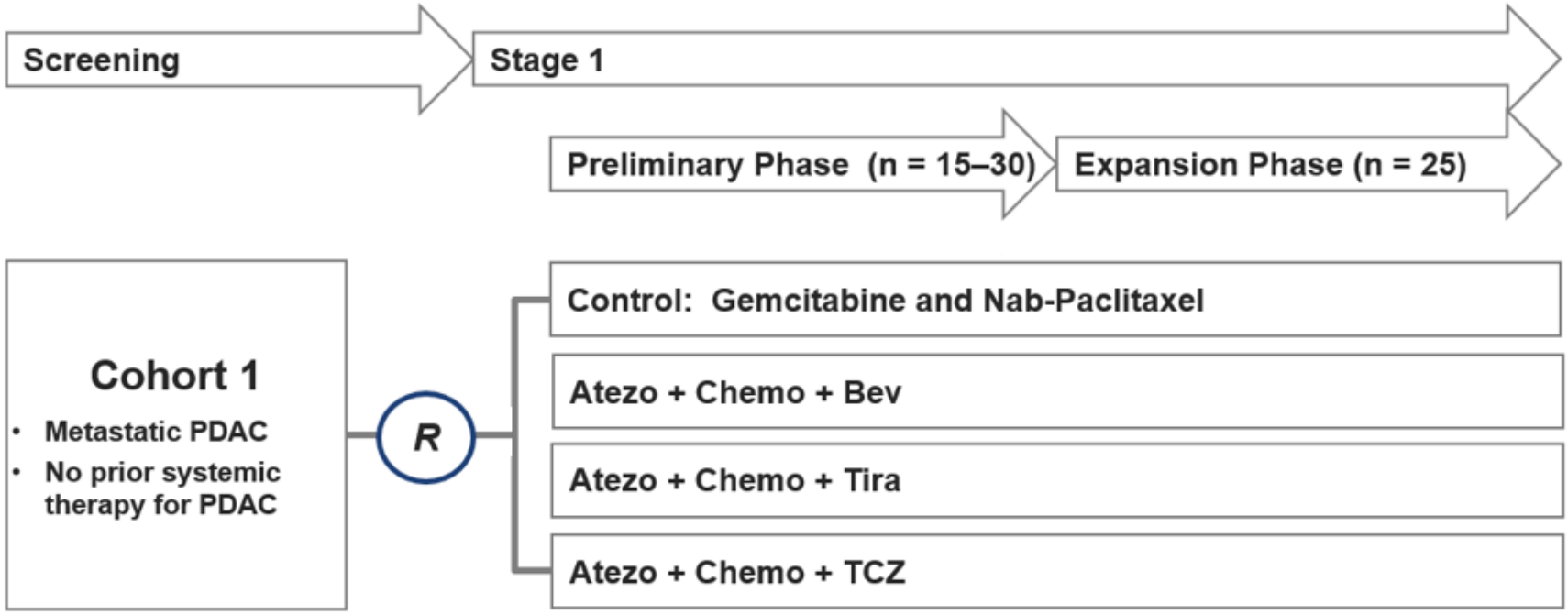
[b] The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), [redacted] (see Section 4.2 for details).

[c] 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. Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion.

[d] Randomization will be suspended in the Atezo + Chemo + Tira, and Atezo + Chemo + TCZ arms to allow for a safety evaluation in a minimum of 6 patients (see Section 3.1.3 for details).

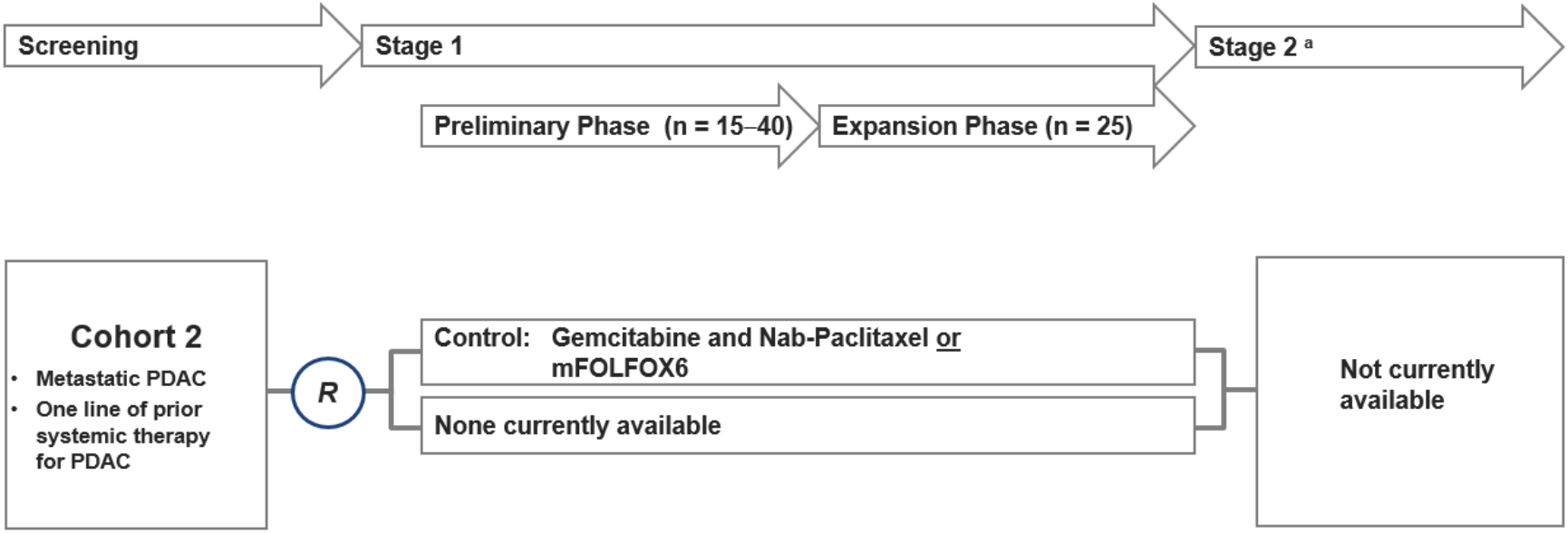
[e] Approximately 30 patients will be enrolled in the Atezo + Chemo + TCZ arm during the preliminary phase to ensure a sufficient number of patients with high C-reactive protein levels to facilitate the evaluation of benefit and risk in this subpopulation.

Figure 2 Detailed Study Design: Cohort 1



Atezo = atezolizumab; Bev = bevacizumab; Chemo = chemotherapy (nab-paclitaxel and gemcitabine); nab-paclitaxel = nanoparticle albumin–bound paclitaxel; PDAC = pancreatic ductal adenocarcinoma; R = randomization; TCZ = tocilizumab; Tira = tiragolumab.

Figure 3 Detailed Study Design: Cohort 2



mFOLFOX6 = 5-fluorouracil, leucovorin, and oxaliplatin; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; PDAC = pancreatic ductal adenocarcinoma; R = randomization; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Patients in Cohort 2 who experience disease progression per RECIST v1.1, loss of clinical benefit as determined by the investigator (details provided below), or unacceptable toxicity during Stage 1 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 Appendices 7, 12, 14–16).

Table 5 Treatment Arms with Completed Enrollment and Patient Follow-Up

Stage	Cohort	Arm Name	Treatment	Number of Patients Enrolled		Protocol Versions Describing Arm
				Preliminary Phase	Expansion Phase	
1	1	Atezo + Chemo + Seli	Atezolizumab, nab-paclitaxel, gemcitabine, and selicrelumab	9	0	4–9
1	*1*	*Atezo + Chemo + AB928*	*Atezolizumab, nab-paclitaxel, gemcitabine, and AB928*	*15*	*0*	*8-15*
1	2	Atezo + BL-8040	Atezolizumab and BL-8040	16	0	1–5
1	2	Atezo + Cobi	Atezolizumab and cobimetinib	15	0	1–9
1	2	Atezo + PEGPH20	Atezolizumab and PEGPH20	40	26	1–9
1	2	Atezo + RO6874281 Q2W	Atezolizumab and RO6874281 Q2W	15	0	4–9
1	2	Atezo + RO6874281 Q3W	Atezolizumab and RO6874281 Q3W	16	0	4–9
2	2	Atezo + Cobi	Atezolizumab and cobimetinib	14	N/A	1–9
2	2	Atezo + RO6874281 Q2W	Atezolizumab and RO6874281 Q2W	1	N/A	4–9
2	2	Atezo + RO6874281 Q3W	Atezolizumab and RO6874281 Q3W	6	N/A	4–9

Atezo = atezolizumab; Chemo = chemotherapy (nab-paclitaxel and gemcitabine); Cobi = cobimetinib; N/A = not applicable; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; Q2W = every 2 weeks; Q3W = every 3 weeks; Seli = selicrelumab.

Patients in the control arms will continue to receive treatment until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). Patients in the experimental arms will continue to 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). 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 atezolizumab and other CITs, radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving treatment with a CIT combination will be permitted to continue 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 Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

3.1.3 Safety Evaluation Phase

To account for potential overlapping toxicities in the Atezo+Chemo+Tira, and Atezo+Chemo+TCZ arms, enrollment within each arm will be suspended after approximately 6 patients have been enrolled to allow for a safety evaluation. The safety evaluation will be based on safety data from a minimum of 6 patients who have received at least one dose of treatment (i.e., one dose of each agent for a given combination) and completed safety follow-up assessments during at least one full treatment cycle. If the combination is determined to be sufficiently safe, enrollment will be resumed in that arm.

3.1.4 Second-Line Treatment for Cohort 1 Control Arm

Patients in the Cohort 1 control arm who experience disease progression per RECIST v1.1 will be given the option of enrolling in Cohort 2 (if open for enrollment), provided they meet eligibility criteria (see Section 4.1).

3.1.5 Stage 2 Treatment for Cohort 2

Patients in the Cohort 2 control arm who experience disease progression per RECIST v1.1 and patients in a Cohort 2 experimental arm who experience loss of clinical benefit as determined by the investigator (as described above) during Stage 1 will be given the option of receiving a different treatment combination during Stage 2, as outlined in Table 6, provided they meet eligibility criteria (see Section 4.1) and Stage 2

arms are open for enrollment. Patients who experience unacceptable toxicity during Stage 1 may be eligible to receive treatment during Stage 2. Patients in Cohort 2 who are eligible for more than one Stage 2 treatment arm will be assigned to a treatment arm by the Sponsor. Stage 2 treatment must begin within 3 months after the patient has experienced disease progression per RECIST v1.1, loss of clinical benefit, or unacceptable toxicity in Stage 1 and will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator. However, it is recommended that patients begin Stage 2 treatment as soon as possible.

Table 6 Stage 2 Treatment Regimens for Cohort 2

Arm Name	Treatment	Appendix
No Stage 2 treatment currently available		—

Enrollment in a treatment arm may be stopped during Stage 2 on the basis of [redacted] from these arms during Stage 1 [redacted]. The Sponsor may also decide to discontinue enrollment in Stage 2 treatment arms on the basis of a review of all available safety data, preliminary efficacy data, and supportive information [redacted], as appropriate.

3.1.6 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). [redacted]

Patients will undergo tumor assessments every 6 weeks (from Day 1 of Cycle 1) during the first 48 weeks and then every 6 or 12 weeks thereafter (see Section 4.5.5 and Appendices 7, 12, 14–16 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 control arm be submitted for evaluation by an Independent Review Facility.

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, provided the tissue was obtained within 3 months prior to enrollment and the patient has not received any anti-cancer therapy since the time of the biopsy. If deemed clinically feasible by the investigator, tumor tissue will also be collected for patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator. For patients enrolled in an experimental arm during the

expansion phase, an on-treatment tumor tissue sample will be collected 6 weeks after initiation of Stage 1 treatment for patients in the Atezo + Chemo + TCZ arm or 4 weeks after initiation of Stage 1 treatment in other experimental arms (if deemed clinically feasible by the investigator), unless on-treatment tissue samples have already been collected and determined to be evaluable from a minimum of 15 patients treated with the same CIT combination. These samples will be utilized for [redacted] and details on tissue sample collection in Section 4.5.7).

To characterize the pharmacokinetic (PK) properties and/or immunogenicity of atezolizumab and the other therapeutic agents, blood samples will be taken 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.

A schedule of activities is provided for each treatment arm in Appendices 7, 12, 14–16.

3.1.7 Internal Monitoring 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, 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.

3.1.8 Scientific Oversight Committee

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, [redacted] from the time of the first meeting of the SOC. 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.

3.2 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 (LPLV), including survival follow-up visits conducted by telephone or in the clinic.

3.3 *DURATION OF PARTICIPATION*

Treatment will continue until disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1. (RECIST v1.1). The total duration of study, from screening of the first patient to the end of the study, is expected to be approximately 7 years or 9 years if expansion is ungated.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Patient Population

Pancreatic cancer is a disease of high unmet medical need with an overall 5-year survival rate of $<5\%$. Chemotherapy remains the standard-of-care treatment for metastatic disease, as described in Section 1. Despite recent improvements in treatment, the prognosis for patients with metastatic PDAC remains poor, with a median OS of approximately 8.5–11.1 months (Conroy et al. 2011; Von Hoff et al. 2013). Patients who receive second-line treatment for their disease have an even more limited prognosis, with a median OS of approximately 4.3–6.1 months (Oettle et al. 2014; Zaanan et al. 2014, Wang-Gillam et al. 2016). Approved therapies are associated with significant toxicities (e.g., neuropathy, febrile neutropenia, myelosuppression, and alopecia) that negatively affect quality of life. Therefore, there is a continuing need for more efficacious, better-tolerated treatments for patients with metastatic PDAC.

3.4.2 Rationale for Immunotherapy-Based Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response, partial response, 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 3.1.2). 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 3.1.2 for details).

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

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

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

- Age ≥18 years at the time of signing Informed Consent Form
- ECOG Performance Status of 0 or 1 (see Appendix 3)
- Histologically or cytologically confirmed metastatic PDAC

  The definitive diagnosis of metastatic PDAC is made by evaluating the histopathologic data within the context of clinical and radiographic data.

  Patients with endocrine or acinar pancreatic carcinoma are not eligible for the study.
- For patients in Cohort 1: no prior systemic treatment for PDAC
- For patients in Cohort 2: disease progression during administration of either 5FU– or gemcitabine-based first-line chemotherapy in the metastatic or locally advanced setting and, for patients treated in the locally advanced setting, occurrence of metastasis within 6 months after initiation of chemotherapy

  Prior chemotherapy administered as a radiation sensitizer will not be considered first-line chemotherapy. Patients who had disease progression during or within 6 months after administration of capecitabine plus gemcitabine are not eligible for the study.
- Life expectancy ≥3 months, as determined by the investigator
- Availability of a representative tumor specimen that is suitable for determination of PD-L1 and/or additional biomarker status via 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, provided the tissue was obtained from a biopsy performed within 3 months prior to enrollment and the patient has not received any anti-cancer therapy since the time of the biopsy.

  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. Refer to Section 4.5.7 for additional information on tumor specimens collected at screening.

4.1.1.2 Inclusion Criteria for Stage 1 and Stage 2

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

- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- 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:

- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- 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 Appendices 7, 12, 14–16
- 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 Appendices 7, 12, 14–16

4.1.1.3 Inclusion Criteria for Stage 2

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

- ECOG Performance Status of 0, 1, or 2 (see Appendix 3)
- Patients randomly allocated to the control arm during Stage 1: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity or disease progression per RECIST v1.1 while receiving control treatment
- Patients randomly allocated to 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 3.1.2 for details) while receiving Stage 1 treatment
- Availability of a tumor specimen from a biopsy performed upon discontinuation of Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator

4.1.2 Exclusion Criteria

Patients will be excluded from enrollment in specific arms during Stage 1 or enrollment during Stage 2 if they meet any of the criteria outlined in subsequent sections, as specified by treatment arm below:

Stage	Cohort	Treatment Arm	Applicable Exclusion Criteria
1	1	Control	Sections 4.1.2.1 and 4.1.2.2
		Atezo + Chemo + Bev	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.3
		Atezo + Chemo + Tira	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.5
		Atezo + Chemo + TCZ	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.6

Atezo + atezolizumab; Bev = bevacizumab; Chemo = chemotherapy (nab-paclitaxel and gemcitabine); TCZ = tocilizumab; Tira = tiragolumab.

4.1.2.1 Exclusion Criteria for Stage 1

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

- Prior treatment with T-cell co-stimulating or immune checkpoint blockade therapies (including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies)
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Systemic treatment for PDAC within 2 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Adverse events from prior anti-cancer therapy that have not resolved to Grade ≤ 1 or better, with the exception of alopecia of any grade and Grade ≤ 2 peripheral neuropathy
- For patients in Cohort 2: known dihydropyrimidine dehydrogenase deficiency
- Eligible only for the control arm

4.1.2.2 Exclusion Criteria for Stage 1 and Stage 2

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

- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (i.e., more than one time per month)
- Uncontrolled tumor-related pain

[redacted]

- Symptomatic, untreated, or actively progressing CNS metastases

  Patients with a history of treated CNS lesions are eligible, provided that all of the following criteria are met:

[redacted]

- Uncontrolled hypercalcemia [redacted], or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

  Patients who are receiving bisphosphonate therapy for other reasons (e.g., bone metastasis or osteoporosis) and who do not have a history of clinically significant hypercalcemia are eligible for the study.

- History of leptomeningeal disease
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- Positive HIV test at screening or at any time prior to screening
- [redacted]
- [redacted]
- [redacted]
- Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, fatty liver disease, and inherited liver disease

- Active tuberculosis (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 Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 12 months prior to initiation of study treatment, or unstable arrhythmia or unstable angina within 3 months prior to initiation of study treatment
- Grade ≥ 3 hemorrhage or bleeding event within 28 days prior to initiation of study treatment
- Prior allogeneic stem cell or solid organ transplantation
- 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 course of the study

  Placement of a central venous access catheter (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.
- History of malignancy other than pancreatic carcinoma within 2 years prior to screening, with the exception of those 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
- 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, or may render the patient at high risk from treatment complications
- Pregnant or breastfeeding, or intending to become 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.
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during treatment with atezolizumab or within 5 months after the last dose of atezolizumab
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or recombinant human antibodies

- Known allergy or hypersensitivity to any of the study drugs or any of their excipients
- 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 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 immunosuppressive medication during the course of the study, with the following exceptions:

- 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 Exclusion Criteria for Bevacizumab-Containing Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the bevacizumab-containing arms during Stage 1:

- Inadequately controlled hypertension, defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg (average of at least three readings at two or more sessions)

  Anti-hypertensive therapy to achieve these parameters is allowed.
- History of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of study treatment
- History of hemoptysis (≥ 2.5 mL of bright red blood per episode) within 1 month prior to initiation of study treatment
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (<10 days prior to initiation of study treatment) use of aspirin (>325 mg/day) or clopidogrel (>75 mg/day)

Use of full-dose oral or parenteral anticoagulants for therapeutic purpose is permitted as long as the INR and/or aPTT is within therapeutic limits (according to institution standards) within 7 days prior to initiation of study treatment and the patient has been on a stable dose of anticoagulants for ≥2 weeks prior to initiation of study treatment. Prophylactic use of anticoagulants is allowed.

- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to initiation of study treatment
- History of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months prior to initiation of study treatment
- History of intestinal obstruction and/or clinical signs or symptoms of GI obstruction, including subocclusive or occlusive syndrome related to the underlying disease, within 6 months prior to initiation of study treatment or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding within 6 months prior to initiation of study treatment

  Patients with signs or symptoms of subocclusive or occlusive syndrome or with intestinal obstruction at the time of initial diagnosis may be enrolled if they had received definitive (surgical) treatment for symptom resolution.
- Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Grade ≥2 proteinuria, as demonstrated by ≥2+ protein on dipstick urinalysis and ≥1.0 g of protein in a 24-hour urine collection

  All patients with ≥2+ protein on dipstick urinalysis at screening must undergo a 24-hour urine collection for protein. Patients with <2+ protein on dipstick urinalysis are eligible for the study.
- Metastatic disease that involves major airways or blood vessels, or centrally located mediastinal tumor masses (<30 mm from the carina) of large volume
- History of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including, but not limited to, peptic ulcer disease, diverticulitis, or colitis
- Radiotherapy within 28 days or abdominal/pelvic radiotherapy within 60 days prior to initiation of study treatment
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to initiation of study treatment; or abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 60 days prior to initiation of study treatment; or anticipation of need for major surgical procedure during the course of the study or non-recovery from side effects of any such procedure

4.1.2.4 Exclusion Criteria for Tiragolumab-Containing Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the tiragolumab-containing arm during Stage 1:

- Prior treatment with an anti-TIGIT agent
- [redacted]

4.1.2.5 Exclusion Criteria for Tocilizumab-Containing Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the tocilizumab-containing arm during Stage 1:

- Preexisting CNS demyelinating or seizure disorders
- History of diverticulitis, chronic ulcerative lower GI disease (e.g., Crohn's disease, ulcerative colitis), or other symptomatic lower GI conditions that might predispose a patient to GI perforation
- Current liver disease unrelated to the underlying cancer diagnosis, as determined by the investigator
- Active current infection or history of recurrent bacterial, viral, fungal (excluding fungal infections of the nail bed), mycobacterial, or other infection, including, but not limited to, atypical mycobacterial disease, [redacted]

  In the setting of a pandemic or epidemic, screening for active infections should be considered according to local or institutional guidelines or those of applicable professional societies (e.g., ASCO or ESMO).
- Active TB as documented by a positive purified protein derivative (PPD) skin test or TB blood test and confirmed by a positive chest X-ray within 3 months prior to initiation of study treatment

  Patients with a positive PPD skin test or TB blood test followed by a negative chest X-ray may be eligible for the study.
- Untreated, latent TB
- History of, or currently active, primary or secondary immunodeficiency
- [redacted]

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and Stage 1 treatment assignment from the interactive voice or web-based response system (IxRS). Patients who enroll in Stage 2 will be assigned to treatment through use of the IxRS and will retain the same patient identification number that was assigned in Stage 1.

For Stage 1, this study will employ a permuted-block randomization method with dynamically changing randomization ratios to account for fluctuation in the number of treatment arms that are open for enrollment over the course of the study. At study initiation, patients will be randomly assigned with an approximately equal ratio [redacted] to one of four treatment arms (three experimental arms plus control arm) (initial randomization scheme) until approximately 15 patients have been enrolled within each arm. Thereafter, the randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), [redacted]

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). [redacted]

Patients in Cohort 2 may be eligible for treatment in Stage 2. Patients who are eligible for more than one Stage 2 treatment arm will be assigned a treatment arm by the Sponsor.

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 randomized in Stage 1 to reach the target number of treated patients planned for analysis.

4.3 STUDY TREATMENT

Details on the therapeutic agents for each treatment arm are provided in the respective appendix for that treatment arm, as outlined in Appendices 7, 12, 14–16.

4.3.1 Investigational Medicinal Product Accountability

The IMPs for this study are atezolizumab, 5-FU, leucovorin, oxaliplatin, nab-paclitaxel, gemcitabine, bevacizumab, tiragolumab, and tocilizumab. Appendix 17 identifies all investigational medicinal products for this study. 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 using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will 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.

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, as outlined in Appendices 7, 12, 14–16.

4.5 STUDY ASSESSMENTS

A schedule of activities to be performed during the study is provided for each treatment arm in Appendices 7, 12, 14–16. 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 dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening

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

Written informed consent must also be obtained before performing screening evaluations for Stage 2.

Screening evaluations are to be performed within 28 days prior to initiation of study treatment (Day 1) in Stage 1 or Stage 2. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment.

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 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 Day 1 (within 14 days prior to Day 1 for laboratory tests) may be used; such tests do not need to be repeated for screening or re-screening.

4.5.2 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, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline.
The patient's molecular profile for pancreatic cancer, 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 Appendices 7, 12, 14–16). At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, 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.

4.5.4 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 within 60 minutes prior to administration of each study treatment and, if clinically indicated, during or after treatment administration. In addition, vital signs should be measured at other specified timepoints as outlined for each arm in the schedules of activities in Appendices 7, 12, 14–16.

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 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, except in the case of patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.2 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/or evaluable lesions should be assessed and documented at screening (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 initiation of study treatment do not have to be repeated at screening.

Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or magnetic resonance imaging (MRI) scans (with IV contrast) of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. 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 (with IV contrast, if feasible) of the abdomen and pelvis should be performed. A CT scan with contrast or MRI scan with contrast of the head, bone scans, and CT scans of the neck should be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

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

All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. 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). To facilitate evaluation of post-progression tumor changes while treatment is ongoing, 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) at all subsequent assessments.

Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1). 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.

4.5.6 Chest X-Ray

A chest X-ray will be performed at screening for patients in Cohort 1, for patients who have a positive tuberculin PPD skin test or TB blood test, provided a tocilizumab-containing arm is open for enrollment.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)

- Chemistry panel (serum or plasma): CPK (performed for specified arms only; details provided in schedules of activities), bicarbonate or 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
- Coagulation: INR and aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- Ferritin and γ-glutamyl transferase (performed for specified arms only; details provided in schedules of activities)

- Tuberculin PPD skin test or TB blood test (performed at screening, provided a tocilizumab-containing arm is open for enrollment; see Appendix 6)
- C-reactive protein
- LDH
- CA19-9

- 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.

  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 urinalysis is permitted. However, patients in Cohort 1 with ≥2+ protein on dipstick urinalysis at screening must undergo a 24-hour urine collection for protein if a bevacizumab-containing arm is open for enrollment.

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: antinuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody
- Plasma or serum samples for PK analysis through use of validated assays (see Appendices 7, 12, 14–16)
- Plasma or serum samples for immunogenicity analysis through use of validated assays (see Appendices 7, 12, 14–16)
- [redacted]
- Tumor tissue sample collected at baseline for determination of PD-L1 expression and for [redacted]

- Patients enrolled in an experimental arm during the expansion phase: tumor tissue sample collected 4 weeks (±7 days) after initiation of Stage 1 treatment or 6 weeks (±7 days) after initiation of Stage 1 treatment for patients in the Atezo+Chemo+TCZ arm (if deemed clinically feasible by the investigator) for [redacted]
- Tumor tissue sample collected during Stage 1, at the time of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details), if deemed clinically feasible by the investigator, for [redacted]

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 [redacted] (see Section 4.5.11), biological samples will be destroyed when the final Clinical Study Report has been completed, 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 Clinical Study Report has been completed.

- [redacted] will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the exception of the samples that undergo [redacted] which will be stored until they are no longer needed or until they are exhausted. However, the storage period for the [redacted] samples will be in accordance with the Institutional Review Board or Ethics Committee (IRB/EC) approved Informed Consent Form and applicable laws (e.g., health authority requirements).

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.

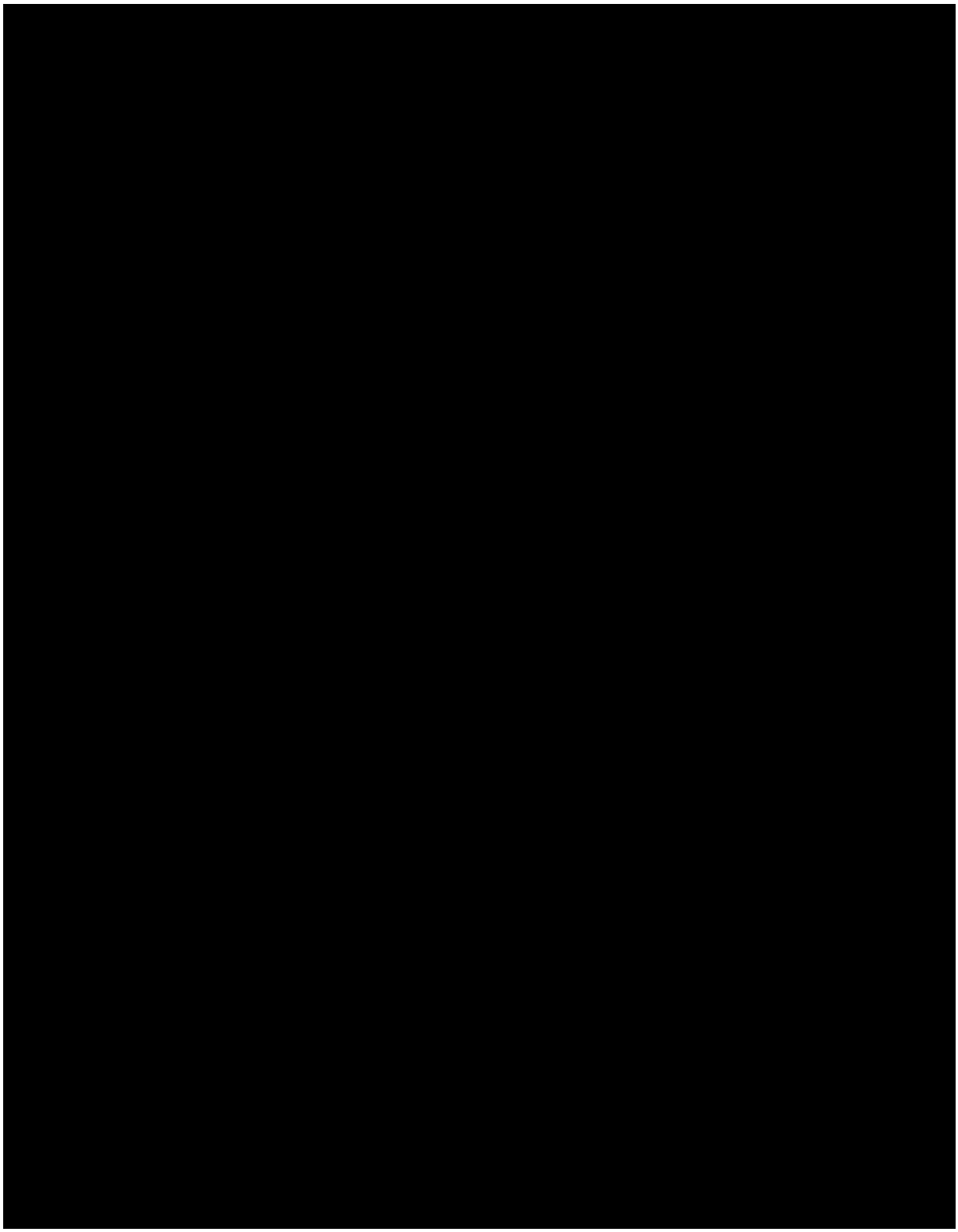
Given the complexity and [redacted], data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

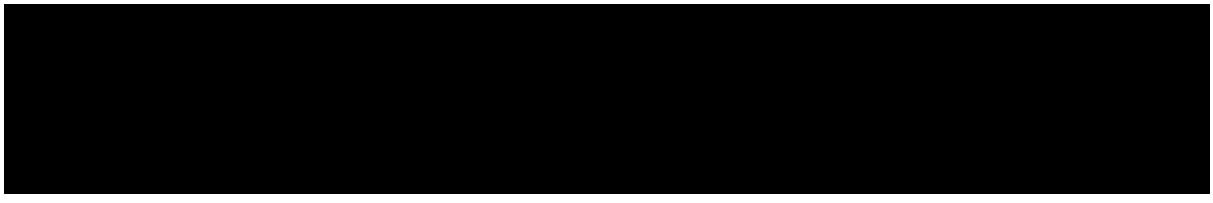
4.5.8 Electrocardiograms

An ECG is required at screening and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. It is recommended that patients be resting 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.

[redacted]





[redacted]

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 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 [redacted] assays and establish the performance characteristics of these assays

4.5.11.2 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 4.5.11) will not be applicable at that site.

4.5.11.3 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:

- Blood samples collected on Day 1 of Cycle 1 during Stage 1 and Stage 2
- Leftover blood, serum, plasma, PBMC, and tumor tissue 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 [redacted]

Genomics is increasingly informing researchers' understanding of disease pathobiology. [redacted] 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).

4.5.11.4 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.

4.5.11.5 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.

4.5.11.6 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. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. 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 Study WO39608 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study WO39608.

4.5.11.7 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 anti-cancer therapy
- Pregnancy
- Experimental arms: 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 3.1.2 for details)
- Control arm: radiographic disease progression per RECIST v1.1

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 will continue to undergo tumor response assessments as outlined in the schedule of activities provided for each arm in Appendices 7, 12, 14–16.

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 (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 the 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 approximately 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. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients who withdraw from the study will not be replaced.

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, as outlined in Appendices 7, 12, 14–16.

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

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 5.3.5.12.

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study 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, as outlined in Appendices 7, 12, 14–16.

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 5.3.5.12–5.6.

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

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study 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).

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

Table 7 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.

[redacted]

[redacted]

[redacted]

[redacted]

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 9):

- 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 9 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 or Injection Reactions and [redacted]

There may be significant overlap in signs and symptoms of infusion-related reactions (IRRs) and [redacted] While IRRs occur during or within 24 hours after treatment administration, time to onset of [redacted] may vary. Differential diagnosis should be applied, particularly for [redacted] (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, [redacted] 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 or injection should be captured on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction," "injection-site reaction," or "[redacted]"). Avoid ambiguous terms such as "systemic reaction." [redacted]

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

In recognition of the challenges in clinically distinguishing between IRRs and [redacted], consolidated guidelines for medical management of IRRs and [redacted] are provided in Appendix 2.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than IRRs (see Section 5.3.5.1), 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 PDAC 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 PDAC

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

5.3.5.12 Reporting Requirements for 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, 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, bevacizumab, tiragolumab, and tocilizumab, 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, bevacizumab, tiragolumab, and tocilizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor

immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- 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.

5.4 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)

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

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

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

5.4.1 Emergency Medical Contacts

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

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

5.4.2 Reporting Requirements for Serious Adverse Events 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 Serious 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

[redacted]

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 Serious 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 [redacted] after the last dose of study treatment 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, as outlined in Appendices 7, 12, 14–16.

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 adverse event reporting period [redacted], 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 Serious 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 will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

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

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

- Atezolizumab Investigator's Brochure
- E.U. Summary of Product Characteristics for nab-paclitaxel
- Ireland Summary of Product Characteristics for 5-FU, leucovorin, oxaliplatin, and gemcitabine
- Bevacizumab Investigator's Brochure
- Tiragolumab Investigator's Brochure
- Tocilizumab Investigator's Brochure

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

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

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

In both cohorts, the analysis results will be summarized by the treatment regimen that patients actually received, as well as by stage (Stage 1 or Stage 2). Data will be described and summarized as warranted by sample size. Continuous variables will be summarized through use of means, standard deviations, medians, and ranges. Categorical variables will be summarized through use of counts and percentages. Listings will be used in place of tables in the event of small sample sizes.

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 4.5.5. 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 metastatic PDAC. Cohort 1 will consist of patients who have received no prior systemic therapy for metastatic PDAC, and Cohort 2 will consist of patients who have received one line of prior systemic therapy for PDAC.

Approximately 290–470 patients will be randomly allocated to the control and experimental arms during the study: approximately 110–250 patients in Cohort 1 and approximately 180–220 patients in Cohort 2.

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 the safety-evaluable population, 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 Performance Status) will be summarized overall and by treatment arm within each stage.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is objective response during Stage 1, as defined in Section 2 (see Table 2). Patients with missing or no response assessments will be classified as non-responders.

ORR, the proportion of patients with a complete or partial response, will be calculated for each arm, along with 95% confidence intervals (Clopper–Pearson method).
The difference in ORR between the experimental arms and the control arm will also be calculated, along with 95% confidence intervals, using the Wald method with continuity correction.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are PFS, OS, OS at specific timepoints (e.g., 6 months), duration of response (DOR), and disease control during Stage 1, as defined in Section 2 (see Table 2). 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 complete or partial response.

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% confidence intervals constructed through use of the Brookmeyer and Crowley method. OS rate at specific timepoints will also be estimated using the Kaplan-Meier

method, with 95% confidence intervals calculated on the basis of Greenwood's estimate for the variance.

Disease control rate, the proportion of patients with stable disease for ≥12 weeks, a partial response, or a complete response, will be calculated for each treatment arm, with 95% confidence intervals estimated through use of Clopper-Pearson's exact method.

[redacted]

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, [redacted]

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 ≥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 tests will be

used to summarize the baseline and maximum post-baseline severity grade. Changes in vital signs and ECGs will be summarized.

6.6 PHARMACOKINETIC ANALYSES

Sparse samples will be collected for potential PK analyses of atezolizumab (patients who receive at least one dose of atezolizumab) and specified 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 may 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 may 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. Atezolizumab 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.

6.7 IMMUNOGENICITY ANALYSES

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

For other study treatments for which ADAs are tested, ADA positivity will be determined according to standard methods established for previous studies of these drugs.

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. Food and Drug Administration 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 [redacted], 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.

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 (i.e., LPLV).

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 4.5.7. 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 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. 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. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

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

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1
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.[1]

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 $\leq$ 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 $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 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").

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

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 at prior timepoints (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.

REFERENCES

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Appendix 2
Management of Atezolizumab-Specific Adverse Events

[redacted]

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

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

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the *subsequent* subsections.

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

- [redacted]

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. COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table A2-1.

Table A2-1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
[redacted]	

Table A2-1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

a

b

c

d

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 A2-2.

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 A2-2 Management Guidelines for Hepatic Events

Event	Management
[redacted]	

a [redacted]

b [redacted]

c [redacted]

Table A2-2 Management Guidelines for Hepatic Events (cont.)

Event	Management
[redacted]	

a [redacted]

b

c

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table A2-3.

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 A2-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
[redacted]	

[redacted]

a [redacted]

b [redacted]

c [redacted]

Table A2-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
[redacted]	
[redacted]	
a [redacted]	
b	
c	

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table A2-4.

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

pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table A2-4 Management Guidelines for Endocrine Events

Event	Management
[redacted]	

Table A2-4 Management Guidelines for Endocrine Events (cont.)

[redacted]

a [redacted]

b [redacted]

c [redacted]

Table A2-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
[redacted]	

[redacted]

a [redacted]

b

c

Table A2-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
[redacted]	

[redacted]

a [redacted]

b [redacted]

c [redacted]

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table A2-5.

Table A2-5 Management Guidelines for Ocular Events

Event	Management
[redacted]	

[redacted]

a [redacted]

b

c

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 clinical practice.
Management guidelines for cardiac events are provided in Table A2-6.

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 *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 longitudinal strain*, 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 A2-6.

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 A2-6. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table A2-6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
[redacted]	

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, antipyretic 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 A2-7.

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.

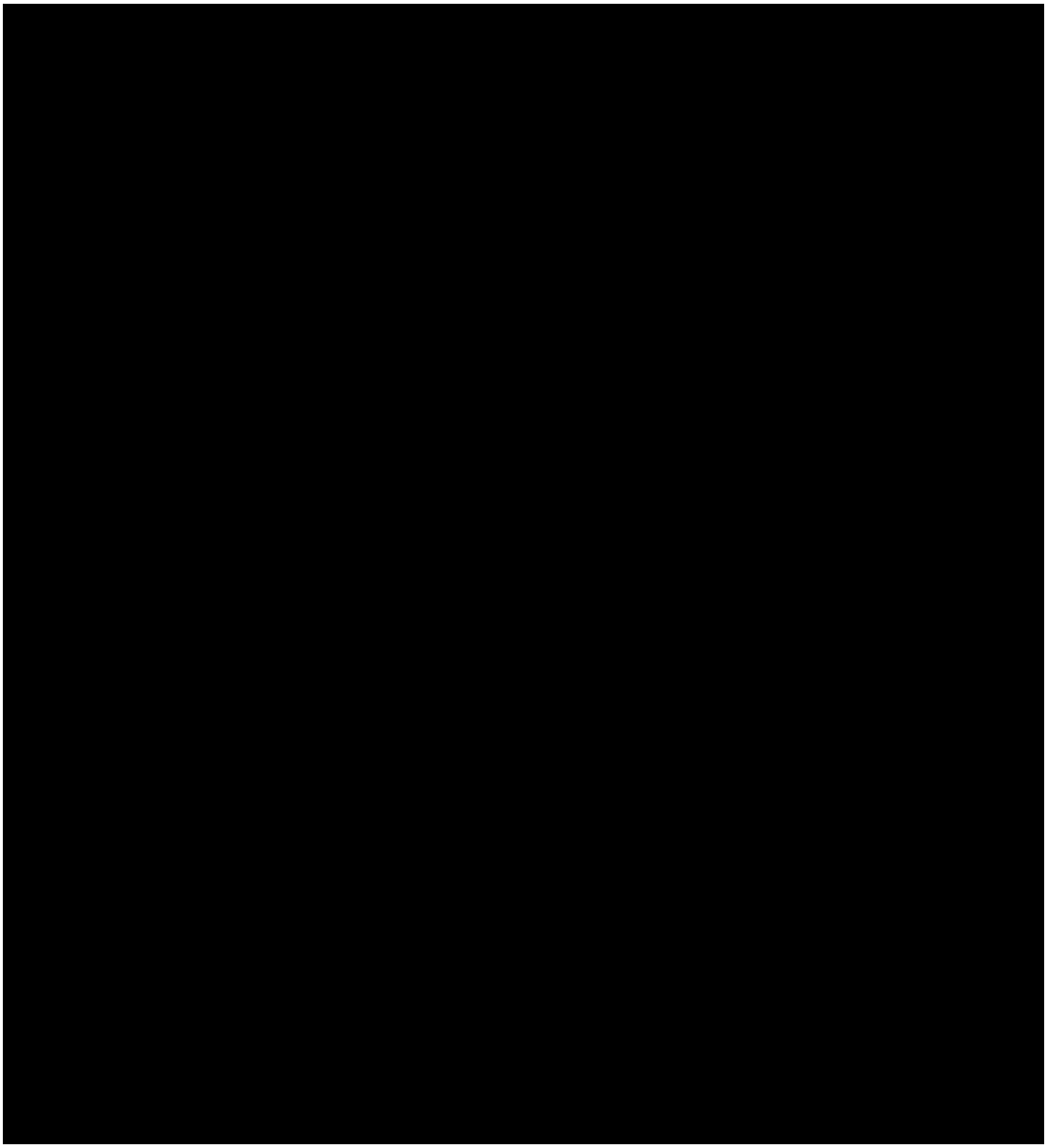
Table A2-7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome

Event	Management
[redacted]	

Table A2-7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

Event	Management
[redacted]	

Table A2-7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)



PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table A2-8.

Table A2-8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
[redacted]	

[redacted]

a [redacted]

b

c

Table A2-8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
[redacted]	

a [redacted]

b [redacted]

c [redacted]

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 uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table A2-9.

Table A2-9 Management Guidelines for Dermatologic Events

Event	Management
[redacted]	
[redacted]	
a [redacted]	
b	
c	

Table A2-9 Management Guidelines for Dermatologic Events (cont.)

Event	Management
[redacted]	

[redacted]

a [redacted]

b

c

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. *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 A2-10, with specific guidelines for myelitis provided in Table A2-11.

Table A2-10 Management Guidelines for Neurologic Disorders

Event	Management
[redacted]	

Appendix 2: Management of Atezolizumab-Specific Adverse Events

[redacted]

a [redacted]

b [redacted]

c [redacted]

Table A2-11 Management Guidelines for Immune-Mediated Myelitis

Event	Management
[redacted]	

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 A2-12.

Table A2-12 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
[redacted]	

RENAL EVENTS

Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as

non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A2-13.

Table A2-13 Management Guidelines for Renal Events

Event	Management
[redacted]	

a [redacted]

b

c

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/*creatine phosphokinase* 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 section on immune-mediated myocarditis)* and myasthenia gravis *(bulbar symptoms such as dysphagia, dysphoria, and dyspnea; see 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 A2-14.

Table A2-14 Management Guidelines for Immune-Mediated Myositis

Event	Management
[redacted]	

[redacted]

a [redacted]

b

c

Table A2-14 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
[redacted]	

Table A2-14 Management Guidelines for Immune-Mediated Myositis (cont.)

a

b

c

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 A2-15.

Table A2-15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis

Event	Management
[redacted]	

REFERENCES

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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 for patients who have previously experienced a severe or life-threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

Appendix 5
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Oxygen
- Epinephrine for SC, IV, 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. Maintain an adequate airway.
3. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
4. Continue to observe the patient and document observations.

Appendix 6
Schedules of Activities for Screening

Table A6-1 Schedule of Activities for Stage 1 Screening: Cohort 1

Assessment/Procedure	Stage 1 Screening [a] (Day –28 to –1)
Informed consent	x [b]
Demographic data	x
Medical history and baseline conditions	x
Molecular profile of pancreatic cancer (if available)	x
Vital signs [c]	x
Weight	x
Height	x
Complete physical examination [d]	x
ECOG Performance Status	x
ECG [e]	x
TB test	x [f]
Chest X-ray	x [g]
Hematology [h]	x [i]
Chemistry [j]	x [i]
Coagulation (INR, aPTT)	x [i]
TSH, free T3 (or total T3 [k]), free T4	x [i]
[redacted]	
C-reactive protein	x [i]
LDH	x [i]
Pregnancy test [m]	x [i]
Urinalysis [n]	x [i]
Serum autoantibody sample [o]	x [i]
Tumor biopsy [p]	x
Baseline tumor assessments [q]	x
Concomitant medications [r]	x
Adverse events [s]	x

CT = computed tomography; EBNA = Epstein-Barr nuclear antigen; [redacted]
ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; [redacted]; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; TB = tuberculosis; TSH = thyroid-stimulating hormone; VCA = viral capsid antigen.

Table A6-1 Schedule of Activities for Stage 1 Screening: Cohort 1 (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 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 Day 1 (within 14 days prior to Day 1 for laboratory tests) 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, 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.

[e] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[f] TB test will be performed only if a tocilizumab-containing arm is open for enrollment. Patients will undergo a tuberculin purified protein derivative (PPD) skin test or a TB blood test within 28 days prior to initiation of study treatment.

[g] A chest X-ray will be performed at screening for patients who have a positive tuberculin PPD skin test or TB blood test, provided a tocilizumab-containing arm is open for enrollment.

[h] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[i] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[j] 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.

[k] Total T3 may be performed for sites where free T3 is not performed.

[l] [redacted]

[m] All women of childbearing potential will have a serum pregnancy test at screening.

[n] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. Patients with $\geq 2+$ protein on dipstick urinalysis at screening must undergo a 24-hour urine collection for protein, but only if a bevacizumab-containing arm is open for enrollment.

[o] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

Table A6-1 Schedule of Activities for Stage 1 Screening: Cohort 1 (cont.)

[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, provided that the tissue was obtained from a biopsy performed within 3 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the biopsy. Refer to Section 4.5.7 for tissue sample requirements.

[q] All measurable and/or 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. 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. A spiral CT scan of the chest may be obtained but is not a requirement. 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 (with IV contrast, if feasible) of the abdomen and pelvis should be performed. A CT scan with contrast or MRI scan with contrast of the head, bone scans, and CT scans of the neck should be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 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 within 10 days prior to initiation of study treatment.

[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 A6-2 Schedule of Activities for Stage 1 Screening: Cohort 2

Assessment/Procedure	Stage 1 Screening [a] (Day –28 to –1)
Informed consent	x [b]
Demographic data	x
Medical history and baseline conditions	x
Molecular profile of pancreatic cancer (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 (INR, aPTT)	x [g]
TSH, free T3 (or total T3 [i]), free T4	x [g]
[redacted]	
C-reactive protein	x [g]
LDH	x [g]
Pregnancy test [k]	x [g]
Urinalysis [l]	x [g]
Serum autoantibody sample [m]	x [g]
Tumor biopsy [n]	x
Baseline tumor assessments [o]	x [o]
Concomitant medications [p]	x
Adverse events [q]	x

Table A6-2 Schedule of Activities for Stage 1 Screening: Cohort 2 (cont.)

CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; [redacted]; MRI = magnetic resonance imaging; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

[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 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 Day 1 (within 14 days prior to Day 1 for laboratory tests) 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, 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.

[e] 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), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST.

[i] Total T3 may be performed for sites where free T3 is not performed.

[j] [redacted]

[k] All women of childbearing potential will have a serum pregnancy test at screening.

[l] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[m] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

Table A6-2 Schedule of Activities for Stage 1 Screening: Cohort 2 (cont.)

[n] 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, provided that the tissue was obtained from a biopsy performed within 3 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the biopsy. Refer to Section 4.5.7 for tissue sample requirements.

[o] All measurable and/or 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. 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. A spiral CT scan of the chest may be obtained but is not a requirement. 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 (with IV contrast, if feasible) of the abdomen and pelvis should be performed. A CT scan with contrast or MRI scan with contrast of the head, bone scans, and CT scans of the neck should be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.

[p] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 10 days prior to initiation of study treatment.

[q] 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 A6-3 Schedule of Activities for Stage 2 Screening: Cohort 2

Assessment/Procedure	Stage 2 Screening [a]
Informed consent	x [b]
Molecular profile of pancreatic cancer (if available)	x
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]
Coagulation (INR, aPTT)	x [g]
TSH, free T3 (or total T3 [i]), free T4	x [g]
[redacted]	
C-reactive protein	x [g]
LDH	x [g]
Pregnancy test [k]	x [g]
Urinalysis [l]	x [g]
Tumor response assessments [m]	x [m, n]
Concomitant medications [o]	x
Adverse events [p]	x

CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; [redacted]

MRI = magnetic resonance imaging; 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 "n" 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.

Table A6-3 Schedule of Activities for Stage 2 Screening: Cohort 2 (cont.)

[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.

[e] 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), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST.

[i] Total T3 may be performed for sites where free T3 is not performed.

[j] [redacted]

[k] All women of childbearing potential will have a urine or serum pregnancy test at screening.

[l] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[m] All measurable and/or 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. 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. A spiral CT scan of the chest may be obtained but is not a requirement. 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 (with IV contrast, if feasible) of the abdomen and pelvis should be performed. A CT scan with contrast or MRI scan with contrast of the head, bone scans, and CT scans of the neck should be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.

[n] 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.

Table A6-3 Schedule of Activities for Stage 2 Screening: Cohort 2 (cont.)

[o] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 10 days prior to initiation of study treatment.

[p] 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.

Appendix 7
Study Details Specific to Control Arm (Cohorts 1 and 2)

TABLE OF CONTENTS

A7–1 MATERIALS AND METHODS SPECIFIC TO CONTROL ARM

A7–1.1 TREATMENT IN CONTROL ARM

A7–1.1.1 Formulation, Packaging, and Handling

For information on the formulation, packaging, and handling of the control agents, refer to the local prescribing information for each agent.

A7–1.1.2 Dosage, Administration, and Compliance

In Cohort 1, patients in the control arm will receive nanoparticle albumin–bound paclitaxel (nab-paclitaxel) and gemcitabine. In Cohort 2, patients in the control arm will receive treatment with one of two treatment regimens (see Table A7-1), as determined on the basis of the patient's first-line treatment regimen. Patients who progressed on a prior fluoropyrimidine-based regimen will receive nab-paclitaxel and gemcitabine. Patients who progressed on a prior gemcitabine-based regimen will receive mFOLFOX6 (5-fluorouracil [5-FU], leucovorin, and oxaliplatin). Patients will receive treatment until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). It is recommended that [redacted] Treatment will be administered according to institutional standards 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.

Table A7-1 Treatment Regimens for Control Arm

Cohort	Treatment Regimen	Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
1	Nab-paclitaxel and gemcitabine	28 days	• Nab-paclitaxel 125 mg/m^2 IV over 30 (±5) minutes on Days 1, 8, and 15 of each cycle • Gemcitabine 1000 mg/m^2 IV over 30 (±5) minutes on Days 1, 8, and 15 of each cycle
2	Nab-paclitaxel and gemcitabine [a]	28 days	• Nab-paclitaxel 125 mg/m^2 IV over 30 (±5) minutes on Days 1, 8, and 15 of each cycle • Gemcitabine 1000 mg/m^2 IV over 30 (±5) minutes on Days 1, 8, and 15 of each cycle
	mFOLFOX6 [b]	28 days	• Oxaliplatin 85 mg/m^2 IV over 2 hours (±5 minutes) on Days 1 and 15 of each cycle • Leucovorin 400 mg/m^2 IV over 2 hours (±15 minutes) on Days 1 and 15 of each cycle • 5-Fluorouracil 400 mg/m^2 IV push on Days 1 and 15 of each cycle • 5-Fluorouracil 2400 mg/m^2 IV continuous infusion over 46 (±2) hours on Days 1 and 2 and on Days 15 and 16 of each cycle

mFOLFOX6=5-fluorouracil, leucovorin, and oxaliplatin; nab-paclitaxel=nanoparticle albumin–bound paclitaxel.

[a] Patients who progressed on a prior fluoropyrimidine-based regimen will receive nab-paclitaxel and gemcitabine.

[b] Patients who progressed on a prior gemcitabine-based regimen will receive mFOLFOX6.

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

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with a medication error should be recorded on the Adverse Event eCRF.

A7–1.1.3 Second-Line Treatment for Cohort 1 Control Arm

Patients in the Cohort 1 control arm who experience disease progression per RECIST v1.1 will be given the option of enrolling in Cohort 2, provided they meet eligibility criteria (see Section 4.1) and the cohort is open for enrollment.

A7–1.1.4 Stage 2 Treatment for Cohort 2 Control Arm

Patients in the Cohort 2 control arm who experience disease progression per RECIST v1.1 will be given the option of receiving a different treatment combination during Stage 2, as outlined in Table A7-2, provided they meet eligibility criteria (see Section 4.1) and the arm is open for enrollment. Patients who experience unacceptable toxicity may also be eligible to receive treatment during Stage 2, provided they meet eligibility criteria and the arm is open for enrollment. The Medical Monitor is available to advise as needed. [redacted] However, it is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of disease progression 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 A7-2 Stage 2 Treatment Regimens Available for the Control Arm of Cohort 2

Study Treatment	Appendix
No Stage 2 treatment currently available	

A7–1.2 CONCOMITANT THERAPY, PROHIBITED FOOD, AND OTHER RESTRICTIONS FOR CONTROL 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 10 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.

For information on permitted, prohibited, or cautionary therapy, prohibited foods, and other restrictions (as applicable) for the control agents, refer to the local prescribing information for each agent.

A7–1.3 CONTRACEPTION REQUIREMENTS FOR CONTROL ARM

Contraception requirements for women and men in the control 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 6 months after the last dose of study treatment. 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 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 6 months after the last dose of study treatment. 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 6 months after the last dose of study treatment 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.

  Male patients receiving mFOLFOX6 should be advised regarding the conservation of sperm prior to treatment because of the possibility of irreversible infertility resulting from therapy with 5-FU and oxaliplatin.

A7–2 ASSESSMENT OF SAFETY FOR CONTROL ARM

A7–2.1 SAFETY PLAN FOR CONTROL ARM

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 control agents 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.

A7–2.1.1 Risks Associated with Control Agents

Risks associated with each control agent can be found in the local prescribing information for that agent. Patients receiving mFOLFOX6 should be advised to avoid prolonged exposure to sunlight because of the risk of photosensitivity with 5-FU.

Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection; however, this is not specific to the risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic and COVID-19 vaccination on the benefit–risk assessment, please refer to Section 1.5.

A7–2.1.2 Management of Patients Who Experience Specific Adverse Events in the Control Arm

Guidelines for management of patients who experience specific adverse events (including dose modifications and treatment interruptions) can be found for each control agent in the local prescribing information for that agent.

A7–2.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR CONTROL 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 control 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.

A7–2.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN CONTROL ARM

A7–2.3.1 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 6 months after the last dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study 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.

A7–2.3.2 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 study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. 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.

A7–2.3.3 Abortions

Any 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).

A7–2.3.4 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).

A7–3 SCHEDULE OF ACTIVITIES FOR CONTROL ARM

Table A7-3 Schedule of Activities for Control Arm (Cohorts 1 and 2)

	Stage 1 Screening (see Appendix 6)	Treatment Cycles (28-day cycles) [a]						Stage 2 Scrn. (see Appendix 6) [d] or Treat. Discon. [e]	Follow-Up [e]
		Cycle 1 [b]			Cycles ≥ 2				
	Day –28 to –1	Day 1	Day 8 [c] (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 8 [c] (±3 days)	Day 15 (±3 days)		Every 3 Months
Molecular profile of pancreatic cancer (if available)	See Appendix 6	Whenever updated information becomes available							
Vital signs [f]		x	x [c]	x	x	x [c]	x	x	
Weight		x [g]	x [c, g]	x [g]	x [g]	x [c, g]	x [g]	x	
Complete physical examination [h]								x	
Limited physical examination [i]		x [g]	x [c, g]	x [g]	x [g]	x [c, g]	x [g]		
ECOG Performance Status		x [g]			x [g]			x	
ECG [j]		Perform as clinically indicated [g]							
Hematology [k]		x [l, m]	x [c, l]	x [l]	x [l]	x [c, l]	x [l]	x [l]	
Chemistry [n]		x [l, m]	x [c, l]	x [l]	x [l]	x [c, l]	x [l]	x [l]	
CA19-9		x [l]			x [l]			x	
Pregnancy test [o]		x [l, m]			x [l]			x	x [o]
Urinalysis [p]		Perform as clinically indicated							

[redacted]

Table A7-3 Schedule of Activities for Control Arm (Cohorts 1 and 2) (cont.)

	Stage 1 Screening (see Appendix 6)	Treatment Cycles (28-day cycles) [a]						Stage 2 Scrn. (see Appendix 6) [d] or Treat. Discon. [e]	Follow-Up [e]
		Cycle 1 [b]			Cycles ≥ 2				
	Day –28 to –1	Day 1	Day 8 [c] (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 8 [c] (±3 days)	Day 15 (±3 days)		Every 3 Months
[redacted]									
Tumor response assessments	See Appendix 6	x [v, w, x]							
Concomitant medications [y]		x	x [c]	x	x	x [c]	x	x	
Adverse events [z]		x	x [c]	x	x	x [c]	x	x [z]	x [z]
Nab-paclitaxel and gemcitabine administration [aa, bb]		x	x	x	x	x	x		
mFOLFOX6 administration [bb, cc]		x		x	x		x		
Survival follow-up and anti-cancer treatment									x [dd]

Table A7-3 Schedule of Activities for Control Arm (Cohorts 1 and 2) (cont.)

CT = computed tomography; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; mFOLFOX6 = 5-fluorouracil, leucovorin, and oxaliplatin; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; PBMC = peripheral blood mononuclear cell; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Scrn. = screening; Treat. = treatment.

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] It is recommended that treatment be initiated no later than 7 days after randomization.

[c] The Day 8 visit applies only to patients who receive nab-paclitaxel and gemcitabine.

[d] In Cohort 2, patients who experience disease progression per RECIST v1.1 and (if Medical Monitor is in agreement) patients who experience unacceptable toxicity will be given the option of receiving a different treatment combination during Stage 2 (provided Stage 2 is open for enrollment; see Section A7–1.1.4 for details) and will undergo screening assessments to determine eligibility (see Appendix 6). Stage 2 treatment must begin within 3 months after the patient has experienced disease progression or unacceptable toxicity. However, it is recommended that patients begin Stage 2 treatment as soon as possible. Study details specific to the Stage 2 treatment regimens are provided in the applicable appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2, except as noted in footnote "x" below.

[e] Patients in Cohort 1 will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. Patients in Cohort 2 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 disease progression 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 in Cohort 1, and patients in Cohort 2 who do not enter Stage 2, will undergo follow-up assessments after completing the treatment discontinuation visit.

[f] 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 new or worsened clinically significant abnormalities on the Adverse Event eCRF. Vital signs should be measured within 60 minutes prior to study treatment and, if clinically indicated, during or after treatment administration.

[g] Assessment may be performed within 24 hours prior to dosing during the treatment period.

[h] 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 new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Table A7-3 Schedule of Activities for Control Arm (Cohorts 1 and 2) (cont.)

[i] 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.

[j] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[k] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[l] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

[m] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[n] Chemistry panel (serum or plasma) includes bicarbonate or 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.

[o] All women of childbearing potential will have urine or serum pregnancy tests 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.

[p] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[q] [redacted]

[r] [redacted]

[s] 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.

[t] [redacted]

[u] [redacted]

[v] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 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, even if they start new non–protocol-specified anti-cancer therapy.

Table A7-3 Schedule of Activities for Control Arm (Cohorts 1 and 2) (cont.)

[w] 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"). 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). Refer to Section 4.5.5 for further details on tumor assessments.

[x] 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 disease progression per RECIST v1.1 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.

[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 10 days prior to initiation of study treatment until the treatment discontinuation visit.

[z] [redacted] After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[aa] Patients in Cohort 1, and patients in Cohort 2 who progressed on prior fluoropyrimidine-based therapy, will receive nab-paclitaxel and gemcitabine as outlined in Table A7-1 of Appendix 7.

[bb] Treatment will continue until unacceptable toxicity or disease progression per RECIST v1.1.

[cc] Patients in Cohort 2 who progressed on prior gemcitabine-based therapy will receive mFOLFOX6 as outlined in Table A7-1 of Appendix 7.

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

Appendix 8
Placeholder for Future Arm

The atezolizumab plus PEGPH20 arm has been removed, as the treatment arm has met the criteria for closure per Section 4.6.1. The content of Appendix 8 [previously entitled "Study Details Specific to Atezo+PEGPH20 Arm (Cohort 2)]" has been deleted. Appendix 8 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 9
Placeholder for Future Arm

The content of Appendix 9 Schedules of Activities for Screening has been moved to Appendix 6. The previous content of Appendix 6 [previously entitled "Study Details Specific to Control Arm (Cohorts 1 and 2)]" has moved to Appendix 7. Appendix 9 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 10
Placeholder for Future Arm

The content of Appendix 10 Management of Atezolizumab-Specific Adverse Events has been moved to Appendix 2. The previous content of Appendix 2 [previously entitled "Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST)]" has been removed. Appendix 10 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 11
Placeholder for Future Arm

The atezolizumab plus RO6874281 Q2W and the atezolizumab plus RO6874281 Q3W arms have been removed, as the treatment arms have met the criteria for closure per Section 4.6.1. The content of Appendix 11 [previously entitled "Study Details Specific to Atezo + RO6874281 Q2W and Atezo + RO6874281 Q3W Arms (Cohort 2)"] has been deleted. Appendix 11 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 12
Placeholder for Future Arm

The atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus AB928 arm has been removed, as the treatment arm has met the criteria for closure per Section 4.6.1. The content of Appendix 12 [previously entitled "Study Details Specific to Atezo + Chemo + AB928 Arm (Cohort 1)"] has been deleted. Appendix 12 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 13
Placeholder for Future Arm

The atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus selicrelumab arm has been removed, as the treatment arm has met the criteria for closure per Section 4.6.1. The content of Appendix 13 [previously entitled "Study Details Specific to Atezo + Chemo + Seli Arm (Cohort 1)"] has been deleted. Appendix 13 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 14
Study Details Specific to Atezo+Chemo+Tira Arm (Cohort 1)

TABLE OF CONTENTS

A14–1 BACKGROUND ON ATEZO + CHEMO + TIRA ARM

A14–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. 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, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

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

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

A14–1.2 BACKGROUND ON NAB-PACLITAXEL AND GEMCITABINE IN PANCREATIC CANCER

Nanoparticle albumin–bound paclitaxel (nab-paclitaxel) is a microtubule inhibitor that is approved in combination with gemcitabine for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas. Gemcitabine is a nucleoside metabolic inhibitor that is approved for the treatment of locally advanced or metastatic adenocarcinoma of the pancreas.

The combination of nab-paclitaxel and gemcitabine has been established as the standard-of-care chemotherapy regimen for metastatic pancreatic cancer and is

classified as Category 1 (intervention is appropriate based upon high-level evidence) by the National Comprehensive Cancer Network for this indication (Von Hoff et al. 2013; NCCN 2017).

A14–1.3 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/kappa monoclonal antibody that binds TIGIT and prevents its interaction with CD155 (also known as poliovirus receptor [PVR]). Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of 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.

Please refer to the Tiragolumab Investigator's Brochure for additional details on the nonclinical and clinical studies for tiragolumab.

A14–2 RATIONALE FOR ATEZO + CHEMO + TIRA 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

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).

It has been shown that in pancreatic cancer tissues, both PD-L1 and PD-L2 are expressed and that tumor PD-L1, but not PD-L2, expression significantly correlates with postoperative prognosis. Moreover, PD-L1 expression is inversely correlated with tumor-infiltrating lymphocytes, particularly $CD8^+$ T cells (Nomi et al. 2007). However, no clinically significant response to single-agent checkpoint inhibitors has been observed in patients with pancreatic cancer (Royal et al. 2010; Brahmer et al. 2012).

A14–2.2 THE TIGIT PATHWAY

TIGIT is an immune inhibitory receptor that is a member of the immunoglobulin superfamily. TIGIT is expressed on the surface of activated T-cell and natural killer (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 immune checkpoint 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 hematologic tumors, such as multiple myeloma and non-Hodgkin lymphoma, and fluorescence-activated cell sorting 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 was 30%–80% and 50%–80% on tumor-infiltrating $CD4^+$ and $CD8^+$ T cells, respectively (Johnston et al. 2014).

The TIGIT ligand PVR is broadly expressed in solid tumors, including human pancreatic cancer tissues. PVR is mainly expressed in the plasma membrane and cytoplasm of cancer cells and with limited expression in non-cancer tissues, including islet cells. There exists a significant inverse correlation between PVR expression in pancreatic cancer and the presence of tumor-infiltrating $CD4^+$ and $CD8^+$ T cells. Also, high PVR expression correlates with poor prognosis in patients with pancreatic cancer

(Nishiwada et al. 2015). Thus, PVR may play a critical role through both immunologic and non-immunologic mechanisms in pancreatic cancer.

It has been demonstrated that pancreatic tumors with high cytolytic activity exhibit increased expression of multiple immune checkpoint genes, including TIGIT (Balli 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 that blocked antibodies in genetically deficient mice 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.

A14–2.3 COMBINATION TREATMENT WITH CHEMOTHERAPY AND AN ANTI–PD-L1/PD-1 AGENT

In nonclinical immune-competent mouse tumor models, treatment with multiple classes of chemotherapeutic agents resulted in activation or increase of tumor-infiltrating $CD8^+$ T cells and the combination of anti-PD-L1 with several chemotherapeutic agents showed increased efficacy compared with single-agent treatment (Belvin et al. 2016).

Indeed, the addition of anti–PD-L1/PD-1 to standard 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, randomized, Phase III trials in patients with different advanced solid tumors, the addition of anti–PD-L1/PD-1 to standard chemotherapy led to significantly longer overall survival and progression-free survival (PFS) than chemotherapy alone (Gandhi et al. 2018; Horn et al. 2018; Paz-Ares et al. 2018; Schmid et al. 2018). As a result of these trials, anti–PD-L1/PD-1 in combination with chemotherapies have been approved by health authorities for patients with advanced cancer.

A14–2.4 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-tumor 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 suppresses the effector function of chronically stimulated $CD8^+$ T cells, and that inhibiting both TIGIT and PD-L1/PD-1 results in superior efficacy

compared with single-agent treatments (Johnston et al. 2014). Hence, targeting TIGIT and PD-L1 with tiragolumab and atezolizumab, respectively, may enhance the efficacy of PD-L1/PD-1 blockade across different cancer types (see Section A14–2.6 for a description of clinical studies of tiragolumab combined with atezolizumab).

A14–2.5 COMBINATION TREATMENT WITH CHEMOTHERAPY, AN ANTI–PD-L1/PD-1 AGENT, AND AN ANTI-TIGIT AGENT

It is well established that patients with many solid tumor types benefit when chemotherapy is added to an anti–PD-L1/PD-1 agent. Phase I clinical data show enhanced clinical efficacy when atezolizumab (anti–PD-L1 agent) and tiragolumab (anti-TIGIT agent) are combined (see Section A14–2.6). Thus, it is hypothesized that adding dual checkpoint inhibition to chemotherapy may result in enhanced and more durable responses than either therapy modality alone. An exploratory study in gastric cancer has shown that after treatment with platinum chemotherapy, patients with a higher percentage of $CD8^+TIGIT^+$ T cells had increased rates of cancer relapse and shorter disease-free survival (Tang et al. 2019). In another study in esophageal cancer, the levels of CD155, the ligand for TIGIT, were increased after chemotherapy (Yoshida et al. 2019). As the TIGIT pathway is associated with immune dysfunction, these findings suggest that TIGIT blockade to restore T-cell function could potentially improve outcomes for patients undergoing chemotherapy. In support of this hypothesis, in vitro studies showed that TIGIT blockade countered the suppression of T-cell proliferation and activation following chemotherapy (Tang et al. 2019). Evaluating the safety of atezolizumab and tiragolumab with chemotherapy in patients with metastatic pancreatic ductal adenocarcinoma (PDAC) in this study will contribute to the clinical understanding of adding anti–PD-L1 and anti-TIGIT agents to chemotherapy.

A14–2.6 CLINICAL STUDIES OF TIRAGOLUMAB

Tiragolumab is currently under investigation in two ongoing clinical studies in patients with solid tumors (Studies GO30103 and GO40290).

A14–2.6.1 Clinical Study of Tiragolumab as a Single Agent or in Combination with Atezolizumab

Study GO30103 is a first-in-human, Phase I, open-label, dose-escalation and dose-expansion study of tiragolumab as a single agent and in combination with atezolizumab 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.

[redacted]

[redacted]

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. [redacted]

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.

A14–2.6.2 Clinical Study of Tiragolumab in Combination with Atezolizumab in Patients with PD-L1–Positive NSCLC

Study GO40290 is a Phase II, randomized, blinded, placebo-controlled study of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated locally advanced unresectable or metastatic PD-L1–positive (defined as tumor proportion score [TPS] $\geq$ 1%) NSCLC.

As of the data cutoff date of 30 June 2019, a total of 135 patients with a PD-L1 TPS $\geq$ 1% received tiragolumab plus atezolizumab (n = 67) or placebo plus atezolizumab (n = 68). In the intent-to-treat (ITT) population, the confirmed objective response rate (ORR) was higher in the tiragolumab plus atezolizumab arm (31.3%) than 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.

In the ITT population, investigator-assessed progression-free survival (PFS) was improved in the tiragolumab plus atezolizumab arm over the placebo plus atezolizumab arm (stratified hazard ratio [HR] = 0.57 [95% CI: 0.37, 0.90]; median PFS, 5.4 vs. 3.6 months, respectively). In the subgroup of patients with TPS $\geq$ 50%, investigator-assessed PFS was improved in the tiragolumab plus atezolizumab arm over

the placebo plus atezolizumab arm (unstratified HR = 0.33 [95% CI: 0.15, 0.72]; median PFS, not estimable vs. 3.9 months, respectively).

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 have been balanced between the two treatment arms, with the exception of a higher frequency of infusion-related reaction and rash reported in the atezolizumab plus tiragolumab arm.

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.

A14–2.7 CLINICAL STUDY OF ATEZOLIZUMAB IN COMBINATION WITH NAB-PACLITAXEL AND GEMCITABINE

An ongoing Phase I study (GO30140) includes an arm that is evaluating atezolizumab in combination with nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic cancer.

Adverse events observed to date are consistent with the known risks of atezolizumab, nab-paclitaxel, and gemcitabine. Atezolizumab in combination with cytotoxic chemotherapy has not been associated with additive severe (Grade ≥ 3) toxicities, indicating that atezolizumab can be safely combined with standard chemotherapy. As of the data cutoff date of 24 October 2017, the confirmed objective response rate was 41.7%, the median progression-free survival was 7 months, and the median overall survival was 10.6 months for 24 efficacy-evaluable patients with metastatic pancreatic cancer.

A14–2.8 BENEFIT–RISK ASSESSMENT

Metastatic PDAC is an incurable disease with a high unmet need for improved medical intervention. Taking into account the potentially synergistic mechanisms of action of

tiragolumab and atezolizumab, as well as the preliminary efficacy and manageable safety profiles of the above-described combinations, treatment with atezolizumab, chemotherapy (nab-paclitaxel and gemcitabine), and tiragolumab (Atezo + Chemo + Tira) appears to have therapeutic potential in solid tumors such as PDAC.

Because of the potential for overlapping toxicities, a minimum of 6 patients in the Atezo+ Chemo + Tira arm must complete a safety evaluation before additional patients can be enrolled in that arm. Refer to Section 3.1.3 for details.

COVID-19 Benefit–Risk Assessment

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those patients with pancreatic cancer, are a more vulnerable population. In some retrospective analyses, infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with higher mortality in patients with cancer. It is unclear whether or how cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of COVID-19. At this time, there is insufficient evidence for a causal association between atezolizumab or tiragolumab and an increased risk of COVID-19. Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in patients receiving atezolizumab in combination with chemotherapy; however, this is not specific to the risk of infection with SARS-CoV-2 (see Section A14–5.1).

For the evaluation of the impact of the COVID-19 pandemic and COVID-19 vaccination on the benefit–risk assessment, please refer to Section 1.5.

A14–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + CHEMO + TIRA 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), which is an approved dosage for atezolizumab.

[redacted]

[redacted]

A14–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + CHEMO + TIRA ARM

A14–4.1 TREATMENT IN ATEZO + CHEMO + TIRA ARM

A14–4.1.1 Formulation, Packaging, and Handling

A14–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a [redacted] The vial contains approximately [redacted] of atezolizumab solution.

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

A14–4.1.1.2 Tiragolumab

The tiragolumab drug product will be supplied in [redacted] The vial contains [redacted] of tiragolumab. The approximate concentration of tiragolumab antibody in each vial is [redacted].

For information on the formulation and handling of tiragolumab, see the pharmacy manual and the Tiragolumab Investigator's Brochure.

A14–4.1.1.3 Nab-Paclitaxel

For information on the formulation, packaging, and handling of nab-paclitaxel, refer to the local prescribing information.

A14–4.1.1.4 Gemcitabine

For information on the formulation, packaging, and handling of gemcitabine, refer to the local prescribing information.

A14–4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + Chemo + Tira 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 3.1.2 for details). [redacted]

Table A14-1 Treatment Regimen for Atezo + Chemo + Tira Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Atezolizumab 840 mg IV on Days 1 and 15 of each cycle • Tiragolumab 420 mg IV on Days 1 and 15 of each cycle [a] • Nab-paclitaxel 125 mg/m^2 IV on Days 1, 8, and 15 of each cycle [b] • Gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 of each cycle

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] On Day 1 of Cycle 1, tiragolumab will be administered [redacted] minutes after completion of the atezolizumab infusion. The interval between subsequent infusions will be [redacted] minutes if the previous atezolizumab infusion was given [redacted] and tolerated without an IRR or [redacted] minutes if the patient experienced an IRR with the previous atezolizumab infusion.

[b] On Day 1 of Cycle 1, nab-paclitaxel will be administered 60 minutes after completion of the tiragolumab infusion. The interval between subsequent infusions will be 30 minutes if the previous tiragolumab infusion was tolerated without an IRR or 60 minutes if the patient experienced an IRR with the previous tiragolumab infusion.

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

Medication errors 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 5.3.5.12. No safety data related to overdosing of atezolizumab or tiragolumab are available. For information on overdosing of nab-paclitaxel or gemcitabine, refer to the local prescribing information for each agent.

A14–4.1.2.1 Atezolizumab

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 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, 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 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 2.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A14–5.1.6. Atezolizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A14–4.1.2.2 Tiragolumab

Tiragolumab will be administered by IV infusion at a fixed dose of 420 mg on Days 1 and 15 of each 28-day cycle. On Day 1 of Cycle 1, tiragolumab will be administered [redacted] minutes after completion of the atezolizumab infusion. The interval between subsequent infusions will be [redacted] minutes if the previous atezolizumab infusion was tolerated without an IRR or [redacted] minutes if the patient experienced an IRR with the previous atezolizumab infusion.

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. Atezolizumab infusions will be administered per the instructions outlined in Table A14-3.

Table A14-3 Administration of First and Subsequent Tiragolumab Infusions

First Infusion	Subsequent Infusions
[redacted]	

Guidelines for medical management of IRRs for atezolizumab are provided in Appendix 2.

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A14–5.1.6. Tiragolumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the

duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A14–4.1.2.3 Nab-Paclitaxel and Gemcitabine

On Days 1, 8, and 15, patients will receive nab-paclitaxel 125 mg/m^2, administered by IV infusion over 30 (±5) minutes, followed by gemcitabine 1000 mg/m^2, administered by IV infusion over 30 (±5) minutes. On Day 1 of Cycle 1, nab-paclitaxel will be administered 60 minutes after completion of the tiragolumab infusion to allow for observation after tiragolumab administration. The interval between subsequent infusions will be 30 minutes if the previous tiragolumab infusion was tolerated without an IRR or 60 minutes if the patient experienced an IRR with the previous tiragolumab infusion.

Nab-paclitaxel and gemcitabine will be administered according to institutional standards 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.

Guidelines for nab-paclitaxel and gemcitabine dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A14–5.1.6. Nab-paclitaxel and gemcitabine treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A14–4.2 CONCOMITANT THERAPY FOR ATEZO + CHEMO + 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 10 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.

A14–4.2.1 Permitted Therapy for Atezo + Chemo + Tira Arm

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

- [redacted]

- Oral contraceptives
- 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 A14–4.2.3).
- Megestrol acetate administered as an appetite stimulant after initiation of study treatment
- 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
- 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 nab-paclitaxel and gemcitabine should be withheld during palliative radiotherapy. Treatment with atezolizumab and tiragolumab 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.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab and tiragolumab 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).

A14–4.2.2 Cautionary Therapy for Atezo + Chemo + Tira Arm

A14–4.2.2.1 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/or 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/or tiragolumab therapy (refer to Appendix 2 for details).

A14–4.2.2.2 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

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

The above lists of cautionary medications are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a

concomitant medication can be safety administered with study treatment. In addition, the Medical Monitor is available to advise if questions arise regarding medications not listed above.

A14–4.2.2.3 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 A14–4.2.3) may be used during the study at the discretion of the investigator.

A14–4.2.3 Prohibited Therapy for Atezo + Chemo + Tira Arm

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

- [redacted]
- [redacted]
- [redacted]
- [redacted]

A14–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + CHEMO + TIRA ARM

Contraception requirements for women and men in the Atezo + Chemo + Tira 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 or tiragolumab, and 6 months after the last dose of nab-paclitaxel or 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 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 methods, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men who are receiving chemotherapy 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 nab-paclitaxel or gemcitabine and men who are not receiving chemotherapy must remain abstinent or use a condom during the treatment period and for 90 days after the last dose of tiragolumab. 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 90 days after the last dose of tiragolumab and 6 months after the last dose of nab-paclitaxel or 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 contraception.

A14–5 ASSESSMENT OF SAFETY FOR ATEZO + CHEMO + TIRA ARM

A14–5.1 SAFETY PLAN FOR ATEZO + CHEMO + TIRA ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab, nab-paclitaxel, gemcitabine, and tiragolumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A14–5.1.1, A14–5.1.2, A14–5.1.3, A14–5.1.4, and A14–5.1.5). Guidelines for management of patients who experience specific adverse events are provided in Section A14–5.1.6.

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. 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.

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, 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 may lead to HLH. Refer to Appendix 2 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A14–5.1.2 Risks Associated with Nab-Paclitaxel

The following are the most common adverse events observed with nab-paclitaxel in patients with PDAC: neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. The following adverse events have also been observed: myelosuppression (primarily neutropenia, anemia, thrombocytopenia), cranial nerve palsies, hypersensitivity reactions, pneumonitis, myalgia, arthralgia, cardiotoxicity (myocardial disorders, cardiac failure, angina, tachycardia, ventricular arrhythmia), cystoid macular edema, Stevens-Johnson syndrome/toxic epidermal necrolysis, sepsis, infusion-site reactions/extravasation, hepatic toxicity (drug-induced liver injury), acute renal failure, scleroderma, and drug-induced lupus erythematous.

For more details regarding the safety profile for nab-paclitaxel, refer to the nab-paclitaxel prescribing information.

A14–5.1.3 Risks Associated with Gemcitabine

The most common adverse events observed with gemcitabine are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased ALP, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema. The following adverse events have also been observed: renal failure, hemolytic-uremic syndrome, interstitial pneumonitis, myocardial infarction, arrhythmia, and heart failure.

For more details regarding the safety profile for gemcitabine, refer to the gemcitabine prescribing information.

A14–5.1.4 Risks Associated with Tiragolumab

[redacted]

A14–5.1.4.2 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. [redacted]

[redacted]

[redacted]

Refer to Section A14–4.1.2.2 for detailed guidance on administration of tiragolumab in this study. Refer to Appendix 5 for guidance on anaphylaxis precautions and Appendix 2 for guidance on the management of IRRs.

A14–5.1.4.3 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 suboptimal doses of myelin oligodendrocyte glycoprotein peptide to induce EAE. In contrast to the wild-type B6 mice, the majority of the TIGIT–/– mice developed severe EAE (Joller et al. 2011).

[redacted]

Patients with a history of autoimmune disease will be excluded from this study. In addition, patients with a history of severe immune-mediated adverse events associated with prior immunotherapy or adverse events that did not resolve to baseline after discontinuation of prior immunotherapy will be excluded from this study. Refer to Section 4.1.2 for details.

In this study, specified immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section A14–5.2 for the list of adverse events of special interest and Section 5.4.2 for reporting instructions).

A14–5.1.4.4 Lymphopenia

The IgG1 backbone of tiragolumab with the intact Fc-effector function may lead to ADCC-mediated reduction in lymphocyte count. [redacted] Transient lymphocyte count decreases without clinical sequelae have been observed in patients treated with tiragolumab, alone or in combination with atezolizumab, in the Phase I study in solid tumors (Study GO30103). Patients with a lymphocyte count $< 0.5 \times 10^9$/L

(500/μL) will be excluded from the study (see Section 4.1.2). Complete blood counts will be monitored throughout the study (see Section A14–6).

[redacted]

[redacted]

A14–5.1.5 Risks Associated with Combination Use of Atezolizumab, Nab-Paclitaxel, Gemcitabine, and Tiragolumab

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab, nab-paclitaxel, gemcitabine, and tiragolumab: immune-mediated toxicities, including HLH, and others (described in Appendix 2), gastrointestinal toxicities, hematologic toxicity, dermatologic toxicities, and hepatic toxicity.

A14–5.1.6 Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm

On Day 1 of each cycle, patients are required to have an ANC of $\geq 1.5 \times 10^9$/L (1500/μL) and a platelet count of $\geq 100 \times 10^9$/L (100,000/μL) to receive treatment with nab-paclitaxel and gemcitabine. Guidelines for management of hematologic toxicities and other toxicities (including guidelines for dose modification and treatment interruption or discontinuation) are provided in Table A14-5.

A14–5.1.6.1 Dose Modifications

[redacted]

For management of drug-related toxicities, the dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times, as outlined in Table A14-4.

Table A14-4 Recommended Dose Reductions for Nab-Paclitaxel and Gemcitabine

	Initial Dose	First Dose Reduction	Second Dose Reduction
Nab-paclitaxel	125 mg/m^2	100 mg/m^2	75 mg/m^2
Gemcitabine	1000 mg/m^2	800 mg/m^2	600 mg/m^2

nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

If further dose reduction is indicated for nab-paclitaxel and/or gemcitabine after two dose reductions, that drug (or both drugs, if applicable) should be discontinued, but the patient may continue other study treatments at the investigator's discretion. After dose reduction, the dose may be escalated during subsequent administrations at the investigator's discretion.

A14–5.1.6.2 Treatment Interruption for Toxicities

Atezolizumab and/or tiragolumab may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. [redacted]

[redacted]

[redacted]

Nab-paclitaxel and/or gemcitabine treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table A14-5).
If nab-paclitaxel or gemcitabine have been withheld for > 56 days because of toxicity, the patient should be discontinued from both chemotherapy agents. However, nab-paclitaxel or gemcitabine can be resumed after being withheld for > 56 days if the

patient is likely to derive clinical benefit. The decision to re-challenge patients with nab-paclitaxel and/or gemcitabine should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.

Refer to Section A14–4.1.2 for information on dose interruptions for reasons other than toxicity.

A14–5.1.6.3 Management Guidelines for Adverse Events

Guidelines for management of patients who experience specific adverse events are provided in Table A14-5. 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 nab-paclitaxel 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.

Table A14-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reactions	
General guidance	• Guidelines for management of IRRs and CRS for atezolizumab and tiragolumab are provided in Appendix 2. • Guidelines for management of IRRs for nab-paclitaxel and gemcitabine are provided below. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue the causative agent.
IRR to chemotherapy, 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 chemotherapy, Grade 2	• Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, administer oral premedication with antihistamine and antipyretic and monitor closely for IRRs.

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TSH = thyroid-stimulating hormone.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A14–5.1.6.1 for details).

Table A14-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm (cont.)

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reactions (cont.)	
IRR to chemotherapy, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue treatment and contact Medical Monitor. [a]
Hemophagocytic lymphohistiocytosis	• Follow guidelines for atezolizumab in Appendix 2. • Withhold all treatment and contact Medical Monitor.
Gastrointestinal toxicity	
Diarrhea or colitis, Grade 1	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine.
Diarrhea or colitis, Grade 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine.
Diarrhea or colitis, Grade 3	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Withhold nab-paclitaxel and gemcitabine. • If event resolves to Grade 1 or better ≤56 days after event onset, resume nab-paclitaxel and gemcitabine with dose reduced by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a]
Diarrhea or colitis, Grade 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Permanently discontinue nab-paclitaxel and gemcitabine. [a]

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TSH = thyroid-stimulating hormone.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A14–5.1.6.1 for details).

Table A14-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Mucositis, Grade 1 or 2	• Continue atezolizumab, tiragolumab, nab-paclitaxel, and gemcitabine.
Mucositis, Grade 3	• Continue atezolizumab and tiragolumab. Withhold nab-paclitaxel and gemcitabine. • If event resolves to Grade 1 or better ≤56 days after event onset, resume nab-paclitaxel and gemcitabine with dose reduced by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a]
Mucositis, Grade 4	• Permanently discontinue atezolizumab, tiragolumab, nab-paclitaxel, and gemcitabine. [a]
Febrile neutropenia	
Grade 3 or 4	• Withhold atezolizumab, tiragolumab, nab-paclitaxel, and gemcitabine. • If fever resolves and ANC improves to $\geq 1.5 \times 10^9$/L (1500/μL) ≤56 days after event onset, resume nab-paclitaxel and gemcitabine with dose reduced by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If fever resolves and ANC improves to $\geq 1.5 \times 10^9$/L (1500/μL) ≤12 weeks after event onset, resume atezolizumab and tiragolumab. If not, permanently discontinue atezolizumab and tiragolumab. [a]

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TSH = thyroid-stimulating hormone.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A14–5.1.6.1 for details).

Table A14-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity at Day 1 (excluding febrile neutropenia)	
ANC $\geq 1.5 \times 10^9$/L (1500/μL) **and** Platelet count $\geq 100 \times 10^9$/L (100,000/μL)	• Continue atezolizumab, tiragolumab, nab-paclitaxel, and gemcitabine.
ANC $< 1.5 \times 10^9$/L (1500/μL) **and/or** Platelet count $< 100 \times 10^9$/L (100,000/μL)	• Continue atezolizumab and tiragolumab. Withhold nab-paclitaxel and gemcitabine. • Permanently discontinue nab-paclitaxel or gemcitabine if withheld > 56 days after event onset. [a]
Hematologic toxicity at Day 8 (excluding febrile neutropenia)	
ANC $\geq 1.0 \times 10^9$/L (1000/μL) **and** Platelet count $\geq 75 \times 10^9$/L (75,000/μL)	• Continue nab-paclitaxel and gemcitabine.
ANC $\geq 0.5 \times 10^9$/L (500/μL) but $< 1.0 \times 10^9$/L (1000/μL) **and/or** Platelet count $\geq 50 \times 10^9$/L (50,000/μL) but $< 75 \times 10^9$/L (75,000/μL)	• Continue nab-paclitaxel and gemcitabine with dose reduced by one level. [b]
ANC $< 0.5 \times 10^9$/L (500/μL) **and/or** Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Withhold nab-paclitaxel and gemcitabine. • If nab-paclitaxel and gemcitabine are withheld > 56 days after event onset, permanently discontinue nab-paclitaxel and gemcitabine. [a]

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TSH = thyroid-stimulating hormone.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A14–5.1.6.1 for details).

Table A14-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity at Day 15 (excluding febrile neutropenia): Day 8 doses given without modification	
ANC $\geq 1.0 \times 10^9$/L (1000/μL) **and** Platelet count $\geq 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab, tiragolumab, nab-paclitaxel, and gemcitabine.
ANC $\geq 0.5 \times 10^9$/L (500/μL) but $< 1.0 \times 10^9$/L (1000/μL) **and/or** Platelet count $\geq 50 \times 10^9$/L (50,000/μL) but $< 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab and tiragolumab. Continue nab-paclitaxel and gemcitabine at current dose followed by WBC growth factors **or** with dose reduced by one level. [b]
ANC $< 0.5 \times 10^9$/L (500/μL) **and/or** Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Withhold atezolizumab, tiragolumab, nab-paclitaxel, and gemcitabine. • If event improves, atezolizumab, tiragolumab, nab-paclitaxel, and/or gemcitabine can be resumed. [a] • If nab-paclitaxel and gemcitabine are withheld > 56 days after event onset, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If atezolizumab and tiragolumab are withheld > 12 weeks after event onset, permanently discontinue atezolizumab and tiragolumab. [a]

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TSH = thyroid-stimulating hormone.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A14–5.1.6.1 for details).

Table A14-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity at Day 15 (excluding febrile neutropenia): Day 8 doses reduced	
ANC $\geq 1.0 \times 10^9$/L (1000/μL) **and** Platelet count $\geq 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab and tiragolumab. Continue nab-paclitaxel and gemcitabine at Day 1 doses followed by WBC growth factors **or** at current dose.
ANC $\geq 0.5 \times 10^9$/L (500/μL) but $< 1.0 \times 10^9$/L (1000/μL) **and/or** Platelet count $\geq 50 \times 10^9$/L (50,000/μL) but $< 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab and tiragolumab. Continue nab-paclitaxel and gemcitabine at current dose followed by WBC growth factors **or** with dose reduced by one level. [b]
ANC $< 0.5 \times 10^9$/L (500/μL) **and/or** Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Withhold atezolizumab, tiragolumab, nab-paclitaxel, and gemcitabine. • If event improves, atezolizumab, tiragolumab, nab-paclitaxel, and/or gemcitabine can be resumed. [a] • If nab-paclitaxel and gemcitabine are withheld > 56 days after event onset, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If atezolizumab and tiragolumab are withheld > 12 weeks after event onset, permanently discontinue atezolizumab and tiragolumab. [a]

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TSH = thyroid-stimulating hormone.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A14–5.1.6.1 for details).

Table A14-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity at Day 15 (excluding febrile neutropenia): Day 8 treatment was withheld	
ANC $\geq 1.0 \times 10^9$/L (1000/μL) **and** Platelet count $\geq 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab and tiragolumab. Continue nab-paclitaxel and gemcitabine at current dose followed by WBC growth factors **or** with dose reduced by one level. [b]
ANC $\geq 0.5 \times 10^9$/L (500/μL) but $< 1.0 \times 10^9$/L (1000/μL) **and/or** Platelet count $\geq 50 \times 10^9$/L (50,000/μL) but $< 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab and tiragolumab. Continue nab-paclitaxel and gemcitabine with dose reduced by one level followed by WBC growth factors **or** with dose reduced by two levels. [b]
ANC $< 0.5 \times 10^9$/L (500/μL) **and/or** Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Withhold atezolizumab, tiragolumab, nab-paclitaxel, and gemcitabine. • If event improves, atezolizumab, tiragolumab, nab-paclitaxel, and/or gemcitabine can be resumed. [a] • If nab-paclitaxel and gemcitabine are withheld > 56 days after event onset, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If atezolizumab and tiragolumab are withheld > 12 weeks after event onset, permanently discontinue atezolizumab and tiragolumab. [a]

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TSH = thyroid-stimulating hormone.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A14–5.1.6.1 for details).

Table A14-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm (cont.)

Event	Action to Be Taken
Neurologic disorder	
Immune-mediated neuropathy, Grade 1 or 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine.
Immune-mediated neuropathy, Grade 3 or 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Continue gemcitabine. Withhold nab-paclitaxel. • If event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel with dose reduced by one level. [b] If not, permanently discontinue nab-paclitaxel. [a]
Non–immune-mediated neuropathy, Grade 1 or 2	• Continue atezolizumab, tiragolumab, nab-paclitaxel, and gemcitabine.
Non–immune-mediated neuropathy, Grade 3 or 4	• Continue atezolizumab, tiragolumab, and gemcitabine. Withhold nab-paclitaxel. • If event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel with dose reduced by one level. [b] If not, permanently discontinue nab-paclitaxel. [a]
Immune-mediated meningoencephalitis, any grade	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Withhold nab-paclitaxel and gemcitabine. • If event stabilizes ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. The Medical Monitor is available to advise as needed.

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TSH = thyroid-stimulating hormone.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A14–5.1.6.1 for details).

Table A14-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm (cont.)

Event	Action to Be Taken
Posterior reversible encephalopathy syndrome	
Posterior reversible encephalopathy syndrome, any grade	• Withhold atezolizumab, tiragolumab, and nab-paclitaxel. Permanently discontinue gemcitabine. [a] • If event improves, atezolizumab, tiragolumab, and/or nab-paclitaxel can be resumed. [a] • If nab-paclitaxel is withheld > 56 days after event onset, permanently discontinue nab-paclitaxel. [a] • If atezolizumab and tiragolumab are withheld > 12 weeks after event onset, permanently discontinue atezolizumab and tiragolumab. [a]
Dermatologic events (other than injection-site reaction)	
Dermatologic event, Grade 1	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine.
Dermatologic event, Grade 2 or 3	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine with dose reduced by one level. [b] • If event persists, permanently discontinue nab-paclitaxel and gemcitabine. [a]

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TSH = thyroid-stimulating hormone.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A14–5.1.6.1 for details).

Table A14-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm (cont.)

Event	Action to Be Taken
Dermatologic events (other than injection-site reaction) (cont.)	
Dermatologic event, Grade 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Permanently discontinue nab-paclitaxel and gemcitabine. [a]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Withhold atezolizumab, nab-paclitaxel, gemcitabine, and tiragolumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab, nab-paclitaxel, gemcitabine, and tiragolumab.

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TSH = thyroid-stimulating hormone.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A14–5.1.6.1 for details).

Table A14-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm (cont.)

Event	Action to Be Taken
Pulmonary events	
Pulmonary event, Grade 1	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine. • If confirmed diagnosis of pneumonitis, permanently discontinue nab-paclitaxel and gemcitabine. [a]
Pulmonary event, Grade 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Withhold nab-paclitaxel and gemcitabine. • If confirmed diagnosis of pneumonitis, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • 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 2. • Permanently discontinue nab-paclitaxel and gemcitabine. [a]

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TSH = thyroid-stimulating hormone.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A14–5.1.6.1 for details).

Table A14-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm (cont.)

Event	Action to Be Taken
Hepatic event	
Hepatic event, Grade 1	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine.
Hepatic event, Grade 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Withhold nab-paclitaxel and gemcitabine for hepatic event other than Grade 2 elevation of AST, ALT, or ALP. • If chemotherapy is withheld and event resolves to Grade 1 or better ≤56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a]
Hepatic event, Grade 3 or 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Withhold nab-paclitaxel and gemcitabine. • If event resolves to Grade 1 or better ≤56 days after event onset, resume nab-paclitaxel and gemcitabine and consider reducing the dose by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a]

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TSH = thyroid-stimulating hormone.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A14–5.1.6.1 for details).

Table A14-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm (cont.)

Event	Action to Be Taken
Endocrine events	
Asymptomatic hypothyroidism	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine.
Symptomatic hypothyroidism	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Withhold nab-paclitaxel and gemcitabine. • When symptoms are controlled and thyroid function is improving, resume nab-paclitaxel and gemcitabine.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Withhold nab-paclitaxel and gemcitabine. • When symptoms are controlled and thyroid function is improving, resume nab-paclitaxel and gemcitabine.

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TSH = thyroid-stimulating hormone.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A14–5.1.6.1 for details).

Table A14-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm (cont.)

Event	Action to Be Taken
Hemolytic-uremic syndrome	
Hemolytic-uremic syndrome, any grade	• Permanently discontinue gemcitabine. [a] Withhold atezolizumab, tiragolumab, and nab-paclitaxel. • If event improves, resume atezolizumab, tiragolumab, and nab-paclitaxel. If not, permanently discontinue atezolizumab, tiragolumab, and nab-paclitaxel. [a]
Capillary leak syndrome	
Capillary leak syndrome, any grade	• Permanently discontinue gemcitabine. [a] Withhold atezolizumab, tiragolumab, and nab-paclitaxel. • If event improves, resume atezolizumab, tiragolumab, and nab-paclitaxel. If not, permanently discontinue atezolizumab, tiragolumab, and nab-paclitaxel. [a]
Chemotherapy-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab, tiragolumab, nab-paclitaxel, and gemcitabine.
Grade 3	• Continue atezolizumab and tiragolumab. Withhold nab-paclitaxel and gemcitabine. • If event resolves to Grade 2 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine and consider reducing dose by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a]
Grade 4	• Withhold atezolizumab, tiragolumab, nab-paclitaxel, and gemcitabine. • If event improves, resume atezolizumab and tiragolumab. If not, permanently discontinue atezolizumab and tiragolumab. [a] • If event resolves to Grade 2 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine and consider reducing dose by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a]

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TSH = thyroid-stimulating hormone.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A14–5.1.6.1 for details).

Table A14-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Tira Arm (cont.)

Event	Action to Be Taken
Atezolizumab and tiragolumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine.
Grade 3 or 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 2. • Withhold nab-paclitaxel and gemcitabine. • If event resolves to Grade 2 or better ≤56 days after event onset, resume nab-paclitaxel and gemcitabine and consider reducing dose by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a]

Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; TSH = thyroid-stimulating hormone.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A14–5.1.6.1 for details).

A14–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + CHEMO + 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 + Chemo + Tira arm are as follows:

- [redacted]
- [redacted]

- 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)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- [redacted]
- [redacted]
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

A14–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + CHEMO + TIRA ARM

A14–5.3.1 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 last dose of atezolizumab, 90 days after the last dose of tiragolumab, or 6 months after the last dose of nab-paclitaxel or gemcitabine. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study 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 90 days after the last dose of tiragolumab or 6 months after the last dose of nab-paclitaxel or gemcitabine. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. 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.

A14–5.3.3 Abortions

Any 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).

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 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).

A14–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + CHEMO + TIRA ARM

Table A14-6 Schedule of Activities for Atezo + Chemo + Tira Arm (Cohort 1)

	Screening (see Appendix 6)	Treatment Cycles (28-day cycles) [a]							Follow-Up [c]
		Cycle 1 [b]			Cycles ≥ 2				
	Day –28 to –1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Treat. Discon. [c]	Every 3 Months
Molecular profile of pancreatic cancer (if available)	See Appendix 6	Whenever updated information becomes available							
Vital signs [d]		x	x	x	x	x	x	x	
Weight		x [e]	x [e]	x [e]	x [e]	x [e]	x [e]	x	
Complete physical examination [f]								x	
Limited physical examination [g]		x [e]	x [e]	x [e]	x [e]	x [e]	x [e]		
ECOG Performance Status		x [e]			x [e]			x	
ECG [h]		Perform as clinically indicated [e]							
Hematology [i]		x [j, k]	x [j]	x [j]	x [j]	x [j]	x [j]	x	
Chemistry [l]		x [j, k]	x [j]	x [j]	x [j]	x [j]	x [j]	x	
Coagulation (INR and aPTT)		x [j, k]	Perform as clinically indicated					x	
TSH, free T3 (or total T3), free T4 [m]		x [j, k, m]						x	
C-reactive protein		x [j, k]			x [j]				
CA19-9		x [j]			x [j]			x	
Pregnancy test [o]		x [j, k]			x [j]			x	x [o]

Table A14-6 Schedule of Activities for Atezo + Chemo + Tira Arm (Cohort 1) (cont.)

	Screening (see Appendix 6)	Treatment Cycles (28-day cycles) [a]							Follow-Up [c]
		Cycle 1 [b]			Cycles ≥ 2				
	Day –28 to –1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Treat. Discon. [c]	Every 3 Months
Urinalysis [p]		Perform as clinically indicated							
[redacted]	See Appendix 6	[redacted]							
Tumor response assessments		x [v, w]							
Concomitant medications [x]		x	x	x	x	x	x	x	
Adverse events [y]		x	x	x	x	x	x	x [y]	x [y]
Atezolizumab administration [z, aa]		x		x	x		x		
Tiragolumab administration [aa, bb]		x		x	x		x		
Nab-paclitaxel and gemcitabine administration [aa, cc]		x	x	x	x	x	x		
Survival follow-up and anti-cancer treatment									x [dd]

Table A14-6 Schedule of Activities for Atezo + Chemo + Tira Arm (Cohort 1) (cont.)

ADA = anti-drug antibody; Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab ; CIT = cancer immunotherapy; CT = computed tomography; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; [redacted]; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; 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] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.

[b] It is recommended that treatment be initiated no later than 7 days after randomization.

[c] 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 disease progression is confirmed may be used as the treatment discontinuation visit. Patients will then undergo follow-up assessments.

[d] 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 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 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. For the first infusion of tiragolumab, vital signs should be measured within [redacted] minutes prior to the infusion and [redacted] after the infusion. For subsequent infusions of tiragolumab, vital signs should be measured within [redacted] minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and [redacted] minutes after the infusion.

[e] Assessment may be performed within 24 hours prior to dosing during the treatment period.

[f] 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 new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] 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.

[h] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[i] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[j] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

[k] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

Table A14-6 Schedule of Activities for Atezo + Chemo + Tira Arm (Cohort 1) (cont.)

[l] 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.

[m] 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.).

[n] [redacted]

[o] All women of childbearing potential will have urine or serum pregnancy tests 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.

[p] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[q] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[r] Autoantibody analysis should be repeated for patients who develop signs or symptoms suggestive of autoimmune disease (e.g., lupus erythematosus).

[s] 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.

[t] [redacted]

[u]

Table A14-6 Schedule of Activities for Atezo + Chemo + Tira Arm (Cohort 1) (cont.)

[v] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression, even if they start new non–protocol-specified anti-cancer therapy.

[w] All measurable and/or evaluable lesions identified at baseline should be re-assessed at each subsequent tumor evaluations according to the tumor assessment schedule described above (see footnote "v"). 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). Refer to Section 4.5.5 for further details on tumor assessments.

[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 10 days prior to initiation of study treatment until the treatment discontinuation visit.

[y] [redacted]

After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). 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.

[z] 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 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 A14–4.1.2.1, Table A14-2, for details on atezolizumab infusions (including measurement of vital signs).

[aa] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details).

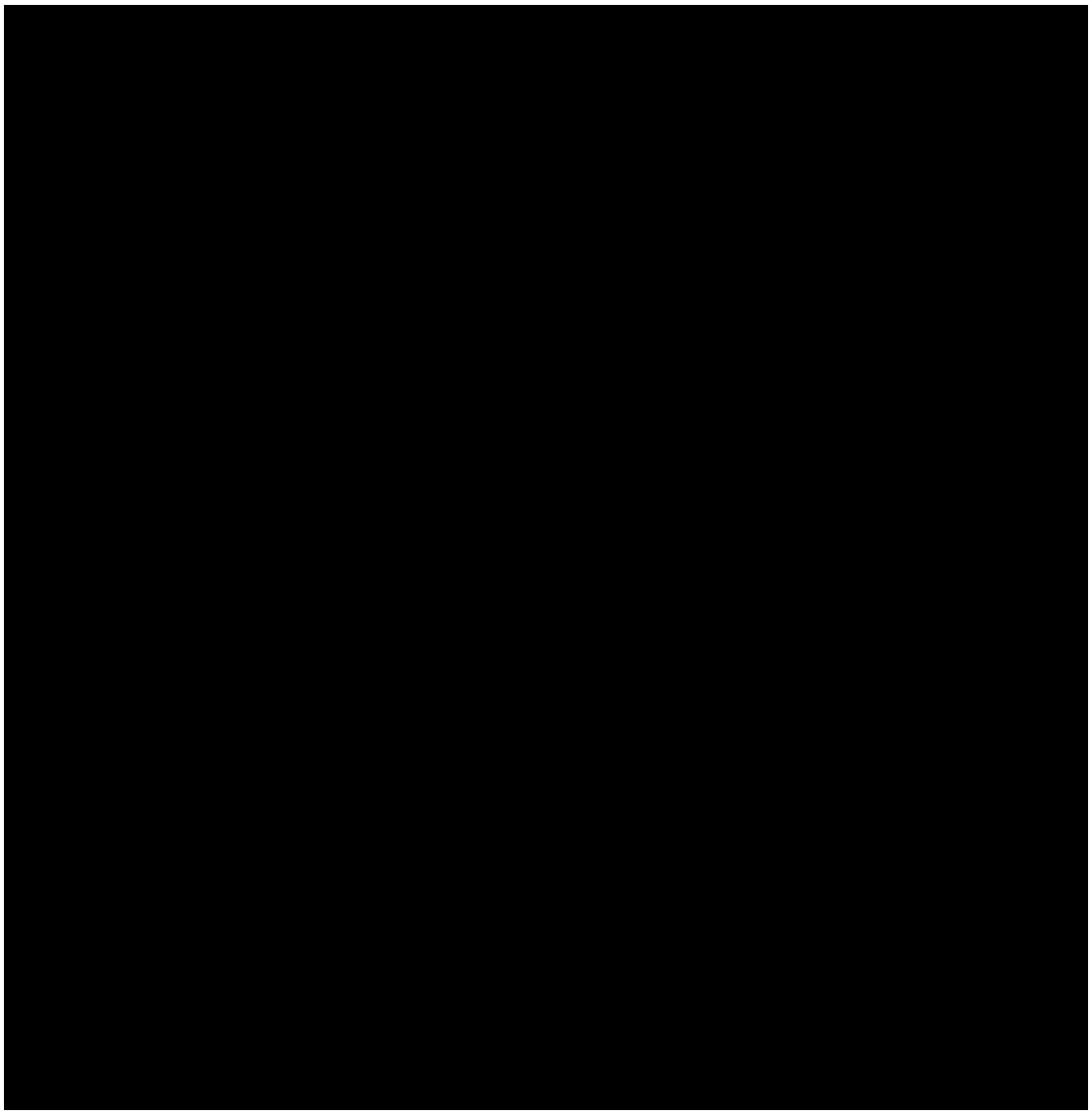
Table A14-6 Schedule of Activities for Atezo + Chemo + Tira Arm (Cohort 1) (cont.)

[bb] Tiragolumab will be administered by IV infusion at a fixed dose of 420 mg on Days 1 and 15 of each 28-day cycle. The initial dose of tiragolumab will be delivered over [redacted] minutes. Subsequent infusions will be delivered over [redacted] minutes if the previous infusion was tolerated without infusion-associated adverse events, or [redacted] minutes if the patient experienced an infusion-associated adverse event with the previous infusion. On Day 1 of Cycle 1, tiragolumab will be administered [redacted] minutes after completion of the atezolizumab infusion. The interval between subsequent infusions will be [redacted] minutes if the previous atezolizumab infusion was tolerated without an IRR or [redacted] minutes if the patient experienced an IRR with the previous atezolizumab infusion. Refer to Section A14–4.1.2.2, Table A14-3, for details on tiragolumab infusions (including measurement of vital signs and patient observation after infusions).

[cc] On Days 1, 8, and 15, patients will receive nab-paclitaxel 125 mg/m^2, administered by IV infusion over 30 (±5) minutes, followed by gemcitabine 1000 mg/m^2, administered by IV infusion over 30 (±5) minutes. On Day 1 of Cycle 1, nab-paclitaxel will be administered 60 minutes after completion of the tiragolumab infusion to allow for observation after tiragolumab administration. The interval between subsequent infusions will be 30 minutes if the previous tiragolumab infusion was tolerated without an IRR or 60 minutes if the patient experienced an IRR with the previous tiragolumab infusion.

[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 the 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 approximately 20% of patients will be discontinued from the study).

Table A14-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Chemo + Tira Arm (Cohort 1): Preliminary and Expansion Phases



ADA = anti-drug antibody; Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; 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 A14-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Chemo + Tira Arm (Cohort 1): Preliminary and Expansion Phases (cont.)

ADA = anti-drug antibody; Atezo + Chemo + Tira = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tiragolumab; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; 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.

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Appendix 15
Study Details Specific to Atezo+Chemo+Bev Arm (Cohort 1)

TABLE OF CONTENTS

A15–1 BACKGROUND ON ATEZO + CHEMO + BEV ARM

A15–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. 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, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

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

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

A15–1.2 BACKGROUND ON NAB-PACLITAXEL AND GEMCITABINE IN PANCREATIC CANCER

Nanoparticle albumin–bound paclitaxel (nab-paclitaxel) is a microtubule inhibitor that is approved in combination with gemcitabine for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas. Gemcitabine is a nucleoside metabolic inhibitor that is approved for the treatment of locally advanced or metastatic adenocarcinoma of the pancreas.

The combination of nab-paclitaxel and gemcitabine has been established as the standard-of-care chemotherapy regimen for metastatic pancreatic cancer and is

classified as Category 1 (intervention is appropriate based upon high-level evidence) by the National Comprehensive Cancer Network for this indication (Von Hoff et al. 2013; NCCN 2017).

A15–1.3 BACKGROUND ON BEVACIZUMAB

Vascular endothelial growth factor (VEGF) is the most important pro-angiogenic factor and a key regulator of physiological angiogenesis. It is also implicated in pathological angiogenesis such as that associated with tumor growth. Increased levels of VEGF have been found in many tumors examined to date, including pancreatic cancer tumors where overexpression is associated with a poorer prognosis (Seo et al. 2000; Kuwahara et al. 2003; Costache et al. 2015).

Bevacizumab is a recombinant humanized monoclonal antibody that recognizes all isoforms of VEGF. It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor microenvironment. Additional anti-tumor activity may be on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells (Jain 2001).

Bevacizumab is approved worldwide for the first-line and second-line treatment of metastatic colorectal cancer (mCRC), first-line treatment of advanced NSCLC, metastatic breast cancer, advanced renal cell carcinoma, and ovarian cancer, and treatment of recurrent glioblastoma. Bevacizumab is currently being tested in combination with atezolizumab in Phase I and Phase II clinical trials. Bevacizumab has been generally well tolerated, and adverse events have been manageable.

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

A15–2 RATIONALE FOR ATEZO + CHEMO + BEV 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, 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).

It has been shown that in pancreatic cancer tissues, both PD-L1 and PD-L2 are expressed and that tumor PD-L1, but not PD-L2, expression significantly correlates with postoperative prognosis. Moreover, PD-L1 expression is inversely correlated with tumor-infiltrating lymphocytes, particularly $CD8^+$ T cells (Nomi et al. 2007). However, no clinically significant response to single-agent checkpoint inhibitors has been observed in patients with pancreatic cancer (Royal et al. 2010; Brahmer et al. 2012).

A15–2.2 ANTI-VEGF CANCER TREATMENT

VEGF, a diffusible glycoprotein produced by normal and neoplastic cells, is an important regulator of physiological and pathological angiogenesis. Increased levels of VEGF expression have been found in most human malignancies examined to date, including tumors of the lung, breast, thyroid, gastrointestinal (GI) tract, kidney, bladder, ovary, cervix, and pancreas, as well as angiosarcomas and glioblastomas (Ferrara and Davis-Smyth 1997; von Marschall et al. 2000; Luo et al. 2001). Increased VEGF serum levels have been correlated with poor survival. Targeting the VEGF pathway with bevacizumab has demonstrated activity in patients across a broad range of advanced malignancies when used in combination with chemotherapy.

The role of bevacizumab in pancreatic cancer remains controversial. An earlier single-arm Phase II study (NCI-2675) indicated that the addition of bevacizumab to gemcitabine chemotherapy may be beneficial in patients with advanced pancreatic cancer. However, the National Cancer Institute–sponsored Phase III trial CALGB80303 could not confirm the Phase II findings (see Bevacizumab Investigator's Brochure for detailed efficacy results). In a Phase II study of bevacizumab combined with gemcitabine followed by infusional 5-fluorouracil (5-FU) in patients with advanced pancreatic cancer, a statistically significant benefit was demonstrated for

progression-free survival (PFS), the primary endpoint (Martin et al. 2012). In a Phase III study of bevacizumab combined with gemcitabine and erlotinib in patients with metastatic pancreatic adenocarcinoma (Study BO17706), a statistically significant benefit was not demonstrated for overall survival, the primary endpoint. However, PFS was significantly longer in the bevacizumab group compared with the placebo group (see Bevacizumab Investigator's Brochure for detailed efficacy results).

A15–2.3 COMBINED INHIBITION OF THE PD-L1 AND VEGF PATHWAYS AS POTENTIAL ANTI-CANCER THERAPY

A strong scientific rationale and emerging clinical data suggest that the combined PD-L1/VEGF blockade may be clinically beneficial in a number of tumor types.

T-cell activation results in expression of PD-L1 as an adaptive response of tumor cells to interferon-γ that is released as a consequence of the immune response within the tumor microenvironment (Kim et al. 2005; Lee et al. 2005; Wilke et al. 2011). The result is that effector T cells can be suppressed by PD-L1 produced by the tumor or tumor-associated macrophages. This negative feedback loop can be nullified by blocking PD-L1 from binding its receptor through atezolizumab. Moreover, on the basis of the experimental data, blockade of PD-L1 or PD-1 is not expected to stimulate de novo immune responses but rather to enhance ongoing immune responses against tumor antigens because this axis is mostly implicated in the effector phase and not during priming of the cellular immune response (Merelli et al. 2014).

Overexpression of VEGF and its receptors occurs in $>$90% of pancreatic cancer cases and correlates with vascular density, tumor invasiveness and metastasis, and poor prognosis (Itakura et al. 1997; Seo et al. 2000; Kuwahara et al. 2003). VEGF-A is a pro-angiogenic molecule produced by endothelium, tumors, and tumor-associated macrophages. The VEGF pathway also plays a crucial role in exerting and maintaining an immunosuppressive tumor microenvironment through several mechanisms. For example, VEGF-A inhibits the maturation of dendritic cells (DCs) (Gabrilovich et al. 1996), promotes the expression of inhibitory immune checkpoint molecules on intratumoral $CD8^+$ T-cells that express VEGF-R2 (Voron et al. 2015), and induces Fas ligand (FasL) expression on endothelial cells, which acquired the ability to kill effector $CD8^+$ T cells, but not regulatory T cells (Motz et al. 2014). Anti-VEGF agents such as bevacizumab are well known to promote the normalization of tumor vasculature and thereby increase access of therapeutic agents (Jain 2005). Furthermore, bevacizumab can restore and/or maintain the antigen-presentation capacity of DCs, leading to enhanced T-cell infiltration in tumors (Oelkrug and Ramage 2014; Wallin et al. 2016). Administration of anti–VEGF-A has been shown to attenuate tumor endothelial FasL expression and produce a significant increase in the influx of tumor-rejecting $CD8^+$ T cells, leading to tumor growth suppression (Motz et al. 2014). In addition, anti-VEGF

therapies can reduce the frequency of myeloid-derived suppressor cells, decrease production of suppressive cytokines, and lower expression of inhibitory checkpoints on $CD8^+$ T cells in tumors (Roland et al. 2009; Voron et al. 2015). The immunomodulatory effect of bevacizumab is expected to increase $CD8^+$ T-cell recruitment and relieve intratumoral immunosuppression, thereby boosting the effects of atezolizumab.

There is precedent for a beneficial effect of anti-angiogenesis in the context of immunotherapy. In a murine melanoma model, VEGF blockade was shown to synergize with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). High pretreatment serum VEGF was associated with poor survival following ipilimumab (anti-CTLA-4) monotherapy (Yuan et al. 2014), and synergistic effects were observed in a clinical study combining ipilimumab and bevacizumab, as shown by increased T-cell frequency in post-treatment biopsies, as well as marked increases in central memory cells in peripheral blood in the majority of patients (Hodi et al. 2014).

The above-described data suggest that combined treatment with atezolizumab and bevacizumab may augment the anti-tumor immune response, resulting in improved and more durable clinical benefit.

A15–2.4 CLINICAL STUDIES OF ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB

Study GP28328 is an ongoing, Phase Ib, open-label, multicenter study combining atezolizumab (1200 mg Q3W) with bevacizumab (15 mg/kg Q3W) in patients with advanced solid tumors, with expansion arms for patients with renal cell carcinoma, mCRC, gastric cancer, and ovarian cancer. Safety findings have been consistent with the known single-agent safety profiles for each drug; no new safety signals have been identified. The regimen has been well tolerated, and adverse events have been manageable. Another Phase Ib, open-label, multicenter study (GO30140) is investigating a similar dose of atezolizumab combined with bevacizumab in patients with hepatocellular carcinoma.

Study WO29637 is an ongoing, Phase III, randomized study in which atezolizumab plus bevacizumab is compared with sunitinib in patients with untreated metastatic renal cell carcinoma. As of 29 September 2017, the data cutoff date, 915 patients (454 receiving atezolizumab plus bevacizumab and 461 receiving sunitinib) had been enrolled and were evaluable for efficacy. The objective response rate was 37% in the atezolizumab plus bevacizumab arm and 33% in the sunitinib arm. Median PFS based on investigator assessment was 11.2 months in the atezolizumab plus bevacizumab arm and 8.4 months in the sunitinib arm, with a hazard ratio of 0.83 (95% CI 0.70, 0.97). Patients in the atezolizumab plus bevacizumab arm had fewer high-grade treatment-related

adverse events and delayed symptom interference with daily life compared with patients in the sunitinib arm.

Study GO29436 is an ongoing, Phase III, randomized study of bevacizumab plus chemotherapy (carboplatin and paclitaxel) with or without atezolizumab in patients with untreated non-squamous metastatic NSCLC. As of 15 September 2017, the data cutoff date, 356 patients had been enrolled in the bevacizumab plus chemotherapy plus atezolizumab (Bev + Chemo + Atezo) arm and 336 had been enrolled in the bevacizumab plus chemotherapy (Bev + Chemo) arm. In the primary analysis population, the objective response rate and median duration of response were 64% and 9.0 months, respectively, for the Bev + Chemo + Atezo arm, compared with 48% and 5.7 months, respectively, for the Bev + Chemo arm. Median PFS was 8.3 months for the Bev + Chemo + Atezo arm and 6.8 months for the Bev + Chemo arm, with a hazard ratio of 0.62 ($p < 0.0001$). The combination of bevacizumab, carboplatin, paclitaxel, and atezolizumab appears to be well tolerated.

Detailed clinical study results for atezolizumab and bevacizumab can be found in the Atezolizumab Investigator's Brochure and the Bevacizumab Investigator's Brochure, respectively.

A15–2.5 CLINICAL STUDY OF ATEZOLIZUMAB IN COMBINATION WITH NAB-PACLITAXEL AND GEMCITABINE

An ongoing Phase I study (GO30140) includes an arm that is evaluating atezolizumab in combination with nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic cancer.

Adverse events observed to date are consistent with the known risks of atezolizumab, nab-paclitaxel, and gemcitabine. Atezolizumab in combination with cytotoxic chemotherapy has not been associated with additive severe (Grade ≥ 3) toxicities, indicating that atezolizumab can be safely combined with standard chemotherapy. As of the data cutoff date of 24 October 2017, the confirmed objective response rate was 41.7%, the median progression-free survival was 7 months, and the median overall survival was 10.6 months for 24 efficacy-evaluable patients with metastatic pancreatic cancer.

A15–2.6 BENEFIT–RISK ASSESSMENT

Metastatic pancreatic ductal adenocarcinoma (PDAC) is an incurable disease with a high unmet need for improved medical intervention. As described above, bevacizumab has immunomodulatory properties that include increased T-cell trafficking into tumors and the reduction of suppressive cytokines and infiltrating regulatory T cells (Hodi et al. 2010; Wallin et al. 2016). These data, in combination with nonclinical and clinical data for bevacizumab plus an immune checkpoint inhibitor, suggest a potential added benefit

when combining bevacizumab and atezolizumab. In addition, combination treatment with bevacizumab and atezolizumab has shown improved efficacy over atezolizumab alone in patients with renal cell carcinoma (McDermott et al. 2017). Therefore, combining the anti-VEGF effects of bevacizumab with blockade of the PD-L1/PD-1 pathway by atezolizumab may result in an enhanced protective anti-tumor immune response in patients with PDAC.

COVID-19 Benefit–Risk Assessment

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those patients with pancreatic cancer, are a more vulnerable population. In some retrospective analyses, infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with higher mortality in patients with cancer. It is unclear whether or how cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of COVID-19. At this time, there is insufficient evidence for a causal association between atezolizumab and an increased risk of COVID-19. Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in patients receiving atezolizumab in combination with chemotherapy; however, this is not specific to the risk of infection with SARS-CoV-2 (see Section A15–5.1). Based on the safety profiles and mechanism of action, it is not anticipated that bevacizumab will increase the risk of infection with SARS-CoV-2. Additionally, an interaction of bevacizumab with the COVID-19 vaccines is unlikely.

For the evaluation of the impact of the COVID-19 pandemic and COVID-19 vaccination on the benefit–risk assessment, please refer to Section 1.5.

A15–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + CHEMO + BEV ARM

A15–3.1 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), which is an approved dosage for atezolizumab.

A15–3.2 RATIONALE FOR BEVACIZUMAB DOSE AND SCHEDULE

Bevacizumab will be administered at a dose of 10 mg/kg Q2W (10 mg/kg on Days 1 and 15 of each 28-day cycle). This treatment regimen was selected on the basis of nonclinical studies, available clinical data, and the doses recommended for use for indications in which bevacizumab is approved (refer to the Bevacizumab Investigator's Brochure for details).

A15–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + CHEMO + BEV ARM

A15–4.1 TREATMENT IN ATEZO + CHEMO + BEV 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 Bevacizumab

The bevacizumab drug product will be supplied by the Sponsor as a sterile solution in a single-use, 4-mL or 16-mL, preservative-free glass vial. The 4-mL vial contains 100 mg of bevacizumab (25 mg/mL), and the 16-mL vial contains 400 mg of bevacizumab (25 mg/mL).

For information on the formulation and handling of bevacizumab, see the pharmacy manual and the Bevacizumab Investigator's Brochure.

A15–4.1.1.3 Nab-Paclitaxel

For information on the formulation, packaging, and handling of nab-paclitaxel, refer to the local prescribing information.

A15–4.1.1.4 Gemcitabine

For information on the formulation, packaging, and handling of gemcitabine, refer to the local prescribing information.

A15–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab (Atezo + Chemo + Bev) arm will receive treatment as outlined in Table A15-1 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 3.1.2 for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table A15-1 Treatment Regimen for Atezo + Chemo + Bev Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Atezolizumab 840 mg IV on Days 1 and 15 of each cycle • Bevacizumab 10 mg/kg IV on Days 1 and 15 of each cycle [a] • Nab-paclitaxel 125 mg/m^2 IV on Days 1, 8, and 15 of each cycle [b] • Gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 of each cycle

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Bevacizumab will be administered after completion of the atezolizumab infusion.

[b] On Days 1 and 15 of each cycle, nab-paclitaxel will be administered after completion of the bevacizumab infusion.

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

Medication errors 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 5.3.5.12. No safety data related to overdosing of atezolizumab or bevacizumab are available. For information on overdosing of gemcitabine or nab-paclitaxel, refer to the local prescribing information for each agent.

A15–4.1.2.1 Atezolizumab

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 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, 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 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 2.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A15–5.1.6. Atezolizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A15–4.1.2.2 Bevacizumab

Bevacizumab will be administered by IV infusion at a dose of 10 mg/kg on Days 1 and 15 of each 28-day cycle. On Days 1 and 15 of each cycle, bevacizumab will be administered after completion of the atezolizumab infusion.

Administration of bevacizumab 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. Bevacizumab infusions will be administered per the instructions outlined in Table A15-3.

Table A15-3 Administration of First and Subsequent Bevacizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the bevacizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) should be measured within 60 minutes prior to the infusion. • Bevacizumab should be infused over 90 (±15) minutes. • Vital signs should be measured within 30 minutes after completion of 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. • Bevacizumab should be infused over 60 (±10) minutes if the previous 90-minute infusion was tolerated without an infusion-related reaction, or 90 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (±5) minutes thereafter. • Vital signs should be measured within 30 minutes after completion of the infusion.

No dose modification for bevacizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A15–5.1.6. Bevacizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A15–4.1.2.3 Nab-Paclitaxel and Gemcitabine

On Days 1, 8, and 15, patients will receive nab-paclitaxel 125 mg/m^2, administered by IV infusion over 30 (±5) minutes, followed by gemcitabine 1000 mg/m^2, administered by IV infusion over 30 (±5) minutes. On Days 1 and 15 of each cycle, nab-paclitaxel will be administered after completion of the bevacizumab infusion.

Nab-paclitaxel and gemcitabine will be administered according to institutional standards 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.

Guidelines for nab-paclitaxel and gemcitabine dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A15–5.1.6. Nab-paclitaxel and gemcitabine treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A15–4.2 CONCOMITANT THERAPY FOR ATEZO + CHEMO + BEV 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 10 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 Permitted Therapy for Atezo + Chemo + Bev 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) per local practice/institutional guidelines or the American Society of Clinical Oncology guidelines for hematopoietic CSFs (Smith et al. 2006) and American Society of Hematology/American Society of Clinical Oncology guidelines for ESAs (Rizzo et al. 2010)

  Evidence supporting the use of long-acting (PEGylated) forms of G-CSF in patients receiving weekly chemotherapy (i.e., nab-paclitaxel) is limited. Thus, investigators should consider giving preference to conventional formulations of G-CSF.

- Oral contraceptives
- 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 A15–4.2.3).

- Megestrol acetate administered as an appetite stimulant after initiation of study treatment
- 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
- 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, nab-paclitaxel, gemcitabine, and bevacizumab should be withheld 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.

  Note: Treatment with atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab should be withheld during CNS-directed radiation therapy.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab and bevacizumab 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).

A15–4.2.2 Cautionary Therapy for Atezo + Chemo + Bev Arm

A15–4.2.2.1 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 Appendix 2 for details).

A15–4.2.2.2 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

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

The above lists of cautionary medications are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safety administered with study treatment. In addition, the Medical Monitor is available to advise if questions arise regarding medications not listed above.

A15–4.2.2.3 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 A15–4.2.3) may be used during the study at the discretion of the investigator.

A15–4.2.2.4 Bisphosphonates

Osteonecrosis of the jaw has been reported in patients receiving bevacizumab, mainly in combination with bisphosphonates. Thus, caution must be exercised in using bevacizumab in patients receiving concomitant bisphosphonates.

A15–4.2.3 Prohibited Therapy for Atezo + Chemo + Bev 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), 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 A15–4.2.1.
- 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.
- Anti-thrombotic treatment with aspirin (> 325 mg/dL) and clopidogrel (> 75 mg/day) or equivalent are prohibited within 10 days prior to initiation of study treatment and during study treatment.

A15–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + CHEMO + BEV ARM

Contraception requirements for women and men in the Atezo + Chemo + Bev 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, 6 months after the last dose of nab-paclitaxel or gemcitabine, and 6 months after the last dose of bevacizumab. 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 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 methods, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men who are receiving chemotherapy 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 nab-paclitaxel or gemcitabine and men who are not receiving chemotherapy must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of bevacizumab. 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 6 months after the last dose of nab-paclitaxel, gemcitabine, or bevacizumab 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.

A15–5 ASSESSMENT OF SAFETY FOR ATEZO + CHEMO + BEV ARM

A15–5.1 SAFETY PLAN FOR ATEZO + CHEMO + BEV ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A15–5.1.1, A15–5.1.2, A15–5.1.3, A15–5.1.4, and A15–5.1.5). Guidelines for management of patients who experience specific adverse events are provided in Section A15–5.1.6.

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. 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.

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, 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 may lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 2 of the protocol 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 Nab-Paclitaxel

The following are the most common adverse events observed with nab-paclitaxel in patients with PDAC: neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. The following adverse events have also been observed: myelosuppression (primarily neutropenia, anemia, thrombocytopenia), cranial nerve palsies, hypersensitivity reactions, pneumonitis, myalgia, arthralgia, cardiotoxicity (myocardial disorders, cardiac failure, angina, tachycardia, ventricular arrhythmia), cystoid macular edema, Stevens-Johnson syndrome/toxic epidermal necrolysis, sepsis, infusion-site reactions/extravasation, hepatic toxicity (drug-induced liver injury), acute renal failure, scleroderma, and drug-induced lupus erythematous.

For more details regarding the safety profile for nab-paclitaxel, refer to the nab-paclitaxel prescribing information.

A15–5.1.3 Risks Associated with Gemcitabine

The most common adverse events observed with gemcitabine are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased ALP, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema. The following adverse events have also been observed: renal failure, hemolytic-uremic syndrome, interstitial pneumonitis, myocardial infarction, arrhythmia, and heart failure.

For more details regarding the safety profile for gemcitabine, refer to the gemcitabine prescribing information.

A15–5.1.4 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: GI perforations, fistulae, hemorrhage, hypertension, posterior reversible encephalopathy syndrome (PRES), arterial and venous thromboembolic events, congestive heart failure (CHF), other cardiac disorders, neutropenia and infection, wound-healing complications, proteinuria, hypersensitivity or IRRs, osteonecrosis of the jaw, ovarian failure, and pulmonary hypertension. Refer to Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of all anticipated risks for bevacizumab.

A15–5.1.4.1 Perforations and Fistulae

Guidelines for management of patients who develop a perforation or fistula are provided in Table A15-5.

Gastrointestinal Perforation and Fistula

Bevacizumab has been associated with serious cases of GI perforation in patients with mCRC, and a few reports of gallbladder perforation have been reported from the postmarketing experience. Presentation of these events has varied in type and severity, ranging from free air seen only on the plain abdominal X-ray, which resolved without treatment, to a colonic perforation with abdominal abscess and fatal outcome. In some cases, the underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumor necrosis, diverticulitis, or chemotherapy-associated colitis. A causal association of an intra-abdominal inflammatory process and GI perforation to treatment with bevacizumab has not been established. However, caution should be exercised when treating patients with intra-abdominal inflammatory process with bevacizumab. Patients treated with bevacizumab for persistent, recurrent, or metastatic cervical cancer may be at increased risk of fistulae between the vagina and any part of the GI tract. Fatal outcomes have been reported in cases of GI perforations.

Bevacizumab use has been associated with serious cases of fistula, including events resulting in death. Fistulae within the GI tract are common in patients with mCRC and ovarian cancer, but are uncommon or rare in other indications. Patients who develop GI–vaginal fistulae may also have bowel obstructions and may require surgical intervention as well as diverting ostomies.

Non-Gastrointestinal Fistula

Bevacizumab use has been associated with serious cases of non-GI fistula, including events resulting in death. Patients may be at increased risk for the development of non-GI fistulae when treated with bevacizumab. Other fistulae (e.g., bronchopleural, tracheoesophageal, urogenital, biliary) have been reported uncommonly in bevacizumab clinical trials patients and in postmarketing reports.

A15–5.1.4.2 Hemorrhage

In clinical trials, an increased incidence of bleeding events has been observed in patients treated with bevacizumab compared with control. The hemorrhagic events observed in bevacizumab studies were predominantly tumor-associated hemorrhage and minor mucocutaneous hemorrhage. Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, on the basis of imaging procedures or signs and symptoms. Therefore, the risk of CNS hemorrhage in such patients has not been prospectively evaluated in randomized clinical studies. Patients should be monitored for signs and symptoms of CNS bleeding.

Guidelines for management of patients who develop a hemorrhage are provided in Table A15-5.

A15–5.1.4.3 Hypertension

An increased incidence of hypertension has been observed in patients treated with bevacizumab. Clinical safety data suggest the incidence of hypertension is likely to be dose dependent. Preexisting hypertension should be adequately controlled before starting bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating therapy. In most cases, hypertension is controlled adequately by standard anti-hypertensive treatment. Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal. Blood pressure must be assessed before each bevacizumab administration.

Guidelines for management of patients who develop hypertension are provided in Table A15-5.

A15–5.1.4.4 Posterior Reversible Encephalopathy Syndrome

There have been rare reports of patients treated with bevacizumab developing signs and symptoms that are consistent with PRES, a rare neurologic disorder (also known as reversible posterior leukoencephalopathy syndrome). PRES can present with the following signs and symptoms (among others): seizures, headache, altered mental status, or visual disturbance or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by magnetic resonance imaging (MRI) of the brain. In patients developing PRES, treatment of specific symptoms, including control of hypertension, is recommended. The safety of re-initiating

bevacizumab therapy in patients previously experiencing PRES is not known. Adequate brain imaging through use of MRI must be performed as a follow-up measurement for patients with PRES.

Guidelines for management of patients who develop PRES are provided in Table A15-5.

A15–5.1.4.5 Thromboembolism

Guidelines for management of patients who develop a thromboembolism are provided in Table A15-5.

Arterial Thromboembolism

In clinical trials, the incidence of arterial thromboembolism reactions, including cerebrovascular accidents, transient ischemic attack, and myocardial infarction, was higher in patients receiving bevacizumab in combination with chemotherapy compared with those receiving chemotherapy alone. Patients receiving bevacizumab plus chemotherapy with a history of arterial thromboembolism, diabetes, or age >65 years have an increased risk of developing arterial thromboembolic events during bevacizumab therapy. Caution should be taken when treating these patients with bevacizumab.

Venous Thromboembolism

Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism, while receiving bevacizumab. An increased risk of venous thromboembolic events and bleeding has been observed in bevacizumab-treated patients receiving anticoagulation therapy after an initial venous thromboembolic event. Patients with venous thromboembolisms should be managed and monitored with appropriate medical therapy.

A15–5.1.4.6 Congestive Heart Failure

Events consistent with CHF have been reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF requiring treatment or hospitalization. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, has received prior radiotherapy to the left chest wall, or had other risk factors for CHF. Caution should be exercised when administering bevacizumab to patients with clinically significant cardiovascular disease, such as preexisting coronary artery disease, concomitant cardiotoxic therapy, or CHF.

Guidelines for management of patients who develop CHF are provided in Table A15-5.

A15–5.1.4.7 Other Cardiac Disorders

Cardiac disorders, including arrhythmias, have been seen in clinical trials using bevacizumab in combination with 5-FU and leucovorin or bevacizumab in combination with capecitabine and oxaliplatin. However, for the vast majority of cases, the patient's history included preexisting underlying cardiovascular diseases, concomitant treatment with potentially arrhythmogenic medications, or severe intercurrent illnesses.

A15–5.1.4.8 Neutropenia and Infection

Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab compared with chemotherapy alone.

Guidelines for management of patients who develop neutropenia are provided in Table A15-5.

A15–5.1.4.9 Wound-Healing Complications

Bevacizumab may adversely affect the wound-healing process. Serious wound-healing complications with a fatal outcome have been reported. Bevacizumab therapy should not be initiated in patients who have had major surgery within the previous 28 days or patients with a surgical wound that has not fully healed. Bevacizumab therapy should be withheld for a minimum of 28 days prior to major elective surgery. Emergency surgery should be performed as appropriate without delay after a careful benefit–risk assessment.

Necrotizing fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab, usually secondary to wound-healing complications, GI perforation, or fistula formation.

Guidelines for management of patients who develop necrotizing fasciitis or wound dehiscence are provided in Table A15-5.

A15–5.1.4.10 Proteinuria

In clinical studies, the incidence of proteinuria was higher in patients receiving bevacizumab in combination with chemotherapy compared with those receiving chemotherapy alone. Proteinuria reported in patients receiving bevacizumab has ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome. Nephrotic syndrome was seen in up to 1.4% of treated patients. Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. Patients with proteinuria will be excluded from bevacizumab-containing arms.

Guidelines for management of patients who develop proteinuria are provided in Table A15-5.

A15–5.1.4.11 Hypersensitivity or Infusion-Related Reactions

Patients may be at risk of developing hypersensitivity or IRRs to bevacizumab. Patients will be closely monitored during and following administration of bevacizumab. Systematic premedication is not warranted.

Guidelines for management of patients who develop hypersensitivity reactions or IRRs are provided in Table A15-5.

A15–5.1.4.12 Osteonecrosis of the Jaw

Osteonecrosis of the jaw has been reported in patients receiving bevacizumab, mainly in combination with bisphosphonates in the postmarketing setting. The pathogenesis of the osteonecrosis is unclear. Caution must be exercised in using bevacizumab in patients receiving concomitant bisphosphonates.

A15–5.1.4.13 Ovarian Failure

Bevacizumab may impair female fertility. Ovarian function recovered in the majority of women after bevacizumab discontinuation. Fertility preservation strategies should be discussed with women of childbearing potential prior to starting treatment with bevacizumab.

A15–5.1.4.14 Pulmonary Hypertension

Pulmonary hypertension has been seen in patients treated with bevacizumab, primarily in the postmarketing setting. Patients at risk included those with preexisting cardiac disease, pulmonary disease, thromboembolic disease, metastasis to the lungs, or use of other medications associated with pulmonary hypertension.

Guidelines for management of patients who develop hypertension are provided in Table A15-5.

A15–5.1.5 Risks Associated with Combination Use of Atezolizumab, Nab-Paclitaxel, Gemcitabine, and Bevacizumab

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab: IRRs, dermatologic reactions, hepatic toxicity, diarrhea/colitis, pneumonitis, neutropenia, and proteinuria.

A15–5.1.6 Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm

On Day 1 of each cycle, patients are required to have an ANC of $\geq 1.5 \times 10^9$/L (1500/μL) and a platelet count of $\geq 100 \times 10^9$/L (100,000/μL) to receive treatment with nab-paclitaxel and gemcitabine. Guidelines for management of hematologic toxicities and other toxicities (including guidelines for dose modification and treatment interruption or discontinuation) are provided in Table A15-5.

A15–5.1.6.1 Dose Modifications

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

For management of drug-related toxicities, the dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times, as outlined in Table A15-4:

Table A15-4 Recommended Dose Reductions for Nab-Paclitaxel and Gemcitabine

	Initial Dose	First Dose Reduction	Second Dose Reduction
Nab-paclitaxel	125 mg/m^2	100 mg/m^2	75 mg/m^2
Gemcitabine	1000 mg/m^2	800 mg/m^2	600 mg/m^2

Nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

If further dose reduction is indicated for nab-paclitaxel and/or gemcitabine after two dose reductions, that drug (or both drugs, if applicable) should be discontinued, but the patient may continue other study treatments at the investigator's discretion. After dose reduction, the dose may be escalated during subsequent administrations at the investigator's discretion.

A15–5.1.6.2 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 > 12 weeks, 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 investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.

Nab-paclitaxel and/or gemcitabine treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table A15-5). If nab-paclitaxel or gemcitabine have been withheld for > 56 days because of toxicity, the patient should be discontinued from both chemotherapy agents. However, nab-paclitaxel or gemcitabine can be resumed after being withheld for > 56 days if the patient is likely to derive clinical benefit. The decision to re-challenge patients with nab-paclitaxel and/or gemcitabine should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.

Bevacizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If bevacizumab is withheld for > 56 days, the patient will be discontinued from bevacizumab. Bevacizumab can be resumed after being withheld for > 56 days if the patient is likely to derive clinical benefit. The decision to re-challenge patients bevacizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.

If atezolizumab, nab-paclitaxel, gemcitabine, or bevacizumab is discontinued, the other drugs can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section A15–4.1.2 for information on dose interruptions for reasons other than toxicity.

A15–5.1.6.3 Management Guidelines for Adverse Events

Guidelines for management of patients who experience specific adverse events are provided in Table A15-5. 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 nab-paclitaxel 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.

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reactions	
General guidance	• Guidelines for management of IRRs and CRS for atezolizumab are provided in Appendix 2 • Guidelines for management of IRRs for bevacizumab and chemotherapy are provided below. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue the causative agent.
IRR to bevacizumab, Grade 1 or 2	• Reduce infusion rate to ≤50%. • After symptoms have adequately resolved, increase in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle. • For subsequent infusions, monitor closely for IRRs.
IRR to bevacizumab, Grade 3	• Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen) if clinically indicated. • After symptoms have resolved to baseline, resume infusion at ≤50% of the rate prior to the reaction after the patient's symptoms have adequately resolved, and increase in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle. • For subsequent infusions, monitor closely for IRRs.
IRR to bevacizumab, Grade 4	• Stop infusion and permanently discontinue bevacizumab. [a] • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen) if clinically indicated.

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reactions (cont.)	
IRR to chemotherapy, 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 chemotherapy, Grade 2	• Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, administer oral premedication with antihistamine and antipyretic and monitor closely for IRRs.
IRR to chemotherapy, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue treatment and contact Medical Monitor. [a]
Hemophagocytic lymphohistiocytosis	• Follow guidelines for atezolizumab in Appendix 2. • Withhold all treatment and contact Medical Monitor.

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity	
Diarrhea or colitis, Grade 1	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel, gemcitabine, and bevacizumab.
Diarrhea or colitis, Grade 2	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine. Bevacizumab may be continued at the discretion of the investigator. • If bevacizumab is withheld and event resolves to Grade 1 or better ≤ 56 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]
Diarrhea or colitis, Grade 3	• Follow guidelines for atezolizumab in Appendix 2. • Withhold nab-paclitaxel and gemcitabine. Bevacizumab may be continued at the discretion of the investigator. • If event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine with dose reduced by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If bevacizumab is withheld and event resolves to Grade 1 or better ≤ 56 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]
Diarrhea or colitis, Grade 4	• Follow guidelines for atezolizumab in Appendix 2. • Permanently discontinue nab-paclitaxel and gemcitabine. Bevacizumab may be continued at the discretion of the investigator. • If bevacizumab is withheld and event resolves to Grade 1 or better ≤ 56 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Mucositis, Grade 1 or 2	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab.
Mucositis, Grade 3	• Continue atezolizumab and bevacizumab. Withhold nab-paclitaxel and gemcitabine. • If event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine with dose reduced by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a]
Mucositis, Grade 4	• Permanently discontinue atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab. [a]
Gastrointestinal perforation, any grade	• Withhold atezolizumab, nab-paclitaxel and gemcitabine. Permanently discontinue bevacizumab. [a] • Initiate treatment per institutional guidelines. • If event improves, resume atezolizumab, nab-paclitaxel, and gemcitabine. If not, permanently discontinue atezolizumab, nab-paclitaxel, and gemcitabine. [a]
Bowel obstruction, Grade 2	• Withhold atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab for obstruction requiring medical intervention. • If event resolves completely, resume atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab. If not, permanently discontinue atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab. [a]
Bowel obstruction, Grade 3 or 4	• Withhold atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab. • If event resolves completely (including recovery from any surgery), resume atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab. If not, permanently discontinue atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Capillary leak syndrome	
Capillary leak syndrome, any grade	• Permanently discontinue gemcitabine. [a] Withhold atezolizumab, nab-paclitaxel, and bevacizumab. • If event improves, resume atezolizumab, nab-paclitaxel, and bevacizumab. If not, permanently discontinue atezolizumab, nab-paclitaxel, and bevacizumab. [a]
Dermatologic toxicity	
Dermatologic event, Grade 1	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel, gemcitabine, and bevacizumab.
Dermatologic event, Grade 2	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine with dose reduced by one level. [b] Continue bevacizumab. • If event persists, permanently discontinue nab-paclitaxel and gemcitabine. [a]
Dermatologic event, Grade 3	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine with dose reduced by one level. [b] Bevacizumab may be continued at the discretion of the investigator. • If event persists, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If bevacizumab is withheld and event resolves to Grade 2 or better ≤56 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Dermatologic toxicity (cont.)	
Dermatologic event, Grade 4	• Follow guidelines for atezolizumab in Appendix 2. • Permanently discontinue nab-paclitaxel, gemcitabine, and bevacizumab. [a]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Withhold atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab.

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Febrile neutropenia	
Grade 3 or 4	• Withhold atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab. • If fever resolves and ANC improves to $\geq 1.5 \times 10^9$/L (1500/μL) $\leq$ 56 days after event onset, resume nab-paclitaxel and gemcitabine with dose reduced by one level [b] and resume and bevacizumab. If not, permanently discontinue nab-paclitaxel, gemcitabine, and bevacizumab. [a] • If fever resolves and ANC improves to $\geq 1.5 \times 10^9$/L (1500/μL) $\leq$ 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab. [a]
Hematologic toxicity at Day 1 (excluding febrile neutropenia)	
ANC $\geq 1.5 \times 10^9$/L (1500/μL) **and** Platelet count $\geq 100 \times 10^9$/L (100,000/μL)	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab.
ANC $< 1.5 \times 10^9$/L (1500/μL) **and/or** Platelet count $< 100 \times 10^9$/L (100,000/μL)	• Continue atezolizumab and bevacizumab. Withhold nab-paclitaxel and gemcitabine. • Permanently discontinue nab-paclitaxel or gemcitabine if withheld > 56 days after event onset. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity at Day 8 (excluding febrile neutropenia)	
ANC $\geq 1.0 \times 10^9$/L (1000/μL) **and** Platelet count $\geq 75 \times 10^9$/L (75,000/μL)	• Continue nab-paclitaxel and gemcitabine.
ANC $\geq 0.5 \times 10^9$/L (500/μL) but $< 1.0 \times 10^9$/L (1000/μL) **and/or** Platelet count $\geq 50 \times 10^9$/L (50,000/μL) but $< 75 \times 10^9$/L (75,000/μL)	• Continue nab-paclitaxel and gemcitabine with dose reduced by one level. [b]
ANC $< 0.5 \times 10^9$/L (500/μL) **and/or** Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Withhold nab-paclitaxel and gemcitabine. • If nab-paclitaxel and gemcitabine are withheld > 56 days after event onset, permanently discontinue nab-paclitaxel and gemcitabine. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity at Day 15 (excluding febrile neutropenia): Day 8 doses given without modification	
ANC $\geq 1.0 \times 10^9$/L (1000/μL) **and** Platelet count $\geq 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab.
ANC $\geq 0.5 \times 10^9$/L (500/μL) but $< 1.0 \times 10^9$/L (1000/μL) **and/or** Platelet count $\geq 50 \times 10^9$/L (50,000/μL) but $< 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab and bevacizumab. Continue nab-paclitaxel and gemcitabine at current dose followed by WBC growth factors **or** with dose reduced by one level. [b]
ANC $< 0.5 \times 10^9$/L (500/μL) **and/or** Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Withhold atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab. • If event improves, atezolizumab, nab-paclitaxel, gemcitabine, and/or bevacizumab can be resumed. [a] • If nab-paclitaxel, gemcitabine, and bevacizumab are withheld > 56 days after event onset, permanently discontinue nab-paclitaxel, gemcitabine, and bevacizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity at Day 15 (excluding febrile neutropenia): Day 8 doses reduced	
ANC $\geq 1.0 \times 10^9$/L (1000/μL) **and** Platelet count $\geq 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab and bevacizumab. Continue nab-paclitaxel and gemcitabine at Day 1 doses followed by WBC growth factors **or** at current dose.
ANC $\geq 0.5 \times 10^9$/L (500/μL) but $< 1.0 \times 10^9$/L (1000/μL) **and/or** Platelet count $\geq 50 \times 10^9$/L (50,000/μL) but $< 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab and bevacizumab. Continue nab-paclitaxel and gemcitabine at current dose followed by WBC growth factors **or** with dose reduced by one level. [b]
ANC $< 0.5 \times 10^9$/L (500/μL) **and/or** Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Withhold atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab. • If event improves, atezolizumab, nab-paclitaxel, gemcitabine, and/or bevacizumab can be resumed. [a] • If nab-paclitaxel, gemcitabine, and bevacizumab are withheld > 56 days after event onset, permanently discontinue nab-paclitaxel, gemcitabine, and bevacizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity at Day 15 (excluding febrile neutropenia): Day 8 treatment was withheld	
ANC $\geq 1.0 \times 10^9$/L (1000/μL) **and** Platelet count $\geq 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab and bevacizumab. Continue nab-paclitaxel and gemcitabine at current dose followed by WBC growth factors **or** with dose reduced by one level. [b]
ANC $\geq 0.5 \times 10^9$/L (500/μL) but $< 1.0 \times 10^9$/L (1000/μL) **and/or** Platelet count $\geq 50 \times 10^9$/L (50,000/μL) but $< 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab and bevacizumab. Continue nab-paclitaxel and gemcitabine with dose reduced by one level followed by WBC growth factors **or** with dose reduced by two levels. [b]
ANC $< 0.5 \times 10^9$/L (500/μL) **and/or** Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Withhold atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab. • If event improves, atezolizumab, nab-paclitaxel, gemcitabine, and/or bevacizumab can be resumed. [a] • If nab-paclitaxel, gemcitabine, and bevacizumab are withheld > 56 days after event onset, permanently discontinue nab-paclitaxel, gemcitabine, and bevacizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Pulmonary events	
Pulmonary event, Grade 1	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel, gemcitabine, and bevacizumab. • If confirmed diagnosis of pneumonitis, permanently discontinue nab-paclitaxel and gemcitabine. [a]
Pulmonary event, Grade 2	• Follow guidelines for atezolizumab in Appendix 2. • Withhold nab-paclitaxel, and gemcitabine. Bevacizumab may be continued at the discretion of the investigator. • If confirmed diagnosis of pneumonitis, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If bevacizumab is withheld and event resolves to Grade 1 or better ≤ 56 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 2. • Permanently discontinue nab-paclitaxel and gemcitabine. [a] Bevacizumab may be continued at the discretion of the investigator. • If bevacizumab is withheld and event resolves to Grade 1 or better ≤ 56 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Hepatic event	
Hepatic event, Grade 1	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel, gemcitabine, and bevacizumab.
Hepatic event, Grade 2	• Follow guidelines for atezolizumab in Appendix 2. • Withhold nab-paclitaxel and gemcitabine for hepatic event other than Grade 2 elevation of AST, ALT, or ALP. Continue bevacizumab. • If chemotherapy is withheld and event resolves to Grade 1 or better ≤56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a]
Hepatic event, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 2. • Withhold nab-paclitaxel, gemcitabine, and bevacizumab. • If event resolves to Grade 1 or better ≤56 days after event onset, resume nab-paclitaxel, gemcitabine, and bevacizumab and consider reducing the nab-paclitaxel and gemcitabine dose by one level. [b] If not, permanently discontinue nab-paclitaxel, gemcitabine, and bevacizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Neurologic disorder	
Immune-mediated neuropathy, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel, gemcitabine, and bevacizumab.
Immune-mediated neuropathy, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 2. • Continue gemcitabine and bevacizumab. Withhold nab-paclitaxel. • If event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel with dose reduced by one level. [b] If not, permanently discontinue nab-paclitaxel. [a]
Non–immune-mediated neuropathy, Grade 1 or 2	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab.
Non–immune-mediated neuropathy, Grade 3 or 4	• Continue atezolizumab, gemcitabine, and bevacizumab. Withhold nab-paclitaxel. • If event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel with dose reduced by one level. [b] If not, permanently discontinue nab-paclitaxel. [a]
Immune-mediated meningoencephalitis, any grade	• Follow guidelines for atezolizumab in Appendix 2. • Withhold nab-paclitaxel, gemcitabine, and bevacizumab. • If event stabilizes ≤ 56 days after event onset, resume nab-paclitaxel, gemcitabine, and bevacizumab. If not, permanently discontinue nab-paclitaxel, gemcitabine, and bevacizumab. [a]
Posterior reversible encephalopathy syndrome	
Posterior reversible encephalopathy syndrome, any grade confirmed by magnetic resonance imaging	• Withhold atezolizumab and nab-paclitaxel. Permanently discontinue gemcitabine and bevacizumab. [a] • If event improves, atezolizumab and/or nab-paclitaxel can be resumed. [a] • If nab-paclitaxel is withheld > 56 days after event onset, permanently discontinue nab-paclitaxel. [a] • If atezolizumab is withheld > 12 weeks after event onset, permanently discontinue atezolizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Hypertension	
Hypertension, Grade 1	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab.
Hypertension, Grade 2 or 3	• Atezolizumab, nab-paclitaxel, and gemcitabine may be continued at the discretion of the investigator. Withhold bevacizumab. • Initiate anti-hypertensive therapy. • If treatment is withheld and event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If treatment is withheld and event resolves to Grade 1 or better ≤ 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab. [a] • If event resolves to Grade 1 or better ≤ 56 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]
Hypertension, Grade 4	• Withhold atezolizumab, nab-paclitaxel, and gemcitabine. Permanently discontinue bevacizumab. [a] • Initiate anti-hypertensive therapy. • If event improves ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If event improves ≤ 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Hemorrhage	
Hemorrhage, Grade 1 (excluding cerebral hemorrhage)	**All patients:** • Continue atezolizumab, nab-paclitaxel, and gemcitabine. **Patients not receiving full-dose anticoagulation:** • Withhold bevacizumab. • If the bleeding resolves, hemoglobin levels are stable, there is no bleeding diathesis, and there is no anatomic or pathologic condition that would significantly increase the risk of hemorrhage recurrence ≤ 56 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a] • For recurrent pulmonary or CNS (including intracranial) hemorrhage events, permanently discontinue bevacizumab. [a] **Patients receiving full-dose anticoagulation:** • Permanently discontinue bevacizumab. [a]
Hemorrhage, Grade 2 (excluding cerebral hemorrhage)	**All patients:** • Continue atezolizumab. Withhold nab-paclitaxel and gemcitabine. • If event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine and consider reducing the dose by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] **Patients not receiving full-dose anticoagulation:** • Withhold bevacizumab. • If the bleeding resolves, hemoglobin levels are stable, there is no bleeding diathesis, and there is no anatomic or pathologic condition that would significantly increase the risk of hemorrhage recurrence ≤ 56 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a] • For recurrent pulmonary or CNS (including intracranial) hemorrhage events, permanently discontinue bevacizumab. [a] **Patients receiving full-dose anticoagulation:** • Permanently discontinue bevacizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Hemorrhage (cont.)	
Hemorrhage, Grade 3 (excluding cerebral hemorrhage)	• Continue atezolizumab. Withhold nab-paclitaxel and gemcitabine. Permanently discontinue bevacizumab. [a] • If event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine and consider reducing the dose by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a]
Hemorrhage, Grade 4, or cerebral hemorrhage, any grade	• Withhold atezolizumab, nab-paclitaxel, and gemcitabine. Permanently discontinue bevacizumab. [a] • If event improves, resume atezolizumab, nab-paclitaxel, and gemcitabine. If not, permanently discontinue atezolizumab, nab-paclitaxel, and gemcitabine. [a]
Thromboembolic events	
Venous thromboembolic event, Grade 1	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab.
Venous thromboembolic event, Grade 2	• Withhold atezolizumab, nab-paclitaxel, and gemcitabine. Continue bevacizumab. • Initiate anticoagulant treatment per institutional guidelines. • If patient becomes asymptomatic ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If patient becomes asymptomatic ≤ 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Thromboembolic events (cont.)	
Venous thromboembolic event, Grade 3	• Withhold atezolizumab, nab-paclitaxel, and gemcitabine. Withhold bevacizumab for at least 3 weeks. • Initiate anticoagulant treatment per institutional guidelines. • If patient becomes asymptomatic ≤56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If patient becomes asymptomatic ≤12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab. [a] • If anticoagulation therapy is stabilized ≤56 days after event onset, resume bevacizumab (provided that bevacizumab has been withheld for at least 3 weeks). If not, permanently discontinue bevacizumab. [a] • For recurrent events, permanently discontinue bevacizumab. [a]
Venous thromboembolic event, Grade 4	• Withhold atezolizumab, nab-paclitaxel, and gemcitabine. Permanently discontinue bevacizumab. [a] • Initiate anticoagulant treatment per institutional guidelines. • If patient becomes asymptomatic ≤56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If patient becomes asymptomatic ≤12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab. [a]
Arterial thromboembolic event, any grade	• Withhold atezolizumab, nab-paclitaxel, and gemcitabine. Permanently discontinue bevacizumab. [a] • If patient becomes asymptomatic ≤56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If patient becomes asymptomatic ≤12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Hemolytic-uremic syndrome	
Hemolytic-uremic syndrome, any grade	• Permanently discontinue gemcitabine. [a] Withhold atezolizumab, nab-paclitaxel, and bevacizumab. • If event improves, resume atezolizumab, nab-paclitaxel, and bevacizumab. If not, permanently discontinue atezolizumab, nab-paclitaxel, and bevacizumab.
Proteinuria	
Proteinuria, Grade 1 (1+ by dipstick; urinary protein < 1.0 g/24 hr)	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab.
Proteinuria, Grade 2 (2+ by dipstick; urinary protein 1.0–3.4 g/24 hr)	• Continue atezolizumab, nab-paclitaxel, and gemcitabine. • If 24-hour urine protein results are not available, continue bevacizumab. If 24-hour urine protein results are available, continue bevacizumab if urine protein is < 2 g/24 hr and withhold bevacizumab if urine protein is ≥ 2 g/24 hr. • If bevacizumab is withheld and urine protein improves to < 2 g/24 hr ≤ 56 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a] • Collect 24-hour urine for determination of total protein within 3 days prior to subsequent scheduled bevacizumab administrations until proteinuria has improved to < 1 g/24 hr.

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Proteinuria (cont.)	
Proteinuria, Grade 3 (urinary protein ≥ 3.5 g/24 hr) with no diagnosis of nephrotic syndrome	• Atezolizumab, nab-paclitaxel, and gemcitabine may be continued at the discretion of the investigator. • Collect 24-hour urine (if not already available) to determine if bevacizumab can be administered. Continue bevacizumab if urine protein is < 2 g/24 hr and withhold bevacizumab if urine protein is ≥ 2 g/24 hr. • If urine protein improves to < 2 g/24 hr ≤ 56 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a] • If treatment is withheld and event improves ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If treatment is withheld and event improves ≤ 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab. [a] • Collect 24-hour urine for determination of total protein within 3 days prior to subsequent scheduled bevacizumab administrations until proteinuria has improved to < 1 g/24 hr.
Nephrotic syndrome	• Atezolizumab, nab-paclitaxel, and gemcitabine may be continued at the discretion of the investigator. Permanently discontinue bevacizumab. [a] • If treatment is withheld and event improves ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If treatment is withheld and event improves ≤ 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Fistula	
Tracheoesophageal fistula, any grade	• Withhold atezolizumab, nab-paclitaxel, and gemcitabine. Permanently discontinue bevacizumab. [a] • If event improves, resume atezolizumab, nab-paclitaxel, and gemcitabine. If not, permanently discontinue atezolizumab, nab-paclitaxel, and gemcitabine. [a]
Fistula (non-tracheoesophageal), Grade 1, 2, or 3	• Atezolizumab, nab-paclitaxel, and gemcitabine may be continued at the discretion of the investigator. Consider withholding bevacizumab. • If treatment is withheld and event improves, resume bevacizumab. If not, permanently discontinue bevacizumab. [a] • If treatment is withheld and event improves ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If treatment is withheld and event improves ≤ 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab. [a]
Fistula (non-tracheoesophageal), Grade 4	• Withhold atezolizumab, nab-paclitaxel, and gemcitabine. Permanently discontinue bevacizumab. [a] • If event improves, resume atezolizumab, nab-paclitaxel, and gemcitabine. If not, permanently discontinue atezolizumab, nab-paclitaxel, and gemcitabine. [a]
Necrotizing fasciitis	
Necrotizing fasciitis, any grade	• Withhold atezolizumab, nab-paclitaxel, and gemcitabine. Permanently discontinue bevacizumab. • If event improves, resume atezolizumab, nab-paclitaxel, and gemcitabine. If not, permanently discontinue atezolizumab, nab-paclitaxel, and gemcitabine. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Wound dehiscence	
Wound dehiscence, any grade requiring medical or surgical therapy	• Atezolizumab, nab-paclitaxel, and gemcitabine may be continued at the discretion of the investigator. Permanently discontinue bevacizumab. [a] • If treatment is withheld and event improves ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If treatment is withheld and event improves ≤ 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab. [a]
Congestive heart failure	
Congestive heart failure, Grade 1 or 2	• Atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab may be continued at the discretion of the investigator. • If treatment is withheld and event improves ≤ 56 days after event onset, resume nab-paclitaxel, gemcitabine, and bevacizumab. If not, permanently discontinue nab-paclitaxel, gemcitabine, and bevacizumab. [a] • If treatment is withheld and event improves ≤ 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab. [a]
Congestive heart failure, Grade 3 or 4	• Atezolizumab, nab-paclitaxel, and gemcitabine may be continued at the discretion of the investigator. Permanently discontinue bevacizumab. [a] • If treatment is withheld and event improves, resume atezolizumab, nab-paclitaxel, and gemcitabine. If not, permanently discontinue atezolizumab, nab-paclitaxel, and gemcitabine. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Chemotherapy-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab.
Grade 3	• Continue atezolizumab and bevacizumab. Withhold nab-paclitaxel and gemcitabine. • If event resolves to Grade 2 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine and consider reducing dose by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a]
Grade 4	• Withhold atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. [a] • If event resolves to Grade 2 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine and consider reducing dose by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If event improves, resume bevacizumab. If not, permanently discontinue bevacizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Bevacizumab-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab.
Grade 3	• Continue atezolizumab. Withhold bevacizumab, nab-paclitaxel, and gemcitabine. • If event resolves to Grade 2 or better ≤ 56 days after event onset, resume nab-paclitaxel, gemcitabine, and bevacizumab and consider reducing nab-paclitaxel and gemcitabine dose by one level. [b] If not, permanently discontinue nab-paclitaxel, gemcitabine, and bevacizumab. [a]
Grade 4	• Withhold atezolizumab, nab-paclitaxel, gemcitabine, and bevacizumab. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. [a] • If event resolves to Grade 2 or better ≤ 56 days after event onset, resume nab-paclitaxel, gemcitabine, and bevacizumab and consider reducing nab-paclitaxel and gemcitabine dose by one level. [b] If not, permanently discontinue nab-paclitaxel, gemcitabine, and bevacizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

Table A15-5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + Bev Arm (cont.)

Event	Action to Be Taken
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel, gemcitabine, and bevacizumab.
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 2. • Withhold nab-paclitaxel, gemcitabine, and bevacizumab. • If event resolves to Grade 2 or better ≤ 56 days after event onset, resume nab-paclitaxel, gemcitabine, and bevacizumab and consider reducing nab-paclitaxel and gemcitabine dose by one level. [b] If not, permanently discontinue nab-paclitaxel, gemcitabine, and bevacizumab. [a]

Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CRS = cytokine release syndrome; IRR = infusion-related reaction; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A15–5.1.6.1 for details).

A15–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + CHEMO + BEV 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 + Chemo + Bev 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
- 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)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- [redacted]
- Grade ≥ 3 hypertension
- Grade ≥ 3 proteinuria
- Any grade GI perforation, abscess, or fistula
- Grade ≥ 2 non-GI fistula or abscess
- Grade ≥ 3 wound-healing complication
- Hemorrhage
  - Any grade CNS bleeding
  - Grade ≥ 2 hemoptysis
  - Other Grade ≥ 3 hemorrhagic event
- Any grade arterial thromboembolic event
- Grade ≥ 3 venous thromboembolic event
- Any grade PRES
- Grade ≥ 3 CHF/left ventricular systolic dysfunction
- [redacted]
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

A15–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + CHEMO + BEV ARM

A15–5.3.1 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 last dose of atezolizumab, 6 months after the last dose of bevacizumab, or 6 months after the last dose of nab-paclitaxel or gemcitabine. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF.
The investigator should discontinue study 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 6 months after the last dose of bevacizumab, nab-paclitaxel, or gemcitabine. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. 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.

A15–5.3.3 Abortions

Any 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).

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).

A15–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + CHEMO + BEV ARM

Table A15-6 Schedule of Activities for Atezo + Chemo + Bev Arm (Cohort 1)

	Stage 1 Screening (see Appendix 6)	Treatment Cycles (28-day cycles) [a]							Follow-Up [c]
		Cycle 1 [b]			Cycles ≥ 2				
	Day –28 to –1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Treat. Discon. [c]	Every 3 Months
Molecular profile of pancreatic cancer (if available)	See Appendix 6	Whenever updated information becomes available							
Vital signs [d]		x	x	x	x	x	x	x	
Weight		x [e]	x [e]	x [e]	x [e]	x [e]	x [e]	x	
Complete physical examination [f]								x	
Limited physical examination [g]		x [e]	x [e]	x [e]	x [e]	x [e]	x [e]		
ECOG Performance Status		x [e]			x [e]			x	
ECG [h]		Perform as clinically indicated [e]							
Hematology [i]		x [j, k]	x [j]	x [j]	x [j]	x [j]	x [j]	x	
Chemistry [l]		x [j, k]	x [j]	x [j]	x [j]	x [j]	x [j]	x	
Coagulation (INR and aPTT)		x [j, k]			x [j]			x	
TSH, free T3 (or total T3), free T4 [m]		x [j, k, m]						x	
CA19-9		x [j]			x [j]			x	
Pregnancy test [o]		x [j, k]			x [j]			x	x [o]

Table A15-6 Schedule of Activities for Atezo + Chemo + Bev Arm (Cohort 1) (cont.)

	Stage 1 Screening (see Appendix 6)	Treatment Cycles (28-day cycles) [a]							Follow-Up [c]
		Cycle 1 [b]			Cycles ≥ 2				
	Day –28 to –1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Treat. Discon. [c]	Every 3 Months
Urinalysis [p]	See Appendix 6	x [q]			x [r]			x	
Serum autoantibody sample [s]		Perform as clinically indicated [t]							
[redacted]		[redacted]							
Tumor response assessments		x [y, z]							
Concomitant medications [aa]		x	x	x	x	x	x	x	
Adverse events [bb]		x	x	x	x	x	x	x [bb]	x [bb]
Atezolizumab administration [cc, dd]		x		x	x		x		
Bevacizumab administration [dd, ee]		x		x	x		x		
Nab-paclitaxel and gemcitabine administration [dd, ff]		x	x	x	x	x	x		
Survival follow-up and anti-cancer treatment									x [gg]

Table A15-6 Schedule of Activities for Atezo + Chemo + Bev Arm (Cohort 1) (cont.)

ADA = anti-drug antibody; Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; CIT = cancer immunotherapy; CT = computed tomography; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; [redacted]; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; 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] 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 at least 7 days after the baseline tumor biopsy (performed at study entry if deemed feasible by the investigator), and it is recommended that treatment be initiated no later than 7 days after randomization.

[c] 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 disease progression is confirmed may be used as the treatment discontinuation visit. Patients will then undergo follow-up assessments.

[d] 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 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 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. For bevacizumab, vital signs should be measured within 60 minutes prior to and within 30 minutes after the infusion.

[e] Assessment may be performed within 24 hours prior to dosing during the treatment period.

[f] 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 new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] 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.

[h] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[i] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[j] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

[k] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

Table A15-6 Schedule of Activities for Atezo + Chemo + Bev Arm (Cohort 1) (cont.)

[l] 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.

[m] 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 third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[n] [redacted]

[o] All women of childbearing potential will have urine or serum pregnancy tests 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.

[p] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[q] Baseline urinalysis to be performed only if screening urinalysis is not performed within 7 days prior to initiation of study treatment. Patients with $\geq$2+ protein on dipstick urinalysis must undergo a 24-hour urine collection and demonstrate $<$1 g of protein in 24 hours.

[r] Urinalysis may be performed up to 72 hours prior to Day 1 of each cycle, as results must be available prior to treatment administration. Patients with Grade 2 proteinuria must undergo a 24-hour urine collection prior to the subsequent bevacizumab infusion. Patients with Grade 3 proteinuria must undergo a 24-hour urine collection prior to the current bevacizumab infusion. Refer to Table A15-5 for details on management of proteinuria.

[s] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[t] Autoantibody analysis should be repeated for patients who develop signs or symptoms suggestive of autoimmune disease (e.g., lupus erythematosus).

[u] 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 A15-6 Schedule of Activities for Atezo + Chemo + Bev Arm (Cohort 1) (cont.)

[redacted]

[redacted]

[redacted]

y Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression, even if they start new non–protocol-specified anti-cancer therapy.

z 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 “y”). 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). Refer to Section 4.5.5 for further details on tumor assessments.

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 10 days prior to initiation of study treatment until the treatment discontinuation visit.

Table A15-6 Schedule of Activities for Atezo + Chemo + Bev Arm (Cohort 1) (cont.)

[bb] [redacted]

After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). 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] 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 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 A15–4.1.2.1, Table A15-2, for details on atezolizumab infusions (including measurement of vital signs).

[dd] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details).

[ee] Bevacizumab will be administered by IV infusion at a dose of 10 mg/kg on Days 1 and 15 of each 28-day cycle. The initial dose of bevacizumab will be delivered over 90 (±15) minutes. Bevacizumab should be infused over 60 (±10) minutes if the previous 90-minute infusion was tolerated without an infusion-related reaction, or 90 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (±5) minutes thereafter. Bevacizumab will be administered after completion of the atezolizumab infusion. Bevacizumab must be administered ≥3 days after any on-treatment biopsy, but only after adequate wound healing has been demonstrated. Refer to Section A15–4.1.2.2, Table A15-3, for details on bevacizumab infusions (including measurement of vital signs).

[ff] On Days 1, 8, and 15, patients will receive nab-paclitaxel 125 mg/m^2, administered by IV infusion over 30 (±5) minutes, followed by gemcitabine 1000 mg/m^2, administered by IV infusion over 30 (±5) minutes. On Days 1 and 15 of each cycle, nab-paclitaxel will be administered after completion of the bevacizumab infusion.

Table A15-6 Schedule of Activities for Atezo + Chemo + Bev Arm (Cohort 1) (cont.)

[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 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 the 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 approximately 20% of patients will be discontinued from the study).

Table A15-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Chemo + Bev Arm (Cohort 1): Preliminary and Expansion Phases

Visit	Time	Sample Type
[redacted]		

ADA = anti-drug antibody; Atezo + Chemo + Bev = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus bevacizumab; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; 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.

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Appendix 16
Study Details Specific to Atezo+Chemo+TCZ Arm (Cohort 1)

TABLE OF CONTENTS

A16–1 BACKGROUND ON ATEZO + CHEMO + TCZ ARM

A16–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. 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, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

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

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

A16–1.2 BACKGROUND ON NAB-PACLITAXEL AND GEMCITABINE IN PANCREATIC CANCER

Nanoparticle albumin–bound paclitaxel (nab-paclitaxel) is a microtubule inhibitor that is approved in combination with gemcitabine for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas. Gemcitabine is a nucleoside metabolic inhibitor that is approved for the treatment of locally advanced or metastatic adenocarcinoma of the pancreas.

The combination of nab-paclitaxel and gemcitabine has been established as the standard-of-care chemotherapy regimen for metastatic pancreatic cancer and is classified as Category 1 (intervention is appropriate based upon high-level evidence) by the National Comprehensive Cancer Network for this indication (Von Hoff et al. 2013; NCCN 2017).

A16–1.3 BACKGROUND ON TOCILIZUMAB

Tocilizumab 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.

Tocilizumab is approved for the treatment of rheumatoid arthritis, systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, cytokine release syndrome (CRS), Castleman disease, giant cell arteritis, and Takayasu arteritis.

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

A16–2 RATIONALE FOR ATEZO + CHEMO + TCZ ARM

A16–2.1 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, 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).

It has been shown that in pancreatic cancer tissues, both PD-L1 and PD-L2 are expressed and that tumor PD-L1 expression significantly correlates with postoperative prognosis. Moreover, PD-L1 expression is inversely correlated with tumor-infiltrating lymphocytes, particularly $CD8^+$ T cells (Nomi et al. 2007). However, no clinically significant response to single-agent checkpoint inhibitors has been observed in patients with pancreatic cancer (Royal et al. 2010; Brahmer et al. 2012).

A16–2.2 THE IL-6 PATHWAY AND PANCREATIC CANCER

IL-6 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, glycoprotein 130 (gp130), JAK, and STAT3 (Chang et al. 2014).

Binding to gp130 initiates the activation of JAK/STAT3, MAPK, and PI3K pathways (Fisher et al. 2014). sIL-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, regulatory T cells, and myeloid-derived suppressor cells (Rose-John et al. 2006; Scheller et al. 2011; Fisher et al. 2014).

IL-6 is the major regulator of the acute phase response, an innate defense mechanism in response to inflammation and injury including cancer. Importantly, C-reactive protein (CRP) is a prominent marker of the acute phase response and IL-6 production (Heinrich et al. 1990). In cancer, there is a significant and direct correlation between serum IL-6 and CRP levels, with both correlating high levels to poor prognosis and lower overall survival (Mahmoud and Rivera 2002).

In pancreatic cancer, activating *KRAS* mutations that occur in 90% of patients induce an inflammatory response leading to the upregulation of IL-6 (Almoguera et al. 1988; Ancrile et al. 2007). IL-6 signaling is required for tumor maintenance and progression (Fukuda et al. 2011; Lesina et al. 2011; Zhang et al. 2013), with high serum IL-6 and CRP levels correlating with advanced tumor stage and poor overall survival (Falconer et al. 1995; Talar-Wojnarowska et al. 2009; Farren et al. 2016).

Additional data indicates that IL-6 interacts with the tumor microenvironment to promote tumor progression in multiple ways. The pancreatic cancer tumor microenvironment is characterized as highly hypoxic and rich with a dense desmoplastic stroma that includes the extracellular matrix, growth factors, enzymes, and cytokines, in addition to fibroblasts, stellate cells, and immune cells (Feig et al. 2012). In pancreatic cancer, IL-6 expression is enhanced by hypoxia (Feurino et al. 2007; Bao et al. 2012), a condition that supports resistance to chemotherapy and radiotherapy, increasing the potential for a more invasive and aggressive disease (Le et al. 2004; Brown 2007). Current data indicate that in pancreatic cancer, IL-6 is produced by several cells including immunosuppressive tumor-associated macrophages and pancreatic stellate cells resident in the tumor stroma (Lesina et al. 2011; Nagathihalli et al. 2016; Wu et al. 2016). Increased IL-6 secretion induces expression of vascular endothelial growth factor (VEGF) and matrix metalloproteinase-2 (MMP2), which can promote angiogenesis and tumor invasion (Masui et al. 2002; Tang et al. 2005; Huang et al. 2010). Moreover, IL-6 may promote a pro-tumorigenic environment by stimulating secretion of Th2 cytokines and suppressing dendritic cell differentiation and activation (Feurino et al. 2007; Bharadwaj et al. 2007). Together, these data indicate that IL-6 contributes to a pro-tumorigenic microenvironment in pancreatic cancer.

A16–2.3 COMBINED INHIBITION OF THE PD-L1 AND ANTI–IL-6 PATHWAYS AS POTENTIAL ANTI-CANCER THERAPY

Preclinical studies show that dual blockade of IL-6 and PD-L1 improved efficacy compared with blockade of either PD-L1 or IL-6 alone in mice bearing subcutaneous tumors of pancreatic cancer (Mace et al. 2018). Observed tumor regression was dependent on the T-effector CD8+ lymphocyte population, and was associated with a concomitant increase in infiltrating T cells and a decrease in fibrotic stroma in the pancreas. Moreover, the combined inhibition of both IL-6 and PD-L1 resulted in more circulating T cells with Th1 phenotypic characteristics and intratumoral effector T cells, suggesting that the tumor microenvironment was becoming less immunosuppressive and more anti-tumorigenic (Mace et al. 2018). Likewise, similar results demonstrating the synergistic effects of IL-6 and PD-L1/PD-1 dual blockade providing improved efficacy have been observed in preclinical tumor lung and melanoma models (Tsukamoto et al. 2018; Ramos-Castaneda et al. 2019).

A16–2.4 CLINICAL STUDIES OF ATEZOLIZUMAB IN COMBINATION WITH TOCILIZUMAB

There are many therapies targeting the IL-6 pathway. However, only tocilizumab and siltuximab are being evaluated in combination with anti-PD-L1/PD-1 therapies in cancer. Tocilizumab, an IL-6 receptor inhibitor, is a drug approved for autoimmune disorders, severe inflammation, and others. Although there have been few evaluations of tocilizumab in patients with cancer, the efficacy and safety of atezolizumab in combination with tocilizumab as a treatment for patients with metastatic urothelial cancer is currently being investigated in Study WO39613. A recent Internal Monitoring Committee (IMC) review of safety data from 10 safety evaluable patients randomized to the atezolizumab plus tocilizumab treatment arm concluded that the combination was well-tolerated, and safety findings were consistent with the known safety profile of each agent. In addition, no new safety signals were identified (Roche data on file).

Two additional on-going studies are evaluating dual IL6 and PD-L1/PD-1 blockade in pancreatic cancer: tocilizumab in combination with nivolumab, ipilimumab, and radiation in patients with advanced pancreatic cancer (NCT04258150); and siltuximab in combination with spartalizumab in patients with metastatic pancreatic cancer (NCT04191421).

A16–2.5 CLINICAL STUDY OF ATEZOLIZUMAB IN COMBINATION WITH NAB-PACLITAXEL AND GEMCITABINE

An ongoing Phase I study (GO30140) includes an arm that is evaluating atezolizumab in combination with nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic cancer.

Adverse events observed to date are consistent with the known risks of atezolizumab, nab-paclitaxel, and gemcitabine. Atezolizumab in combination with cytotoxic chemotherapy has not been associated with additive severe (Grade ≥ 3) toxicities, indicating that atezolizumab can be safely combined with standard chemotherapy. As of the data cutoff date of 24 October 2017, the confirmed objective response rate was 41.7%, the median progression-free survival was 7 months, and the median overall survival was 10.6 months for 24 efficacy-evaluable patients with metastatic pancreatic cancer.

A16–2.6 CLINICAL STUDIES OF TOCILIZUMAB IN COMBINATION WITH CHEMOTHERAPY

Although there have been few evaluations of tocilizumab in patients with cancer, a Phase I dose-escalation study evaluated tocilizumab in combination with carboplatin and doxorubicin in patients with recurrent epithelial ovarian cancer (Dijkgraaf et al. 2015). Patients receiving the 8 mg/kg dose of tocilizumab in combination with carboplatin ad doxorubicin (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$-\alpha$ (TNF-α). There were no dose-limiting toxicities among the 18 patients treated with tocilizumab at doses of up to 8 mg/kg, administered by IV infusion every 4 weeks (Q4W). The most frequent treatment-related events were fatigue, nausea or vomiting, and anorexia, and the most frequent Grade 3 or 4 events were neutropenia, febrile neutropenia, and ileus. There were no treatment-related deaths.

Study JapicCTI-090889 is a Phase I/II multicenter, open-label study that evaluated tocilizumab in combination with gemcitabine in patients with treatment-naive advanced pancreatic cancer and high inflammatory burden (CRP ≥ 2 mg/dL) (Mitsunaga et al. 2017). Fifteen patients received tocilizumab at a dose of 8 mg/kg every 2 weeks (Q2W) with gemcitabine. CRP levels initially decreased in all patients to below baseline levels after tocilizumab administration; decreases were sustained in 2 patients with partial response and 2 patients with stable disease. Patients with modest CRP elevations (≥ 2 to 10 mg/dL) tended to have better median overall survival compared with patients with high CRP (> 10 mg/dL) (5.8 vs. 1.6 months respectively; $p = 0.0937$). While changes in serum IL-6 were negligible in patients who achieved disease control, serum IL-6 levels tended to increase in patients who experienced disease progression. In general, the Q2W tocilizumab regimen combined with gemcitabine was tolerable, with all treated patients experiencing an adverse event and 13 out of 15 patients (87%) experiencing Grade ≥ 3 adverse events. The most frequent Grade ≥ 3 adverse events were thrombocytopenia (40%), leukopenia (40%), and neutropenia (33%). Given that this study enrolled patients with advanced disease with a median CRP of 10.64 mg/dL and a poorer prognosis, the number of patient deaths (6), study drug withdrawals (1), and treatment interruptions (11) that were observed, irrespective of study treatment relatedness, were not unexpected.

Additionally, there is an ongoing Phase II study evaluating tocilizumab in combination with nab-paclitaxel and gemcitabine in patients with unresectable pancreatic cancer (PACTO; NCT02767557), and a Phase Ib/II study evaluating tocilizumab in combination with nab-paclitaxel and atezolizumab in patients with metastatic triple-negative breast cancer (MORPHEUS-TNBC; NCT03424005).

A16–2.7 BENEFIT–RISK ASSESSMENT

Metastatic pancreatic ductal adenocarcinoma (PDAC) is an incurable disease with a high unmet need for improved medical intervention. As described above, tocilizumab offers the potential to re-set the immune system by decreasing regulatory T cells, increasing effector T cells, and decreasing tumor-associated macrophages and myeloid-derived suppressor cells. Additionally, tocilizumab may be able to reshape the tumor microenvironment to be less fibrotic, a major barrier to treatment in pancreatic cancer. Taking into account the potentially synergistic mechanisms of action of tocilizumab with atezolizumab and chemotherapy based on preclinical and clinical data, as well as the manageable safety profiles of the above-described combinations, treatment with atezolizumab, chemotherapy (nab-paclitaxel and gemcitabine), and tocilizumab (Atezo + Chemo + TCZ) appears to have therapeutic potential in PDAC.

Because of the potential for overlapping toxicities, a minimum of 6 patients in the Atezo + Chemo + TCZ arm must complete a safety evaluation before additional patients can be enrolled in that arm (see Section 3.1.3).

A16–2.8 COVID-19 BENEFIT–RISK ASSESSMENT

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those patients with cancer, are a more vulnerable population. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with higher morbidity and mortality in patients with cancer in some retrospective analyses. It is unclear whether or how cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of COVID-19.

Multiple clinical trials using atezolizumab, both as monotherapy and in different combinations, are ongoing during the COVID-19 pandemic. At this time, there is insufficient evidence for a causal association between atezolizumab and an increased risk of COVID-19.

Although the combination of atezolizumab, chemotherapy, and tocilizumab may potentially increase the risk of developing an infection, this is not specific to the risk of infection with SARS-CoV-2 (see Section A16–5.1). Severe COVID-19 is associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and interferon-γ (IFN-γ). Tocilizumab, as an inhibitor of IL-6, may therefore reduce levels of IL-6, which are thought to be partially responsible for the enhanced inflammatory response if a patient develops SARS-Co-2 infection. A single clinical trial with atezolizumab and tocilizumab is ongoing during this COVID-19 pandemic and, although the patient numbers are small, no increased risk of developing COVID-19 or of having a worse outcome has been

observed in patients receiving this combination. Additionally, an interaction of tocilizumab with the COVID-19 vaccines is unlikely.

For additional information on the evaluation of the impact of the COVID-19 pandemic and COVID-19 vaccination on the benefit–risk assessment, please refer to Section 1.5.

A16–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + CHEMO + TCZ ARM

A16–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1680 mg Q4W (1680 mg on Day 1 of each 28-day cycle), which is an approved dosage for atezolizumab.

A16–3.2 RATIONALE FOR TOCILIZUMAB DOSE AND SCHEDULE

Tocilizumab will be administered at a dose of 8 mg/kg Q4W (8 mg/kg on Day 1 of each 28-day cycle), which is the approved dosage for tocilizumab for the treatment of rheumatoid arthritis. In a Phase I dose-escalation study in patients with recurrent epithelial ovarian cancer (Dijkgraaf et al. 2015), pharmacodynamic effects were observed in patients receiving the 8 mg/kg Q4W dose of tocilizumab in combination with carboplatin and doxorubicin (with and without interferon-α2b). There were no dose-limiting or unexpected toxicities among the 18 patients treated with tocilizumab doses of up to 8 mg/kg Q4W (see Section A16–2.6).

The available information, although not specifically addressing the combination of tocilizumab, checkpoint inhibitors, and chemotherapy, suggests that IV administration of tocilizumab 8 mg/kg Q4W in combination with atezolizumab and chemotherapy is reasonable and expected to result in an acceptable safety profile.

This study contains all the safety measures of an early development study in that it enrolls only a well-defined patient population with good performance status that is selected based on the known safety profile of the combination partners. At the same time, the study implements close safety monitoring, including frequent visits of patients to the site, strict inclusion/exclusion criteria, regular investigator calls, and the implementation of an IMC and a Scientific Oversight Committee.

A16–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + CHEMO + TCZ ARM

A16–4.1 TREATMENT IN ATEZO + CHEMO + TCZ 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 Tocilizumab

The tocilizumab drug product will be supplied by the Sponsor as a sterile solution at a concentration of 20 mg/mL in a single-use vials containing 10 mL.

For information on the formulation and handling of tocilizumab, see the pharmacy manual and the Tocilizumab Investigator's Brochure.

A16–4.1.1.3 Nab-Paclitaxel

For information on the formulation, packaging, and handling of nab-paclitaxel, refer to the local prescribing information.

A16–4.1.1.4 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 Atezo + Chemo + TCZ arm will receive treatment as outlined in Table A16-1 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 3.1.2 for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table A16-1 Treatment Regimen for Atezo + Chemo + TCZ Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Tocilizumab 8 mg/kg IV on Day 1 of each cycle • Atezolizumab 1680 mg IV on Day 1 of each cycle [a] • Nab-paclitaxel 125 mg/m^2 IV on Days 1, 8, and 15 of each cycle [b] • Gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 of each cycle

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

[a] Atezolizumab should be administered 2 hours after completion of the tocilizumab infusion on Day 1 of the first two cycles. On Day 1 of subsequent cycles, atezolizumab can be administered after completion of the tocilizumab infusion, as per instructions outlined in Section A16–4.1.2.2.

[b] Nab-paclitaxel will be administered after completion of the atezolizumab infusion.

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

Medication errors 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 5.3.5.12.
No safety data related to overdosing of atezolizumab is available. For information on overdosing of gemcitabine or nab-paclitaxel, refer to the local prescribing information for each agent. 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 IV dose of up to 28 mg/kg; however, dose-related neutropenia was observed.

A16–4.1.2.1 Tocilizumab

Tocilizumab will be administered by IV infusion at a dose of 8 mg/kg on Day 1 of each 28-day cycle. The maximum dose is 800 mg (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.

Tocilizumab should be infused over 60 (± 15) minutes. The infusion speed must be 10 mL/hr for 15 minutes and the increased to 130 mL/hr to complete the dosing over 60 minutes. In exceptional cases of infusion reactions, the infusion time may be extended to up to 6 hours. Vital signs are recommended to be measured within 60 minutes prior to the infusion, during the infusion if clinically indicated, and at 30 (± 10) minutes after the infusion.

Guidelines for medical management of IRRs for tocilizumab are provided in Section A16–5.1.6.

Guidelines for tocilizumab dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A16–5.1.6. Tocilizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A16–4.1.2.2 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1680 mg on Day 1 of each 28-day cycle. Atezolizumab should be administered 2 hours after completion of the tocilizumab infusion on Day 1 of the first two cycles. On Day 1 of subsequent cycles, if the patient has not experienced an infusion-related reaction with the previous infusion, atezolizumab can be administered 30 minutes after completion of the tocilizumab infusion. If the patient has experienced an infusion-related reaction with the previous infusion, atezolizumab should be administered 2 hours after 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 A16-2.

Table A16-2 Administration of First and Subsequent Atezolizumab Infusions

	First Infusion	Subsequent Infusions
Atezolizumab infusion	• 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.	• 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.
Observation period after atezolizumab infusion	• After the atezolizumab infusion, patient should be observed for 60 minutes. • Vital signs should be recorded at 30 (±10) minutes after the infusion. • Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient tolerated the previous atezolizumab infusion well without infusion-associated adverse events, the observation period after the next and following infusions may be reduced to 30 minutes. • If the patient experienced infusion-associated adverse events in the previous infusion, the observation period should be 60 minutes. • If clinically indicated, vital signs should be recorded at 30 (±10) minutes after the infusion.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 2.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A16–5.1.6. Atezolizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A16–4.1.2.3 Nab-Paclitaxel and Gemcitabine

On Days 1, 8, and 15, patients will receive nab-paclitaxel 125 mg/m^2, administered by IV infusion over 30 (±5) minutes, followed by gemcitabine 1000 mg/m^2, administered by IV infusion over 30 (±5) minutes. On Days 1 and 15 of each cycle, nab-paclitaxel will be administered after completion of the atezolizumab infusion.

Nab-paclitaxel and gemcitabine will be administered according to institutional standards 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.

Guidelines for nab-paclitaxel and gemcitabine dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A16–5.1.6. Nab-paclitaxel and gemcitabine treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A16–4.2 CONCOMITANT THERAPY FOR ATEZO + CHEMO + 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 10 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 + Chemo + TCZ 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) per local practice/institutional guidelines or the American Society of Clinical Oncology guidelines for hematopoietic CSFs (Smith et al. 2006) and American Society of Hematology/American Society of Clinical Oncology guidelines for ESAs (Rizzo et al. 2010)

  Evidence supporting the use of long-acting (PEGylated) forms of G-CSF in patients receiving weekly chemotherapy (i.e., nab-paclitaxel) is limited. Thus, investigators should consider giving preference to conventional formulations of G-CSF.

- Oral contraceptives
- 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 after initiation of study treatment
- 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
- 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, nab-paclitaxel, gemcitabine, and tocilizumab should be withheld 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.

  Note: Treatment with atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab should be withheld during CNS-directed radiation therapy.

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 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).

A16–4.2.2 Cautionary Therapy for Atezo + Chemo + TCZ Arm

A16–4.2.2.1 Corticosteroids

Systemic corticosteroids may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids may be administered at the discretion of the investigator.

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 2 for details).

A16–4.2.2.2 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

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 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 CYP3A4, CYP1A2, or CYP2C9 (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.

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

The above lists of cautionary medications are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safety administered with study treatment. In addition, the Medical Monitor is available to advise if questions arise regarding medications not listed above.

A16–4.2.2.3 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 A16–4.2.3) may be used during the study at the discretion of the investigator.

A16–4.2.3 Prohibited Therapy for Atezo + Chemo + 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, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment until disease 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 A16–4.2.1.
- 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 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.
- Systemic immunosuppressive medications, including, but not limited to, the following are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab and tocilizumab:
  - Thalidomide
  - TNF-α inhibitors (e.g., etanercept, infliximab, adalimumab, certolizumab pegol, golimumab)
  - Anti-IL-1 medications (e.g., anakinra, canakinumab)
  - Abatacept
  - Rituximab
  - Anti-IL–6 medications other than tocilizumab (e.g., sarilumab, siltuximab)
  - Oral JAKs (e.g., tofacitinib, baricitinib, ruxolitinib)
  - Conventional synthetic disease-modifying anti-rheumatic drugs (e.g., azathioprine, chlorambucil, chloroquine, hydroxychloroquine, cyclophosphamide, gold, leflunomide, methotrexate, minocycline, mycophenolate mofetil, mycophenolic acid, d-penicillamine, sulfasalazine)
  - Calcineurin inhibitors (e.g., tacrolimus and cyclosporine)

A16–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + CHEMO + TCZ ARM

Contraception requirements for women and men in the Atezo + Chemo + TCZ 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 3 months after the last dose of tocilizumab, 5 months after the last dose of atezolizumab, 6 months after the last dose of nab-paclitaxel or 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 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 methods, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men who are receiving chemotherapy 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 nab-paclitaxel or gemcitabine and men who are not receiving chemotherapy must remain abstinent or use a condom during the treatment period and for 2 months after the last dose of tocilizumab. 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 2 months after the last dose of tocilizumab and 6 months after the last dose of nab-paclitaxel 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 contraception.

A16–5 ASSESSMENT OF SAFETY FOR ATEZO + CHEMO + TCZ ARM

A16–5.1 SAFETY PLAN FOR ATEZO + CHEMO + TCZ ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab 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, A16–5.1.4, and A16–5.1.5). Guidelines for management of patients who experience specific adverse events are provided in Section A16–5.1.6.

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. 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.

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 may lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 2 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 Nab-Paclitaxel

The following are the most common adverse events observed with nab-paclitaxel in patients with PDAC: neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. The following adverse events have also been observed: myelosuppression (primarily neutropenia, anemia, thrombocytopenia), cranial nerve palsies, hypersensitivity reactions, pneumonitis, myalgia, arthralgia, cardiotoxicity (myocardial disorders, cardiac failure, angina, tachycardia, ventricular arrhythmia), cystoid macular edema, Stevens-Johnson syndrome/toxic epidermal necrolysis, sepsis, infusion-site reactions/extravasation, hepatic toxicity (drug-induced liver injury), acute renal failure, scleroderma, and drug-induced lupus erythematous.

For more details regarding the safety profile for nab-paclitaxel, refer to the nab-paclitaxel prescribing information.

A16–5.1.3 Risks Associated with Gemcitabine

The most common adverse events observed with gemcitabine are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased ALP, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema. The following adverse events have also been observed: renal failure, hemolytic-uremic syndrome, interstitial pneumonitis, myocardial infarction, arrhythmia, and heart failure.

For more details regarding the safety profile for gemcitabine, refer to the gemcitabine prescribing information.

A16–5.1.4 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 infections (including opportunistic and serious infections), hypersensitivity (including anaphylaxis and fatal IRRs), GI disorders (including GI perforation), skin and subcutaneous tissue disorders (rash, pruritus, urticaria), nervous system disorders (including headache and dizziness), hematologic abnormalities (neutropenia, thrombocytopenia), elevated lipids (cholesterol, triglycerides), hepatotoxicity (hepatitis, jaundice, and serious drug-induced liver injury, including acute liver failure), respiratory events (cough, dyspnea), hypertension, conjunctivitis, nephrolithiasis, and hypothyroidism. Additional potential risks include demyelinating disorders, Stevens-Johnson syndrome, malignancies, CYP450 enzyme normalization, and immunogenicity.

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving tocilizumab. The effects of tocilizumab on high-sensitivity CRP, neutrophils, and the signs and symptoms of infection should be considered when evaluating a patient for 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.

Patients should be made aware of the symptoms potentially indicative of diverticular disease, and they should be instructed to alert their doctor as soon as possible if these symptoms arise.

The effect of treatment with tocilizumab on demyelinating disorder is not known; events have rarely been reported. Patients should be closely monitored for signs and symptoms potentially indicative of central demyelinating disorders.

Refer to the Tocilizumab Investigator's Brochure for a detailed description of all anticipated risks for tocilizumab.

A16–5.1.5 Risks Associated with Combination Use of Atezolizumab, Nab-Paclitaxel, Gemcitabine, and Tocilizumab

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab: IRRs, dermatologic events, hepatic events, hypersensitivity, pneumonitis, infections, GI events, neutropenia, and thrombocytopenia.

A16–5.1.6 Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm

On Day 1 of each cycle, patients are required to have an ANC of $\geq 1.5 \times 10^9$/L (1500/μL) and a platelet count of $\geq 100 \times 10^9$/L (100,000/μL) to receive treatment with nab-paclitaxel and gemcitabine. Guidelines for management of hematologic toxicities and other toxicities (including guidelines for dose modification and treatment interruption or discontinuation) are provided in Table A16-4.

A16–5.1.6.1 Dose Modifications

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

For management of drug-related toxicities, the dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times, the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times, and the dose of tocilizumab may be reduced by 4 mg/kg (one dose level) up to one time, as outlined in Table A16-3.

Table A16-3 Recommended Dose Reductions for Nab-Paclitaxel, Gemcitabine and Tocilizumab

	Initial Dose	First Dose Reduction	Second Dose Reduction
Nab-paclitaxel	125 mg/m^2	100 mg/m^2	75 mg/m^2
Gemcitabine	1000 mg/m^2	800 mg/m^2	600 mg/m^2
Tocilizumab	8 mg/kg	4 mg/kg	NA

NA = not applicable; Nab-paclitaxel = nanoparticle albumin–bound paclitaxel.

If further dose reduction is indicated for nab-paclitaxel and/or gemcitabine after two dose reductions, that drug (or both drugs, if applicable) should be discontinued, but the patient

may continue other study treatments at the investigator's discretion. If further dose reduction is indicated for tocilizumab after one dose reduction, tocilizumab should be discontinued, but the patient may continue other study treatments at the investigator's discretion.

After any dose reduction, the dose may be escalated during subsequent administrations at the investigator's discretion.

A16–5.1.6.2 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 > 12 weeks, 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 investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.

Nab-paclitaxel and/or gemcitabine treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table A16-4). If nab-paclitaxel or gemcitabine have been withheld for > 56 days because of toxicity, the patient should be discontinued from both chemotherapy agents. However, nab-paclitaxel or gemcitabine can be resumed after being withheld for > 56 days if the patient is likely to derive clinical benefit. The decision to re-challenge patients with nab-paclitaxel and/or gemcitabine should be based on investigator's assessment of benefit–risk 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. If tocilizumab has been withheld for > 12 weeks, the patient should be discontinued from tocilizumab. However, tocilizumab 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 tocilizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.

If atezolizumab, nab-paclitaxel, gemcitabine, or tocilizumab is discontinued, the other drugs can be continued if the patient is likely to derive clinical benefit, as determined by the investigator, with one exception: if atezolizumab, nab-paclitaxel and gemcitabine are discontinued, tocilizumab should also be discontinued.

Refer to Section A16–4.1.2 for information on dose interruptions for reasons other than toxicity.

A16–5.1.6.3 Management Guidelines for Adverse Events

Guidelines for management of patients who experience specific adverse events are provided in Table A16-4. 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.

The investigator may use discretion in adhering to the guidelines for nab-paclitaxel 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.

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reactions	
General guidance	• Guidelines for management of IRRs and CRS for atezolizumab are provided in Appendix 2. • Guidelines for management of IRRs for tocilizumab and chemotherapy are provided below. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue the causative agent.
IRR to chemotherapy, 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 chemotherapy, Grade 2	• Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, administer oral premedication with antihistamine and antipyretic and monitor closely for IRRs.

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reactions (cont.)	
IRR to chemotherapy, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue treatment and contact Medical Monitor. [a]
IRR to tocilizumab	• If patient has symptoms of anaphylaxis or serious hypersensitivity or requires an interruption of tocilizumab because of symptoms of anaphylaxis or hypersensitivity, permanently discontinue tocilizumab. [a] Obtain blood samples at the time of the event and 8 weeks after the final dose of tocilizumab to enable pharmacokinetic, immunogenicity, and biomarker testing. • For lower grade IRR, initiate treatment as per institutional guidelines for management of IRRs and/or hypersensitivity reactions.
Hemophagocytic lymphohistiocytosis	• Follow guidelines for atezolizumab in Appendix 2. • Withhold all treatment and contact Medical Monitor.

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity	
Diarrhea or colitis, Grade 1	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel, gemcitabine, and tocilizumab.
Diarrhea or colitis, Grade 2	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine. Continue tocilizumab for Grade 2 diarrhea. Withhold tocilizumab for Grade 2 colitis. • If colitis resolved to Grade 1 or better ≤ 12 weeks after event onset, resume tocilizumab. If not, permanently discontinue tocilizumab. [a]
Diarrhea or colitis, Grade 3	• Follow guidelines for atezolizumab in Appendix 2. • Withhold nab-paclitaxel, gemcitabine, and tocilizumab. • If event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine with dose reduced by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If event resolves to Grade 1 or better ≤ 12 weeks after event onset, resume tocilizumab. If not, permanently discontinue tocilizumab. [a]
Diarrhea or colitis, Grade 4	• Follow guidelines for atezolizumab in Appendix 2. • Permanently discontinue nab-paclitaxel, gemcitabine, and tocilizumab. [a]

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Mucositis, Grade 1 or 2	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab.
Mucositis, Grade 3	• Continue atezolizumab. Withhold nab-paclitaxel, gemcitabine, and tocilizumab. • If event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine with dose reduced by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If event resolved to Grade 1 or better ≤ 12 weeks after event onset, resume tocilizumab. If not, permanently discontinue tocilizumab. [a]
Mucositis, Grade 4	• Permanently discontinue atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab. [a]
Hemolytic-uremic syndrome	
Hemolytic-uremic syndrome, any grade	• Permanently discontinue gemcitabine. [a] Withhold atezolizumab, nab-paclitaxel, and tocilizumab. • If event improves, resume atezolizumab, nab-paclitaxel, and tocilizumab. If not, permanently discontinue atezolizumab, nab-paclitaxel, and tocilizumab. [a]
Capillary leak syndrome	
Capillary leak syndrome, any grade	• Permanently discontinue gemcitabine. [a] Withhold atezolizumab, nab-paclitaxel, and tocilizumab. • If event improves, resume atezolizumab, nab-paclitaxel, and tocilizumab. If not, permanently discontinue atezolizumab, nab-paclitaxel, and tocilizumab. [a]

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Dermatologic toxicity	
Dermatologic event, Grade 1	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel, gemcitabine, and tocilizumab.
Dermatologic event, Grade 2	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine with dose reduced by one level. [b] Continue tocilizumab. • If event persists, permanently discontinue nab-paclitaxel and gemcitabine. [a]
Dermatologic event, Grade 3	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel and gemcitabine with dose reduced by one level. [b] Withhold tocilizumab. • If event persists, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If event resolves to Grade 1 or better ≤ 12 weeks after event onset, resume tocilizumab. If not, permanently discontinue tocilizumab. [a]
Dermatologic event, Grade 4	• Follow guidelines for atezolizumab in Appendix 2. • Permanently discontinue nab-paclitaxel, gemcitabine, and tocilizumab. [a]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Withhold atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab.

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Serious Infection	
Any grade	• Withhold atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab. • If infection resolves, atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab may be continued at the discretion of the investigator. • If nab-paclitaxel and gemcitabine are withheld > 56 days after event onset, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If atezolizumab has been withheld for > 12 weeks after event onset, permanently discontinue atezolizumab. [a] • If tocilizumab has been withheld for > 12 weeks after event onset, permanently discontinue tocilizumab. [a]
Febrile neutropenia	
Grade 3 or 4	• Withhold atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab. • If fever resolves and ANC improves to $\geq 1.5 \times 10^9$/L (1500/μL) ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine with dose reduced by one level [b]. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If fever resolves and ANC improves to $\geq 1.5 \times 10^9$/L (1500/μL) ≤ 12 weeks after event onset, resume atezolizumab and tocilizumab. If not, permanently discontinue atezolizumab and tocilizumab. [a] • If treatment is resumed, G-CSF should be strongly considered for subsequent cycles.

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity at Day 1 (excluding febrile neutropenia)	
ANC $\geq 1.5 \times 10^9$/L (1500/μL) **and** Platelet count $\geq 100 \times 10^9$/L (100,000/μL)	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab.
ANC $\geq 0.5 \times 10^9$/L (500/μL) but $< 1.5 \times 10^9$/L (1500/μL) **And/or** Platelet count $\geq 50 \times 10^9$/L (50,000/μL) but $< 100 \times 10^9$/L (100,000/μL)	• Continue atezolizumab. Withhold nab-paclitaxel, gemcitabine, and tocilizumab. • Permanently discontinue nab-paclitaxel and gemcitabine if withheld > 56 days after event onset. [a] • If event improves, resume tocilizumab at 4 mg/kg. If not, permanently discontinue tocilizumab. [a] • For recurrent neutropenia, permanently discontinue tocilizumab. [a] G-CSF should be strongly considered for subsequent cycles.
ANC $< 0.5 \times 10^9$/L (500/μL) **and/or** Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Continue atezolizumab. Withhold nab-paclitaxel and gemcitabine. Permanently discontinue tocilizumab. [a] • Permanently discontinue nab-paclitaxel or gemcitabine if withheld > 56 days after event onset. [a] • For recurrent neutropenia, G-CSF should be strongly considered for subsequent cycles.

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity at Day 8 (excluding febrile neutropenia)	
ANC $\geq 1.0 \times 10^9$/L (1000/μL) **and** Platelet count $\geq 75 \times 10^9$/L (75,000/μL)	• Continue nab-paclitaxel, gemcitabine, and tocilizumab.
ANC $\geq 0.5 \times 10^9$/L (500/μL) but $< 1.0 \times 10^9$/L (1000/μL) **and/or** Platelet count $\geq 50 \times 10^9$/L (50,000/μL) but $< 75 \times 10^9$/L (75,000/μL)	• Continue nab-paclitaxel and gemcitabine with dose reduced by one level. [b] • Continue tocilizumab. • For recurrent neutropenia, permanently discontinue tocilizumab. [a] G-CSF should be strongly considered for subsequent cycles.
ANC $< 0.5 \times 10^9$/L (500/μL) **and/or** Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Withhold nab-paclitaxel and gemcitabine. • Permanently discontinue tocilizumab. [a] • If nab-paclitaxel and gemcitabine are withheld > 56 days after event onset, permanently discontinue nab-paclitaxel and gemcitabine. [a] • For recurrent neutropenia, G-CSF should be strongly considered for subsequent cycles.

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity at Day 15 (excluding febrile neutropenia): Day 8 doses given without modification	
ANC $\geq 1.0 \times 10^9$/L (1000/μL) **and** Platelet count $\geq 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab.
ANC $\geq 0.5 \times 10^9$/L (500/μL) but $< 1.0 \times 10^9$/L (1000/μL) **and/or** Platelet count $\geq 50 \times 10^9$/L (50,000/μL) but $< 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab. Continue nab-paclitaxel and gemcitabine at current dose followed by G-CSF support **or** with dose reduced by one level. [b] • Withhold tocilizumab. • If event improves, resume tocilizumab at 4 mg/kg. If not, permanently discontinue tocilizumab. [a] • For recurrent neutropenia, permanently discontinue tocilizumab. [a] G-CSF should be strongly considered for subsequent cycles.
ANC $< 0.5 \times 10^9$/L (500/μL) **and/or** Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Withhold atezolizumab, nab-paclitaxel, and gemcitabine. • Permanently discontinue tocilizumab. [a] • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. [a] • If nab-paclitaxel and gemcitabine are withheld > 56 days after event onset, permanently discontinue nab-paclitaxel, and gemcitabine. [a] • For recurrent neutropenia, G-CSF should be strongly considered for subsequent cycles.

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity at Day 15 (excluding febrile neutropenia): Day 8 doses reduced	
ANC $\geq 1.0 \times 10^9$/L (1000/μL) **and** Platelet count $\geq 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab. • Continue nab-paclitaxel and gemcitabine at Day 1 doses followed by G-CSF support **or** at current dose. • Continue tocilizumab.
ANC $\geq 0.5 \times 10^9$/L (500/μL) but $< 1.0 \times 10^9$/L (1000/μL) **and/or** Platelet count $\geq 50 \times 10^9$/L (50,000/μL) but $< 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab. Continue nab-paclitaxel and gemcitabine at current dose followed by G-CSF support **or** with dose reduced by one level. [b] • Withhold tocilizumab. • If event improves, resume tocilizumab at 4 mg/kg. If not, permanently discontinue tocilizumab. [a] • For recurrent neutropenia, permanently discontinue tocilizumab. [a] G-CSF should be strongly considered for subsequent cycles.
ANC $< 0.5 \times 10^9$/L (500/μL) **and/or** Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Withhold atezolizumab, nab-paclitaxel, and gemcitabine. • Permanently discontinue tocilizumab. [a] • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. [a] • If nab-paclitaxel and gemcitabine are withheld > 56 days after event onset, permanently discontinue nab-paclitaxel and gemcitabine. [a] • For recurrent neutropenia, G-CSF should be strongly considered for subsequent cycles.

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity at Day 15 (excluding febrile neutropenia): Day 8 treatment was withheld	
ANC $\geq 1.0 \times 10^9$/L (1000/μL) **and** Platelet count $\geq 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab. Continue nab-paclitaxel and gemcitabine at current dose followed by G-CSF support **or** with dose reduced by one level. [b] • Continue tocilizumab.
ANC $\geq 0.5 \times 10^9$/L (500/μL) but $< 1.0 \times 10^9$/L (1000/μL) **and/or** Platelet count $\geq 50 \times 10^9$/L (50,000/μL) but $< 75 \times 10^9$/L (75,000/μL)	• Continue atezolizumab. Continue nab-paclitaxel and gemcitabine with dose reduced by one level followed by G-CSF support **or** with dose reduced by two levels. [b] • Withhold tocilizumab. • If event improves, resume tocilizumab at 4 mg/kg. If not, permanently discontinue tocilizumab. [a] • For recurrent neutropenia, permanently discontinue tocilizumab. [a] G-CSF should be strongly considered for subsequent cycles.
ANC $< 0.5 \times 10^9$/L (500/μL) **and/or** Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Withhold atezolizumab, nab-paclitaxel, and gemcitabine. • Permanently discontinue tocilizumab. [a] • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. [a] • If nab-paclitaxel and gemcitabine are withheld > 56 days after event onset, permanently discontinue nab-paclitaxel and gemcitabine. [a] • For recurrent neutropenia, G-CSF should be strongly considered for subsequent cycles.

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Pulmonary events	
Pulmonary event, Grade 1	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel, gemcitabine, and tocilizumab. • If diagnosis of pneumonitis is confirmed, permanently discontinue nab-paclitaxel and gemcitabine. [a]
Pulmonary event, Grade 2	• Follow guidelines for atezolizumab in Appendix 2. • Withhold nab-paclitaxel, gemcitabine, and tocilizumab. • If diagnosis of pneumonitis is confirmed, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If non-pneumonitis event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If event resolves to Grade 1 or better ≤ 12 weeks after event onset, resume tocilizumab. If not, permanently discontinue tocilizumab. [a] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 2. • Permanently discontinue nab-paclitaxel, gemcitabine, and tocilizumab. [a]

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Elevations in AST, ALT, and/or bilirubin	
General Guidance	• In patients experiencing elevations in AST/ALT and/or bilirubin, concurrent medications, viral hepatitis, and other possible etiologies should be considered and addressed as appropriate.
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin ≤ 2 × ULN	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab. • For persistent increases (two or more consecutive assessments at least 1 month apart) in patients who did not have elevated screening values, either reduce tocilizumab dose to 4 mg/kg or withhold tocilizumab. • If tocilizumab is withheld and values return to baseline within 12 weeks, resume tocilizumab. If not, consult with Medical Monitor to determine if tocilizumab should be permanently discontinued.
AST/ALT > 3 ULN to 5 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue atezolizumab, nab-paclitaxel, and gemcitabine. Withhold tocilizumab if AST/ALT and total bilirubin are elevated from baseline values. • For persistent increases (two or more consecutive assessments at least 1 month apart) in patients who did not have elevated screening values, permanently discontinue tocilizumab. [a] • Monitor LFTs at least weekly. • Consider patient referral to a hepatologist and liver biopsy. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN (or to baseline for patients who had elevated screening values) within 8 weeks, resume tocilizumab and consider reduction the dose to 4 mg/kg if AST/ALT is > ULN. If not, permanently discontinue tocilizumab. [a] **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, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a]

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Elevations in AST, ALT, and/or bilirubin (cont.)	
AST/ALT > 5 × ULN to < 10 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue atezolizumab, nab-paclitaxel, and gemcitabine. Permanently discontinue tocilizumab. [a] • Monitor LFTs at least weekly. • Consider patient referral to hepatologist and liver biopsy. **Suspected immune-mediated events:** • Withhold atezolizumab. • 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 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a]
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin > 2 × ULN	• Withhold atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab. • If event resolves to total bilirubin ≤ 2 × ULN within 56 days, resume nab-paclitaxel and gemcitabine with the dose reduced by one level. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If event resolves to total bilirubin ≤ 2 × ULN within 12 weeks, resume atezolizumab and tocilizumab. If not, permanently discontinue atezolizumab and tocilizumab and contact Medical Monitor. [a] • For persistent increases (two or more consecutive assessments at least 1 month apart) in patients who did not have elevated screening values, permanently discontinue tocilizumab. [a]

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Elevations in AST, ALT, and/or bilirubin (cont.)	
AST/ALT > 3 × ULN to ≤ 10 × ULN with total bilirubin > 2 × ULN	• Withhold atezolizumab, nab-paclitaxel, and gemcitabine. Permanently discontinue tocilizumab. [a] • 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 initiation and event does not improve within 48 hours, considering adding an immunosuppressive agent. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine with the dose reduced by one level. If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks, resume atezolizumab. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a] • Permanently discontinue atezolizumab, nab-paclitaxel, and gemcitabine for life-threatening hepatic events and contact the Medical Monitor. [a]
AST/ALT > 10 × ULN	• Permanently discontinue nab-paclitaxel, gemcitabine, and tocilizumab, and contact Medical Monitor. [a] • 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, considering adding an immunosuppressive agent or escalating the corticosteroid dose. • If event resolved to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN, taper corticosteroids over ≥ 1 month.

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Endocrine events	
Asymptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel, gemcitabine, and tocilizumab.
Symptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 2. • Withhold nab-paclitaxel, gemcitabine and tocilizumab. • When symptoms are controlled and thyroid function is improving, resume nab-paclitaxel, gemcitabine, and tocilizumab.
Asymptomatic hyperthyroidism	**TSH ≥1.0 mU/L and <0.5 mU/L:** • Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel, gemcitabine, and tocilizumab. **TSH ≤1.0 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Follow guidelines for atezolizumab in Appendix 2. • Withhold nab-paclitaxel, gemcitabine, and tocilizumab. • When symptoms are controlled and thyroid function is improving, resume nab-paclitaxel, gemcitabine, and tocilizumab.

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Neurologic disorder	
General guidance	• If the patient has a potential demyelination event, withhold tocilizumab to assess for a demyelinating disorder. • Tocilizumab may be resumed at the discretion of the investigator.
Immune-mediated neuropathy, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel, gemcitabine, and tocilizumab.
Immune-mediated neuropathy, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 2. • Continue gemcitabine and tocilizumab. Withhold nab-paclitaxel. • If event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel with dose reduced by one level and resume tocilizumab. [b] If not, permanently discontinue nab-paclitaxel and tocilizumab. [a]
Non–immune-mediated neuropathy, Grade 1 or 2	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab.
Non–immune-mediated neuropathy, Grade 3 or 4	• Continue atezolizumab, gemcitabine, and tocilizumab. Withhold nab-paclitaxel. • If event resolves to Grade 1 or better ≤ 56 days after event onset, resume nab-paclitaxel with dose reduction by one level. [b] If not, permanently discontinue nab-paclitaxel. [a]
Immune-mediated meningoencephalitis, any grade	• Follow guidelines for atezolizumab in Appendix 2. • Withhold nab-paclitaxel, gemcitabine, and tocilizumab. • If event stabilizes ≤ 56 days after event onset, resume nab-paclitaxel, gemcitabine, and tocilizumab. If not, permanently discontinue nab-paclitaxel, gemcitabine, and tocilizumab. [a]

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Chemotherapy-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab.
Grade 3	• Continue atezolizumab. Withhold nab-paclitaxel, gemcitabine, and tocilizumab. • If event resolves to Grade 2 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine and consider reducing dose by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If event resolves to Grade 2 or better ≤ 12 weeks after event onset, resume tocilizumab and consider reducing dose to 4 mg/kg. If not, permanently discontinue tocilizumab. [a]
Grade 4	• Withhold atezolizumab, tocilizumab, nab-paclitaxel, and gemcitabine. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. [a] • If event resolves to Grade 2 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine and consider reducing dose by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] • If event resolves to Grade 2 or better ≤ 12 weeks after event onset, resume tocilizumab and consider reducing dose to 4 mg/kg. If not, permanently discontinue tocilizumab. [a]

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Tocilizumab-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab, nab-paclitaxel, gemcitabine, and tocilizumab.
Grade 3	• Continue atezolizumab. Withhold tocilizumab, nab-paclitaxel, and gemcitabine. • If event resolves to Grade 2 or better ≤56 days after event onset, resume nab-paclitaxel and gemcitabine, and consider reducing nab-paclitaxel and gemcitabine dose by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] **First event:** • If event resolves to Grade 2 or better ≤12 weeks after event onset, resume tocilizumab and consider reducing dose to 4 mg/kg. If not, permanently discontinue tocilizumab. [a] **Second and subsequent events:** • If event resolves to Grade 1 or better ≤12 weeks after event onset, resume tocilizumab and consider reducing dose to 4 mg/kg. If not, permanently discontinue tocilizumab. [a]
Grade 4	• Withhold atezolizumab, tocilizumab, nab-paclitaxel, and gemcitabine. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. [a] • If event resolves to Grade 2 or better ≤56 days after event onset, resume nab-paclitaxel and gemcitabine, and consider reducing nab-paclitaxel and gemcitabine dose by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] **First event:** • If event resolves to Grade 2 or better ≤12 weeks after event onset, resume tocilizumab and consider reducing dose to 4 mg/kg. If not, permanently discontinue tocilizumab. [a] **Second and subsequent events:** • If event resolves to Grade 1 or better ≤12 weeks after event onset, resume tocilizumab and consider reducing dose to 4 mg/kg. If not, permanently discontinue tocilizumab. [a]

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

Table A16-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Chemo + TCZ Arm (cont.)

Event	Action to Be Taken
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 2. • Continue nab-paclitaxel, gemcitabine, and tocilizumab.
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 2. • Withhold nab-paclitaxel, gemcitabine, and tocilizumab. • If event resolves to Grade 2 or better ≤ 56 days after event onset, resume nab-paclitaxel and gemcitabine, and consider reducing nab-paclitaxel and gemcitabine dose by one level. [b] If not, permanently discontinue nab-paclitaxel and gemcitabine. [a] **First event:** • If event resolves to Grade 2 or better ≤ 12 weeks after event onset, resume tocilizumab and consider reducing dose to 4 mg/kg. If not, permanently discontinue tocilizumab. [a] **Second and subsequent events:** • If event resolves to Grade 1 or better ≤ 12 weeks after event onset, resume tocilizumab and consider reducing dose to 4 mg/kg. If not, permanently discontinue tocilizumab. [a]

Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[b] The dose of nab-paclitaxel may be reduced by 25 mg/m^2 (one dose level) up to two times and the dose of gemcitabine may be reduced by 200 mg/m^2 (one dose level) up to two times (see Section A16–5.1.6.1 for details).

A16–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + CHEMO + 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 for reporting instructions). Adverse events of special interest for the Atezo + Chemo + TCZ 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
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, CRS, influenza-like illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- [redacted]
- Serious and/or medically significant infections
- Myocardial infarction or acute coronary syndrome
- GI perforations
- Malignancies
- Demyelinating disorders
- Stroke
- Serious and/or medically significant bleeding events
- Serious and/or medically significant hepatic events
- [redacted]
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

- Myelitis
- Facial paresis

A16–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + CHEMO + TCZ 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 3 months after the last dose of tocilizumab, 5 months after the last dose of atezolizumab, or 6 months after the last dose of nab-paclitaxel or gemcitabine. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study 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 2 months after the last dose of tocilizumab, or 6 months after the last dose of nab-paclitaxel or gemcitabine. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. 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

Any 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).

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 + CHEMO + TCZ ARM

Table A16-5 Schedule of Activities for Atezo + Chemo + TCZ Arm (Cohort 1)

	Stage 1 Screening (see Appendix 6)	Treatment Cycles (28-day cycles) [a]							Follow-Up [c]
		Cycle 1 [b]			Cycles ≥ 2				
	Day –28 to –1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Treat. Discon. [c]	Every 3 Months
Molecular profile of pancreatic cancer (if available)	See Appendix 6	Whenever updated information becomes available							
Vital signs [d]		x	x	x	x	x	x	x	
Weight		x [e]	x [e]	x [e]	x [e]	x [e]	x [e]	x	
Complete physical examination [f]								x	
Limited physical examination [g]		x [e]	x [e]	x [e]	x [e]	x [e]	x [e]		
ECOG Performance Status		x [e]			x [e]			x	
ECG [h]		Perform as clinically indicated [e]							
Hematology [i]		x [j, k]	x [j]	x [j]	x [j]	x [j]	x [j]	x	
Chemistry [l]		x [j, k]	x [j]	x [j]	x [j]	x [j]	x [j]	x	
Coagulation (INR and aPTT)		Perform as clinically indicated						x	
TSH, free T3 (or total T3), free T4 [m]		x [j, k, m]						x	
[redacted]									
CA19-9		x [j]			x [j]			x	
C-reactive protein		x [j]	x [j]	x [j]	x [j]			x	

Table A16-5 Schedule of Activities for Atezo + Chemo + TCZ Arm (Cohort 1) (cont.)

	Stage 1 Screening (see Appendix 6)	Treatment Cycles (28-day cycles) [a]							
		Cycle 1 [b]			Cycles ≥ 2				Follow-Up [c]
	Day –28 to –1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Treat. Discon. [c]	Every 3 Months
Pregnancy test [o]	See Appendix 6	x [j, k]			x [j]			x	x [o]
Urinalysis [p]		Perform as clinically indicated							
[redacted]		[redacted]							
Tumor response assessments		x [v, w]							
Concomitant medications [x]		x	x	x	x	x	x	x	
Adverse events [y]		x	x	x	x	x	x	x [y]	x [y]
Tocilizumab administration [z, aa]		x			x				
Atezolizumab administration [aa, bb]		x			x				
Nab-paclitaxel and gemcitabine administration [aa, cc]		x	x	x	x	x	x		
Survival follow-up and anti-cancer treatment									x [dd]

Table A16-5 Schedule of Activities for Atezo + Chemo + TCZ Arm (Cohort 1) (cont.)

ADA = anti-drug antibody; Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; CIT = cancer immunotherapy; CT = computed tomography; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; [redacted] nab-paclitaxel = nanoparticle albumin–bound paclitaxel; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; 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] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.

[b] It is recommended that treatment be initiated no later than 7 days after randomization.

[c] 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 disease progression is confirmed may be used as the treatment discontinuation visit. Patients will then undergo follow-up assessments.

[d] 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 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 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. For tocilizumab, vital signs should be measured within 60 minutes prior to, during the infusion if clinically indicated, and within 30 (±10) minutes after the infusion.

[e] Assessment may be performed within 24 hours prior to dosing during the treatment period.

[f] 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 new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] 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.

[h] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[i] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[j] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

Table A16-5 Schedule of Activities for Atezo + Chemo + TCZ Arm (Cohort 1) (cont.)

[k] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[l] 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.

[m] 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 third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[n] [redacted]

[o] All women of childbearing potential will have urine or serum pregnancy tests 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.

[p] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[q] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[r] Autoantibody analysis should be repeated for patients who develop signs or symptoms suggestive of autoimmune disease (e.g., lupus erythematosus).

[s] 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.

[t] [redacted]

[u]

Table A16-5 Schedule of Activities for Atezo + Chemo + TCZ Arm (Cohort 1) (cont.)

[v] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression, even if they start new non–protocol-specified anti-cancer therapy.

[w] 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"). 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). Refer to Section 4.5.5 for further details on tumor assessments.

[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 10 days prior to initiation of study treatment until the treatment discontinuation visit.

[y] [redacted] After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). 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.

[z] Tocilizumab will be administered by IV infusion at a dose of 8 mg/kg on Day 1 of each 28-day cycle, with a maximum dose of 800 mg tocilizumab (for patients weighing >100 kg). Tocilizumab should be infused over 60 (±15) minutes. 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. In exceptional cases of infusion reactions, the infusion time may be extended to up to 6 hours.

[aa] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details).

Table A16-5 Schedule of Activities for Atezo + Chemo + TCZ Arm (Cohort 1) (cont.)

[bb] Atezolizumab will be administered by IV infusion at a fixed dose of 1680 mg on Day 1 of each 28-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 A16–4.1.2.2, Table A16-2, for details on atezolizumab infusions (including measurement of vital signs).

[cc] On Days 1, 8, and 15 of each cycle, patients will receive nab-paclitaxel 125 mg/m^2, administered by IV infusion over 30 (±5) minutes, followed by gemcitabine 1000 mg/m^2, administered by IV infusion over 30 (±5) minutes. On Days 1 and 15 of each cycle, nab-paclitaxel will be administered after completion of the atezolizumab infusion.

[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 the 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 approximately 20% of patients will be discontinued from the study).

Table A16-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Chemo + TCZ Arm (Cohort 1): Preliminary and Expansion Phases

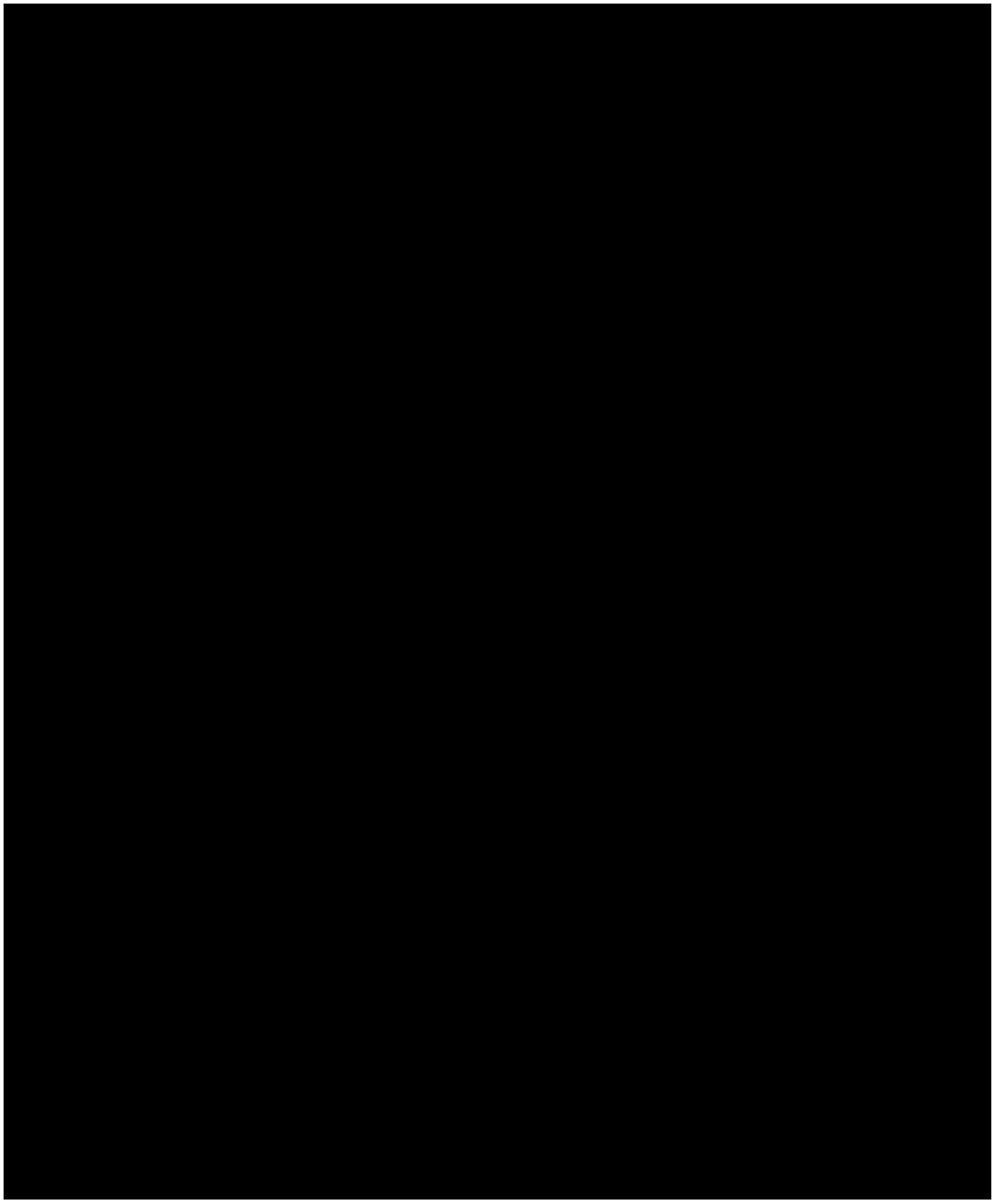

Table A16-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Chemo + TCZ Arm (Cohort 1): Preliminary and Expansion Phases (cont.)

Visit	Time	Sample Type
[redacted]		

ADA = anti-drug antibody; Atezo + Chemo + TCZ = atezolizumab plus chemotherapy (nab-paclitaxel and gemcitabine) plus tocilizumab; nab-paclitaxel = nanoparticle albumin–bound paclitaxel; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; 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.

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Appendix 17
Investigational Medicinal Product Designations (for Use in European Economic Area)

Table A17-1 Investigational Medicinal Product Designations for European Economic Area

Product Name	IMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product)	Approved	No [a]
Nab-paclitaxel	IMP (comparator)	Approved	No [b]
Bevacizumab (RO4876646)	IMP (test product)	Approved	No
Gemcitabine	IMP (comparator)	Approved	No [c]
Fluorouracil	IMP (comparator)	Approved	No [d, e]
Oxaliplatin	IMP (comparator)	Approved	No [a, d]
Leucovorin	IMP (comparator)	Approved	No [d, f]
Tiragolumab (RO7092284)	IMP (test product)	Not approved	Not applicable
AB928 [j]	IMP (test product)	Not approved	Not applicable
Tocilizumab (RO4877533)	IMP (test product)	Approved	No [a]
Cobimetinib (RO5514041) [g]	IMP (test product)	Approved	No [a]
PEGPH20 [g]	IMP (test product)	Not approved	Not applicable
BL-8040 [h]	IMP (test product)	Not approved	Not applicable
Selicrelumab [g]	IMP (test product)	Not approved	Not applicable
Simlukafusp alfa (FAP-IL2v; RO6874281) [g]	IMP (test product)	Not approved	Not applicable
Emactuzumab [i]	IMP (test product)	Not approved	Not applicable

EEA = European Economic Area; IMP = investigational medicinal product.

[a] Atezolizumab, oxaliplatin, tocilizumab, and cobimetinib are not approved in pancreatic cancer.

[b] Nab-paclitaxel is approved in pancreatic cancer in combination with gemcitabine, but not in combination with atezolizumab, bevacizumab, AB928, tiragolumab, or tocilizumab.

[c] Gemcitabine is approved in pancreatic cancer in combination with nab-paclitaxel, but not in combination with atezolizumab, bevacizumab, AB928, tiragolumab, or tocilizumab.

[d] Component of mFOLFOX6: fluorouracil, leucovorin, and oxaliplatin.

[e] Fluorouracil is approved in pancreatic cancer in combination with leucovorin, but not in combination with oxaliplatin.

[f] Leucovorin is approved in cytotoxic therapy in combination with fluorouracil, but not in combination with oxaliplatin.

[g] Cobimetinib (RO5514041), PEGPH20, selicrelumab, and simlukafusp alfa (FAP-IL2v; RO6874281) were removed from Protocol WO39608, Version 11.

[h] BL-8040 was removed from Protocol WO39608, Version 7.

[i] Emactuzumab was removed from Protocol WO39608, Version 5.

[j] *AB928 was removed from Protocol WO39608, Version 16.*

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System identifier: RIM-CLIN-505303

Approval Task	[redacted] Company Signatory 04-Oct-2023 18:46:19 GMT+0000