Official Title: A Phase II, Randomized, Double-Blind Placebo-Controlled Study of Atezolizumab With or Without Bevacizumab in Combination With Cisplatin Plus Gemcitabine in Patients With Untreated, Advanced Biliary Tract Cancer

NCT Number: NCT04677504

Document Date: Protocol Amendment Version 6: 03-February-2023

PROTOCOL

TITLE:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB WITH OR WITHOUT BEVACIZUMAB IN COMBINATION WITH CISPLATIN PLUS GEMCITABINE IN PATIENTS WITH UNTREATED, ADVANCED BILIARY TRACT CANCER**
PROTOCOL NUMBER:	GO42661
STUDY NAME	IMbrave151
VERSION NUMBER:	6
EUDRACT NUMBER:	2020-003759-14
IND NUMBER:	152,455
NCT NUMBER:	NCT04677504
TEST PRODUCTS:	Atezolizumab (RO5541267) Bevacizumab (RO4876646)
MEDICAL MONITOR:	[redacted] M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
6	See electronic date stamp on the final page of this document.
5	23 June 2022
4	14 December 2021
3	3 March 2021
2	7 October 2020
1	27 August 2020

PROTOCOL AMENDMENT, VERSION *6*: RATIONALE

Protocol GO42661 has primarily been amended to *update risks and adverse event management guidelines for atezolizumab to align with the Atezolizumab Investigator's Brochure, Version 19 and Addenda 1 and 2. Substantive c*hanges to the protocol, along with a rationale for each change, are summarized below:

- *The medical term "Wegener granulomatosis" has been replaced by the term "granulomatosis with polyangiitis" to align with the updated preferred term in MedDRA (Section 4.1.2 and Appendix 12).*
- *The list of identified risks for atezolizumab has been revised to include pericardial disorders, myelitis, and facial paresis (Section 5.1.1).*
- *Hemophagocytic lymphohistiocytosis has been updated from a potential risk to an identified risk associated with atezolizumab, and language has been revised accordingly (Section 5.1.1).*
- *The list of adverse events of special interest has been revised to include myelitis and facial paresis (Section 5.2.3).*
- *A description of the technical and organizational security measures taken to protect personal data has been added to align with Clinical Trials Regulation requirements (Section 8.4).*
- *Appendix 12 has been revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a pericardial disorder while receiving another immunostimulatory anti-cancer agent.*
- *Appendix 12 has been revised to include autoimmune myelitis.*
- *The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 19 and Addenda 1 and 2 (Appendix 15).*

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 II, RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB WITH OR WITHOUT BEVACIZUMAB IN COMBINATION WITH CISPLATIN PLUS GEMCITABINE IN PATIENTS WITH UNTREATED, ADVANCED BILIARY TRACT CANCER**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB WITH OR WITHOUT BEVACIZUMAB IN COMBINATION WITH CISPLATIN PLUS GEMCITABINE IN PATIENTS WITH UNTREATED, ADVANCED BILIARY TRACT CANCER**
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PHASE:	II
INDICATION:	Biliary tract cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of atezolizumab with bevacizumab in combination with cisplatin and gemcitabine (CisGem), compared with atezolizumab in combination with CisGem, in patients with advanced biliary tract cancer (BTC) (i.e., intrahepatic cholangiocarcinoma [iCCA], extrahepatic CCA [eCCA], or gallbladder cancer [GBC]) who have not received prior systemic therapy. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

In this protocol, ″study treatment″ refers to the combination of treatments assigned to patients as part of this study. Patients will receive one of the following combinations of treatments:

- Atezolizumab + Bevacizumab+chemotherapy (CisGem), followed by Atezolizumab + Bevacizumab
- Atezolizumab + Placebo+chemotherapy (CisGem), followed by Atezolizumab + Placebo

TABLE 1 OBJECTIVES AND CORRESPONDING ENDPOINTS

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of Atezo + Bev + CisGem compared with Atezo + PBO + CisGem	• PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 or death from any cause (whichever occurs first)
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of Atezo + Bev + CisGem compared with Atezo + PBO + CisGem	• OS, defined as the time from randomization to death from any cause • Confirmed ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1 • DOR, defined as the time from the first occurrence of a confirmed objective response to disease progression as determined by the investigator according to RECIST v1.1 or death from any cause (whichever occurs first) • DCR, defined as the proportion of patients with a CR or a PR on two consecutive occasions ≥4 weeks apart or SD with a minimum duration of 9 weeks, as determined by the investigator according to RECIST v1.1 • TTCD in patient-reported physical functioning, role functioning, and quality of life, as measured by the respective scales of the EORTC QLQ-C30 and/or EORTC IL77, and defined as the time from randomization to the first clinically meaningful deterioration that is either maintained for two consecutive assessments or followed by death from any cause within 3 weeks
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of Atezo + Bev + CisGem compared with Atezo + PBO + CisGem	• PFS rates at specified timepoints (e.g., 6 months and 12 months), defined as the probability that a patient will be alive without experiencing disease progression, as determined by the investigator according to RECIST v1.1, at specified timepoints • OS rates at specific timepoints (e.g., 6 months and 12 months), defined as the probability that a patient will be alive at specified timepoints • Mean scores and changes in mean scores from baseline in all scales of the EORTC QLQ-C30, EORTC IL77, and EORTC QLQ-BIL21 • Proportion of responses on the PGI-CI and PGI-S
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of Atezo + Bev + CisGem compared with Atezo + PBO + CisGem	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results

TABLE 1 OBJECTIVES AND CORRESPONDING ENDPOINTS (CONT.)

Exploratory Safety Objective	Corresponding Endpoints
• To evaluate the treatment-related tolerability of Atezo + Bev + CisGem compared with Atezo + PBO + CisGem from the patient perspective	• Frequency, severity, interference, and/or presence of select symptomatic treatment toxicities, as determined through use of the PRO-CTCAE • Change from baseline in select symptomatic treatment toxicities, as determined by the PRO-CTCAE • Overall troublesomeness with treatment, as determined by the treatment side effects single item of the EORTC QLQ-BIL21
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the pharmacokinetics of atezolizumab when given in combination with bevacizumab and/or gemcitabine/cisplatin	• Serum concentration of atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to atezolizumab	• Prevalence of ADAs to atezolizumab at baseline and incidence of ADAs to atezolizumab during the study
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify and/or evaluate biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	• Relationship between biomarkers in blood, serum, plasma, and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

TABLE 1 OBJECTIVES AND CORRESPONDING ENDPOINTS (CONT.)

ADA = anti-drug antibody; Atezo = atezolizumab; Bev = bevacizumab; CisGem = cisplatin and gemcitabine; CR = complete response; DCR = disease control rate; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; IL = Item Library; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; PBO = placebo; PFS = progression-free survival; PGI-CI = Patient Global Impression of Change, Importance; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic; PR = partial response; PRO-CTCAE = Patient-Reported Outcome Common Terminology Criteria for Adverse Events; QLQ-BIL21 = Quality-of-Life Questionnaire for Cholangiocarcinoma and Cancer of the Gallbladder; QLQ-C30 = Quality-of-Life Questionnaire for Cancer; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; TTCD = time to confirmed deterioration.

STUDY DESIGN

DESCRIPTION OF STUDY

This is a Phase II, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of atezolizumab with bevacizumab in combination with CisGem, compared with atezolizumab in combination with CisGem, in patients with advanced BTC (i.e., iCCA, eCCA, or GBC) who have not received prior systemic therapy.

The study will enroll globally approximately 150 patients, who will be randomized in a 1:1 ratio to one of two treatment arms. The number of patients with either eCCA or GBC will be capped at a maximum of 50% of the total number of patients enrolled.

Treatment will consist of a chemotherapy combination phase followed by a cancer immunotherapy (CIT)/placebo phase as outlined in Table 2.

TABLE 2 STUDY TREATMENT

Treatment Arm	Dose, Route, and Regimen (Drugs Listed in Order of Administration)	
	Chemotherapy Combination Phase [a] Cycles 1–8 (21-Day Cycles)	**CIT/Placebo Phase Cycles 9 and Beyond (21-Day Cycles)**
Arm A	Atezo+Bev+CisGem • Atezolizumab 1200 mg IV on Day 1 • Bevacizumab 15 mg/kg IV on Day 1 • Cisplatin 25 mg/m^2 IV on Days 1 and 8 • Gemcitabine 1000 mg/m^2 IV on Days 1 and 8	Atezo+Bev • Atezolizumab 1200 mg IV on Day 1 • Bevacizumab 15 mg/kg IV on Day 1
Arm B	Atezo+PBO+CisGem • Atezolizumab 1200 mg IV on Day 1 • Placebo IV on Day 1 • Cisplatin 25 mg/m^2 IV on Days 1 and 8 • Gemcitabine 1000 mg/m^2 IV on Days 1 and 8	Atezo+PBO • Atezolizumab 1200 mg IV on Day 1 • Placebo IV on Day 1

Atezo = atezolizumab; Bev = bevacizumab; CisGem = cisplatin and gemcitabine; CIT = cancer immunotherapy; PBO = placebo.

[a] Treatment during the chemotherapy combination phase will be administered on a 21-day cycle until completion of eight cycles, loss of clinical benefit, or unacceptable toxicity, whichever occurs first.

Randomization will be stratified according to the following stratification factors:

- Location of primary tumor (iCCA vs. eCCA vs. GBC)
- Metastatic disease (yes vs. no)
- Geographic region (Asia vs. rest of the world)

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion. Patients are not required to re-sign the Informed Consent Form if they are re-screened within 60 days after previously signing the Informed Consent Form. The investigator will record reasons for screen failure in the screening log.

Patients will continue treatment as indicated in Table 2 until unacceptable toxicity or loss of clinical benefit, as determined by the investigator after an integrated assessment of radiographic and biochemical data and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). In the absence of unacceptable toxicity, patients who meet criteria for disease progression (as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1]) while receiving atezolizumab will be permitted to continue the study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in 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

Patients who transiently withhold or permanently discontinue one component of their treatment (i.e., either atezolizumab, bevacizumab/placebo, or chemotherapy) because of toxicity may continue with the other components of study treatment, as long as the patients are experiencing clinical benefit in the opinion of the investigator. However, bevacizumab/placebo should not be continued as a single agent.

Patients will undergo tumor assessments every 9 ($\pm$1) weeks following treatment initiation. Sites will collect and send imaging used for tumor assessments to an independent review facility to enable potential centralized, independent review of response and progression endpoints.

Following disease progression or loss of clinical benefit, patients will be followed for survival and subsequent anti-cancer therapies until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Patient-reported outcome (PRO) assessments will be completed before starting treatment, at specified timepoints during treatment, and at treatment discontinuation.

Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Serum samples will be collected to monitor the pharmacokinetics of atezolizumab when administered in combination with bevacizumab and/or CisGem. Patient samples, including archival tumor tissues, as well as serum and plasma, will be collected for future exploratory biomarker assessments.

NUMBER OF PATIENTS

Approximately 150 patients with unresectable, recurrent, or metastatic BTC will be enrolled in this study.

TARGET POPULATION

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age $\geq$ 18 years at the time of signing the Informed Consent Form
- Ability to comply with the study protocol
- Considered to be eligible to receive platinum-based chemotherapy, in the investigator's judgment

- Documentation of recurrent/metastatic or locally advanced unresectable disease based on computed tomography (CT) or magnetic resonance imaging (MRI) scans
- Histologically or cytologically confirmed diagnosis of iCCA, eCCA, or GBC

  For patients with recurrent BTC, histologic confirmation of BTC at the time of resection is acceptable
- No prior systemic therapy (including systemic investigational agents) for advanced BTC

  Prior chemotherapy or radiotherapy (with or without radio-sensitizing chemotherapy) in the neoadjuvant or adjuvant setting is permitted provided this is completed at least 6 months prior to Day 1 of Cycle 1.

  Prior treatment with gemcitabine administered as a radiation sensitizer in the neoadjuvant and adjuvant settings surrounding surgery, during and up to 4 weeks after radiation therapy is allowed, provided all toxicities have returned to baseline, or Grade 1 or better.

  Previous use of herbal therapies and traditional Chinese medicines with anti-cancer activity included in the label is allowed, provided that these medications are discontinued prior to Day 1 of Cycle 1.

  The following prior interventions are permitted, provided the patient has fully recovered:

  – Surgery: Non-curative resection with macroscopic residual disease or palliative bypass surgery. Patients who have previously undergone curative surgery must have evidence of non-resectable disease requiring systemic chemotherapy.
  – Photodynamic therapy: Prior photodynamic therapy for localized disease with no evidence of metastatic disease or for localized disease to relieve biliary obstruction in the presence of metastatic disease, provided patient has clear evidence of disease progression requiring systemic chemotherapy.
  – Palliative radiotherapy: Palliative radiotherapy, provided that all adverse events have resolved and the patient has measurable disease outside the field of radiation.
- At least one measurable untreated lesion (per RECIST v1.1)
- Adequate biliary drainage with no evidence of ongoing infection

  If applicable, treatable and clinically relevant biliary duct obstruction must be relieved by internal endoscopic drainage/stenting at least 2 weeks prior to Day 1 of Cycle 1 or by palliative bypass surgery or percutaneous drainage prior to Day 1 of Cycle 1, and the patient has no active or suspected uncontrolled infection.

  Patients fitted with a biliary stent should be clinically stable and free of signs of infection and have total bilirubin $\leq 2\times$ upper limit of normal (ULN) and AST/ALT $\leq 5\times$ ULN for ≥ 2 weeks prior to Day 1 of Cycle 1. Patients with improving biliary function who meet all other inclusion criteria may be re-tested during the screening window.
- Availability of a representative tumor specimen that is suitable for determination of PD-L1 status via central testing

  A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 16 slides containing unstained, freshly cut, serial sections should be submitted along with an associated pathology report within 4 weeks of randomization.

  If FFPE specimens described above are not available, any type of specimen (including fine-needle aspiration, cell pellet specimens [e.g., from pleural effusion], and lavage samples) are also acceptable. This specimen should be accompanied by the associated pathology report.

  If archival tissue is either insufficient or unavailable, a core-needle biopsy specimen should be collected during the screening period, if clinically feasible. Trans-jugular biopsy tissue sample collections for patients who are at high risk of bleeding may be allowed.

  If archival tissue is either insufficient or unavailable and a fresh biopsy is not clinically feasible, the patient may still be eligible.

- Negative HIV test at screening with the following exception: Patients with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count $\geq 200/\mu L$, and have an undetectable viral load
- Documented virology status of hepatitis, as confirmed by screening hepatitis B virus (HBV) or hepatitis C virus (HCV) tests
  - For patients with active HBV: HBV DNA < 500 IU/mL during screening, initiation of anti-HBV treatment at least 14 days prior to Day 1 of Cycle 1 and willingness to continue anti-HBV treatment during the study (per local standard of care [e.g., entecavir])
  - Patients with HCV, either with resolved infection (as evidenced by detectable antibody) or chronic infection (as evidenced by detectable HCV RNA), are eligible
- Eastern Cooperative Oncology Group Performance Status of 0 or 1
- Life expectancy of > 3 months
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 7 days prior to Day 1 of Cycle 1 unless otherwise specified:
  - AST and ALT $\leq 2.5 \times$ ULN with the following exceptions:

    Patients with documented liver metastases: AST and ALT $\leq 5\times$ ULN.
  - Serum bilirubin $\leq 2 \times$ ULN
  - Albumin ≥ 28 g/L (≥ 2.8 g/dL)
  - Creatinine clearance ≥ 60 mL/min (calculated using the Cockcroft-Gault formula)
  - Hemoglobin ≥ 90 g/L (≥ 9 g/dL)

    Patients may be transfused to meet this criterion.
  - Platelet count $\geq 100\times10^9$/L ($\geq 100{,}000/\mu L$) without transfusion
  - Lymphocyte count $\geq 0.5\times10^9$/L ($\geq 500/\mu L$)
  - ANC $\geq 1.5\times10^9$/L ($1500/\mu L$) without granulocyte colony-stimulating factor support
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 2\times$ ULN
  - Proteinuria $< 2+$ on dipstick analysis (within 7 days prior to Day 1 of Cycle 1)

    Patients discovered to have $\geq 2+$ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection (or an alternative method such as protein: creatinine ratio, per local guidance) and must demonstrate < 1 g of protein in 24 hours.
- 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 while they are receiving atezolizumab and bevacizumab and for 5 months after the final dose of atezolizumab and for 6 months after the final dose of bevacizumab or CisGem, whichever is later. Women must refrain from donating eggs during this same period.

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

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

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of bevacizumab or CisGem, whichever is later, to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

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

- Recurrent disease $\leq$6 months after curative surgery or $\leq$6 months after the completion of adjuvant therapy (chemotherapy and/or radiation)
- Prior local regional therapy such as radioembolization
- Combined or mixed hepatocellular/CCA
- Clinically significant hepatic encephalopathy within the 12 months prior to Day 1 of Cycle 12
- National Cancer Institute Common Terminology Criteria for Adverse Events Grade $\geq$2 peripheral neuropathy
- Prior bleeding event due to untreated or incompletely treated esophageal and/or gastric varices within 6 months prior to Day 1 of Cycle 1

  Patients at high risk of esophageal varices are required to undergo an esophagogastroduodenoscopy (EGD) during screening or must have undergone an EGD within 6 months of Day 1 of Cycle 1. All size of varices (small to large) must be assessed and treated per local standard of care prior to Day 1 of Cycle 1. Patients at high-risk of esophageal varices who have had an EGD within 6 months of Day 1 of Cycle 1 do not need to repeat EGD at screening. Criteria for high-risk varices include at least one of the following:

  - Presence or history of cirrhosis
  - Presence or history of portal hypertension
  - Presence or history of primary biliary cirrhosis, or primary sclerosing cholangitis
  - HBV or HCV infection
  - Evidence of gross vascular invasion (portal vein, hepatic vein or collateral vessels)
  - Evidence of splenomegaly
  - Platelet count $< 120 \times 10^9$/L (120,000/μL) and albumin $<$ 36 g/L (3.6 g/dL)
  - Evidence of portal vein occlusion due to malignant invasion or constriction
  - Evidence of varices by imaging

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, *granulomatosis with polyangiitis*, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

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

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

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

  – Rash must cover $<10\%$ of body surface area.
  – Disease is well-controlled at baseline and requires only low-potency topical corticosteroids.
  – There is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the 12 months prior to Day 1 of Cycle 1.
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to Day 1 of Cycle 1, unstable arrhythmia, or unstable angina
- History of malignancy other than BTC within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year overall survival [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
- Symptomatic, untreated, or actively progressing CNS metastases

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

  – Measurable disease, per RECIST v1.1, must be present outside the CNS.
  – The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
  – Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
  – There is no evidence of interim progression between completion of CNS-directed therapy and initiation of study treatment.
  – The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, and neurosurgical resection within 28 days prior to initiation of study treatment.
  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anticonvulsant therapy at a stable dose is permitted.
  – Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.

- For patients with lung metastases, if one of the following criteria applies:
  - Large, centrally located pulmonary metastases
  - Clear tumor infiltration into the thoracic great vessels seen on imaging
  - Clear cavitation of pulmonary lesions seen on imaging
- Active tuberculosis
- Severe infection within 4 weeks prior to Day 1 of Cycle 1, 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 Day 1 of Cycle 1

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease [COPD] exacerbation) are eligible for the study, provided the signs of active infection have resolved.
- Prior allogeneic stem cell or solid organ transplantation
- On the waiting list for liver transplantation
- 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 or within 5 months after the final dose of atezolizumab or within 6 months after the final dose of bevacizumab or CisGem

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to Day 1 of Cycle 1.
- Co-infection with HBV and HCV

  Patients with a history of HCV infection but who are negative for HCV RNA by polymerase chain reaction will be considered to be negative for HCV infection.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected serum calcium $>$ ULN)
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- History of allergic reactions to cisplatin or other platinum-containing compounds
- Known hypersensitivity to gemcitabine
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or bevacizumab formulations
- Treatment with a live, attenuated vaccine within 4 weeks prior to Day 1 of Cycle 1 or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Treatment with investigational therapy within 4 weeks prior to Day 1 of Cycle 1
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to Day 1 of Cycle 1
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to Day 1 of Cycle 1 or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

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

Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for COPD or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

- Inadequately controlled arterial hypertension (defined as systolic blood pressure [BP] $>$150 mmHg and/or diastolic BP $>$100 mmHg), based on an average of at least 3 BP readings at 2 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 Day 1 of Cycle 1
- History of hemoptysis ($\geq$2.5 mL of bright red blood per episode) within 1 month prior to Day 1 of Cycle 1
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (within 10 days of Day 1 of Cycle 1) use of aspirin ($>$325 mg/day) or current or recent treatment with dipyridamole, ticlopidine, clopidogrel, and cilostazol
- Current or recent (within 10 days prior to Day 1 of Cycle 1) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose

  Prophylactic anticoagulation for the patency of venous access devices is allowed provided the activity of the agent results in an INR $<$1.5$\times$ ULN and aPTT is within normal limits (according to institutional standards) within 14 days prior to Day 1 of Cycle 1.

  Prophylactic use of low-molecular-weight heparin (i.e., 40 mg/day enoxaparin) is allowed. However, the use of direct oral anticoagulant therapies such as dabigatran (Pradaxa®) and rivaroxaban (Xarelto®) is not recommended due to bleeding risk.
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to Day 1 of Cycle 1
- History of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months prior to Day 1 of Cycle 1
- 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
- Major surgical procedure within 4 weeks prior to Day 1 of Cycle 1 or anticipation of need for a major surgical procedure during the study
- History of clinically significant and uncontrolled intra-abdominal inflammatory disease within 6 months prior to Day 1 of Cycle 1, including, but not limited to, peptic ulcer disease, diverticulitis, or colitis
- Chronic daily treatment with a non-steroidal anti-inflammatory drug (NSAID)

  Occasional use of NSAIDs for the symptomatic relief of medical conditions such as headache or fever is allowed.
- Preexisting renal impairment, myelosuppression, or hearing impairment

END OF STUDY

The end of this study is defined as the date at which the last data required for study analysis are collected. The end of study will occur once the last patient, last visit occurs following the final OS analysis.

LENGTH OF STUDY

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3–5 years.

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

If the Sponsor decides to terminate the study, patients who are still receiving study treatment or undergoing survival follow-up may be enrolled in an extension study or a non-interventional study, if available.

INVESTIGATIONAL MEDICINAL PRODUCTS

The investigational medicinal products (IMPs) for this study are atezolizumab and bevacizumab/placebo. Cisplatin and gemcitabine are considered non-IMPs.

TEST PRODUCTS (INVESTIGATIONAL DRUGS)

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg every 3 weeks (Q3W) on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, and clinical status.

Bevacizumab (Arm A) at a dose of 15 mg/kg or matching placebo (Arm B) will be administered after atezolizumab by IV infusion on Day 1 of each 21-day cycle. There will be a minimum 5-minute gap between administration of atezolizumab and bevacizumab/placebo.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

Cisplatin will be administered by IV infusion at a dose of 25 mg/m^2 followed by gemcitabine at a dose of 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary efficacy endpoint is investigator-assessed PFS according to RECIST v1.1.

Investigator-assessed PFS is defined as the time from randomization to the occurrence of disease progression as determined by investigator according to RECIST v1.1, or death from any cause, whichever occurs first. Patients who have not experienced disease progression or death at the time of the clinical cutoff date will be censored at the time of the last tumor assessment at which they were known to be progression-free with radiographic evidence as of the clinical cutoff date. Patients with no postbaseline tumor assessment will be censored at the date of randomization.

A stratified Cox proportional-hazards model will be used to estimate the PFS HR and its 95% CI. A stratified two-sided log-rank test will be used to compare the investigator-assessed PFS between Arm A and Arm B at the two-sided significance level of 0.05. The stratification factors for these stratified analyses are location of primary tumor (iCCA vs. eCCA vs. GBC), metastatic disease (yes vs. no), and geographic region (Asia vs. rest of the world). However, if at least one stratum has fewer than 10 events at the time of analysis, the level of stratification factor that contains the smallest number of events will be combined with other levels of the same stratification factor for the stratified analysis. The final set of stratification factors used in the primary endpoint analysis will be applied to all other endpoints where stratified analyses are performed. The stratification information will be obtained from the IxRS at the time of randomization. Results from an unstratified analysis will also be provided. The Kaplan-Meier method will be used to estimate median PFS for each treatment arm. The Brookmeyer-Crowley methodology will be used to calculate the 95% CI for the median PFS of each treatment arm.

To assess the homogeneity of the treatment effect with respect to the primary efficacy endpoint of PFS, forest plots (including the estimated HRs) for clinically relevant subgroups will be provided.

To assess the robustness of the primary PFS analysis, a sensitivity analysis will be performed by incorporating an additional censoring rule for patients who take new anti-cancer therapy prior to occurrence of radiographic progression. These patients will be censored at the last tumor assessment before start of the new treatment, regardless of progression or death afterwards.

DETERMINATION OF SAMPLE SIZE

The purpose of this Phase II study is estimation and hypothesis generation regarding the effect of atezolizumab with bevacizumab in combination with CisGem (Arm A) on PFS relative to atezolizumab in combination with CisGem (Arm B). Point and CI estimates of the true underlying HR of comparing PFS between Arm A and Arm B will be calculated. A total of approximately 150 patients will be randomized at a 1:1 randomization ratio to either Arm A or Arm B. It is assumed that the median duration of PFS in the control arm (Arm B) is 9 months. Operating characteristics (statistical power based on a two-sided significance level of 0.05 and expected total number of events) at the time of the final PFS analysis will occur when approximately 90 PFS events have been observed. The planned sample size of 150 patients, targeting approximately 90 PFS events at the time of the final PFS analysis, is considered to provide sufficient data and precision for the purpose of estimation of the HR point estimate and its 95% CI.

INTERIM ANALYSES

One interim analysis of PFS and objective response rate will be performed at the time when 100 patients have been followed for at least 6 months, and is estimated to occur at approximately 12 months after the first patient is enrolled. All of the planned 150 patients are expected to have been randomized in the study at the time of this planned interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel, who will have full access to unblinded data at the time of analysis. Access to treatment assignment information will follow the Sponsor's standard procedures and will not be given to the Sponsor until the first interim analysis within this study is being conducted.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
BP	blood pressure
BTC	biliary tract cancer
CCA	cholangiocarcinoma
CisGem	cisplatin and gemcitabine
CIT	cancer immunotherapy
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CR	complete response
CRS	cytokine release syndrome
CT	computed tomography (scan)
DCR	disease control rate
DOR	duration of response
EC	Ethics Committee
eCCA	extrahepatic cholangiocarcinoma
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGD	esophagogastroduodenoscopy
EORTC	European Organisation for Research and Treatment of Cancer
Fc	fragment crystallizable
FDA	(U.S.) Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GBC	gallbladder cancer
GHS/QoL	Global Health Status/Quality of Life
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
iCCA	intrahepatic cholangiocarcinoma
ICH	International Council for Harmonisation

Abbreviation	Definition
IL	item library
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRF	independent review facility
IRR	infusion-related reaction
LMWH	low molecular weight heparin
ITT	intent-to-treat
IxRS	interactive voice or Web-based response system
MAS	macrophage activation syndrome
MDSC	myeloid-derived suppressor cell
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAID	non-steroidal anti-inflammatory
NSCLC	non–small-cell lung cancer
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PGI-CI	Patient-Reported Global Impression of Change and Its Importance
PGI-S	Patient-Reported Global Impression of Severity
PK	pharmacokinetics
PR	partial response
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcome Common Terminology Criteria for Adverse Events
Q3W	every 3 weeks
QLQ-BIL21	Quality-of-Life Questionnaire for Cholangiocarcinoma and Cancer of the Gallbladder
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
T3	free triiodothyronine
T4	free thyroxine
TAM	tumor-associated macrophage
TME	tumor microenvironment
Treg	regulatory T-cell

Abbreviation	Definition
TTCD	time to confirmed deterioration
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
WES	whole exome sequencing

1. BACKGROUND

1.1 BACKGROUND ON BILIARY TRACT CANCER

Biliary tract cancers (BTCs) represent a heterogeneous group of epithelial malignancies developing in the biliary tree. Biliary tract cancers include cholangiocarcinoma (CCA) as well as gallbladder cancer (GBC) and ampulla of Vater cancer. Classification of CCA is based on the anatomical site of origin and can be subdivided into intrahepatic CCA (iCCA), arising from the liver, and extrahepatic CCA (eCCA), arising from the extrahepatic bile ducts. Extrahepatic CCA can be further segmented into perihilar and distal subtypes.

Cholangiocarcinoma currently accounts for approximately 15% of all primary liver cancers and approximately 3% of gastrointestinal (GI) malignancies (Banales et al. 2020). Globally, the incidence and mortality rates of BTC show substantial geographical variation, presumably reflecting differences in geographical risk factors and possibly genetic determinants. The incidence of CCA is manifold higher in Asia compared with Western countries. Both the incidence and mortality of CCA are increasing, primarily because of a global rise in iCCA. The incidence of GBC is highest in Asian countries, as well as countries in Latin America.

At the time of diagnosis, 70%–90% of patients with BTC present with unresectable locally advanced or metastatic disease. Cholangiocarcinomas are usually asymptomatic in early stages and are therefore often diagnosed when the disease is already in advanced stages, resulting in a dismal prognosis.

A silent early presentation, coupled with a highly aggressive nature and refractoriness to chemotherapy, contribute to a poor prognosis. Even for patients with resectable disease, postoperative recurrence in $>60\%$ of cases is reported within the first or second year following surgery (Jung et al. 2012) regardless of adjuvant treatment. Unresectable, recurrent, or metastatic BTCs are collectively termed ″advanced BTC.″

1.2 TREATMENT OF ADVANCED BILIARY TRACT CANCER

The current first-line standard of care for advanced BTC is the combination of cisplatin and gemcitabine (hereafter referred to as CisGem) based on the results of the ABC-02 Phase III study (Valle et al. 2010). Compared with single-agent gemcitabine, CisGem conferred a statistically significant overall survival (OS) advantage (hazard ratio [HR]: 0.64; 95% CI: 0.52 to 0.80; $p<0.001$; median OS 11.7 vs. 8.1 months). In addition, CisGem also significantly improved progression-free survival (PFS) and disease control rate (DCR). These data have been confirmed in subsequent randomized studies (Okusaka et al. 2010; Sakai et al. 2018; Morizane et al. 2019).

The limited benefit of first-line treatment with CisGem highlights the need for more effective agents and treatment combinations to improve patient outcomes. Comprehensive genomic profiling has identified several potentially actionable oncogenic

alterations in patients with CCA, notably *FGFR2* and *IDH*, leading to the development of molecularly targeted agents in biomarker-selected patients (Lamarca et al. 2020). However, *FGFR2* and *IDH* mutations are largely confined to $<20\%$ patients with iCCA and are far less common in eCCA or GBC BTC malignancies. Therefore, there remains a significant unmet need for more effective treatments for advanced BTC.

1.2.1 Anti-Vascular Endothelial Growth Factor Treatments in Biliary Tract Cancer

Vascular endothelial growth factor (VEGF), a primary growth factor regulating angiogenesis, is over-expressed in 45%–75% of BTCs. Vascular endothelial growth factor expression is associated with the presence of metastases in iCCA; poorer prognosis in eCCA, and increased microvascular density in both CCA and GBC. These observations have made VEGF-driven angiogenesis a logical target in BTC.

Despite the strong associations between angiogenesis and BTC, a series of randomized Phase II trials in which anti-VEGF agents were added to first-line chemotherapy have failed to demonstrate improved clinical benefit. The ABC-03 study evaluated the effect of adding cediranib (an oral VEGFR1, VEGFR2, and VEGFR3 tyrosine kinase inhibitor, with additional activity against PDGF receptors and c-KIT) to CisGem on PFS in patients with advanced BTC (Valle et al. 2015). The study failed to meet its primary PFS endpoint (HR: 0.93; 80% CI: 0.74 to 1.19; $p=0.72$), although the objective response rate (ORR), a secondary endpoint, was significantly increased in the cediranib arm (44% vs. 19%; $p=0.0036$). Study I3O-MC-JSBF evaluated the addition of ramucirumab (a VEGFR2 antibody) to CisGem in patients with advanced BTC. The addition of ramucirumab to CisGem did not improve the primary endpoint of PFS (HR: 1.123, $p=0.4821$), or OS or ORR, both secondary endpoints (Valle et al. 2020). Gemcitabine combined with sorafenib (a multikinase inhibitor targeting proliferative and angiogenic pathways) failed to improve PFS compared with gemcitabine alone (Moehler et al. 2014).

Bevacizumab-based chemotherapy combinations have been studied in patients with advanced BTC in a series of single-arm Phase II studies. The combination of bevacizumab with gemcitabine/oxaliplatin resulted in an ORR of 40%, a median PFS of 7 months, and a median OS of 12.7 months (Zhu et al. 2010). The combination of bevacizumab, gemcitabine, and capecitabine led to an ORR of 24%, a median PFS of 8.1 months, and a median OS of 10.2 months (Iyer et al. 2018). In both studies, the addition of bevacizumab to chemotherapy did not improve outcomes in patients with advanced BTC, compared with historical controls. Both studies concluded that the respective bevacizumab combinations were associated with manageable toxicity.

1.2.2 Cancer Immunotherapy in Biliary Tract Cancer

Cancer immunotherapy (CIT) with antibodies targeting the PD-1/PD-L1 axis has changed the standard of care in multiple cancers, including hepatocellular carcinoma (HCC). Cancer immunotherapy approaches have garnered significant interest in BTC,

given their etiologic association with inflammation as well as relatively high levels of expression of PD-L1. However, the role of PD-1/PD-L1 inhibition in BTC remains to be established and existing clinical data are limited to small single-arm studies and sub-analyses of basket trials. To date, the efficacy of single-agent anti–PD-1/PD-L1 antibodies has been disappointing and, in most cases, reported ORRs are <10% (Kelley et al. 2020). In the largest study published to date (KEYNOTE-158), the ORR was 5.8% in 104 patients with advanced, previously treated BTC (Bang et al. 2019). Currently, the role of anti–PD-L1 antibodies in BTC is limited to patients with deficient mismatch repair and microsatellite instability–high, which represent <5% of all patients (Lamarca et al. 2020a).

Relatedly, anti–PD-1 antibodies given as monotherapy have failed to improve OS in unresectable HCC, and a retrospective series indicate that liver metastases are less responsive to PD-1 inhibition compared with other anatomic sites (Tumeh et al. 2017; Yau et al. 2019; Finn et al. 2020). These observations point to the highly immunosuppressed nature of the liver tumor microenvironment (TME) in the setting of primary or secondary hepatic tumors.

Given the apparent limitations of anti–PD-L1 antibody monotherapy in BTC, there is strong interest in developing combination immunotherapy strategies in order to abrogate immune-suppressive mechanisms and promote anti-cancer immunity.

Cancers harness several mechanisms of immune escape to restrain or evade antitumor immune responses, including modulation of the TME to create an immunosuppressive milieu that dictates responsiveness to CIT.

In most BTCs, the TME is frequently characterized by poor cytotoxic T-cell infiltration and overexpression of immunosuppressive cell types such as tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), regulatory T-cells (Tregs), and immature dendritic cells. These TME components are believed to be essential in restraining anti-cancer immunity and fostering BTC progression through various mechanisms such as angiogenesis (Loeuillard et al. 2019; Fabris et al. 2020). Infiltration of immunosuppressive cells such as TAMs and MDSCs is associated with poor patient outcomes.

PD-L1 blockade, in combination with agents targeting immune suppressive mechanisms within the TME, is a rational approach, including with both chemotherapy and anti-VEGF drugs, to promote a more immune-permissive TME.

1.3 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 fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

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

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small-cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

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

1.4 BACKGROUND ON BEVACIZUMAB

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human VEGF in in vitro and in vivo assay systems.

Bevacizumab was first granted marketing approval in the United States on 26 February 2004 in combination with IV 5–fluorouracil-based chemotherapy for the first-line treatment of patients with metastatic carcinoma of the colon or rectum. Bevacizumab is approved in over 100 countries for one or more of the following indications: breast cancer, NSCLC, renal cell cancer, glioblastoma multiforme, cervical cancer, epithelial ovarian cancer, primary peritoneal cancer, and fallopian tube cancer.

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

1.5 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.5.1 Rationale for Combining Chemotherapy with Anti–PD-1/PD-L1 Antibodies

Chemotherapy can induce a number of positive immunomodulatory effects in the TME, such as induction of immunogenic cell death and/or depleting immunosuppressive cells (Galluzzi et al. 2015; Heinhuis et al. 2019), providing a rationale to combine with anti–PD-1/PD-L1 antibodies. Multiple clinical studies have demonstrated that chemotherapy, including CisGem, can be effectively and safely combined with anti–PD-1/PD-L1 antibodies in patients with cancer (Galsky et al. 2020).
The immunomodulatory effects of chemotherapy differ according to the type of drug used (Wu and Waxman 2018). Both cisplatin and gemcitabine have been shown to downregulate immune suppressive cells in the TME but are ineffective in inducing

immunogenic cell death (Hato et al. 2014; Galluzi et al. 2017). This latter observation may limit the immune-potentiating effect of CisGem.

To date, anti–PD-L1 antibodies in combination with CisGem have been studied in small single-arm studies in BTC (Ueno et al. 2019; Feng et al. 2020). Despite encouraging response rates, PFS and OS in these non-randomized studies were disappointing, relative to the data for CisGem alone from randomized studies. This observation may suggest that additional treatment modalities may be required to further amplify the immune response.

1.5.2 Rationale for Combined Inhibition of PD-L1 and VEGF

Many immune-suppressive components of the BTC TME are thought to be regulated by VEGF, providing a therapeutic rationale to explore dual blockade of PD-L1 and VEGF pathways in order to promote anti-cancer immunity. Excessive levels of VEGF within the TME can induce tumor-associated immunosuppression either directly or indirectly by means of 4 principal mechanisms: 1) inhibition of dendritic cell maturation and antigen presentation; 2) inhibition of cytotoxic T-cell proliferation, trafficking, and infiltration; 3) promotion of an aberrant tumor vasculature; and 4) recruitment and proliferation of MDSCs, Tregs, and pro-tumor M2-TAMs (Fukumura et al. 2018). Therefore, T cell–mediated cancer-cell killing by PD-L1 blockade could be enhanced through the reversal of VEGF-mediated immunosuppression mechanisms by the addition of anti-VEGF therapy. Combination treatment with anti–PD-L1 and anti-angiogenic agents is now a standard of care in renal cell carcinoma (RCC), NSCLC, and HCC, based on the results of Phase III studies.

Combined PD-L1 and VEGF inhibition with atezolizumab and bevacizumab in patients with HCC was studied in 2 randomized studies. In Arm F of Study GO30140, 119 patients with unresectable HCC were randomly assigned in a 1:1 ratio to receive either atezolizumab alone or atezolizumab in combination with bevacizumab. A statistically and clinically significant improvement in independent review facility (IRF)-assessed PFS per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) was observed in the combination arm versus atezolizumab monotherapy (HR: 0.55; 80% CI: 0.40 to 0.74; $p = 0{\cdot}0108$) (Lee et al. 2020). Study YO40245 (IMbrave150) was a randomized Phase III study in which 501 patients with unresectable HCC were randomly assigned in a 2:1 ratio to receive either atezolizumab plus bevacizumab or sorafenib. Combination treatment with atezolizumab plus bevacizumab resulted in a statistically and clinically significant improvement in OS (HR: 0.58; 95% CI: 0.42 to 0.79; $p = 0.0006$), PFS (HR: 0.59; 95% CI: 0.47 to 0.76; $p < 0.0001$), and ORR (27% vs. 12%; $p < 0.0001$) compared with sorafenib (Finn et al. 2020). In a post-hoc analysis of Study GO30140, the PFS benefit of atezolizumab and bevacizumab compared with atezolizumab alone was enhanced in patients with HCC harboring myeloid, Treg, and VEGFR2 immunosuppressive gene signatures (Zhu et al. 2020).

The effectiveness of combined PD-1/PD-L1 and VEGF inhibition in BTC is yet to be established, with available data limited to small Phase I studies (Arkenau et al. 2018; Lin et al. 2018).

1.5.3 Rationale for Combining Anti–PD-L1, Anti-VEGF, and Chemotherapy

The highly immunosuppressed nature of the TME in BTC, coupled with the limited clinical activity of PD-1 antibodies combined with either anti-VEGF drugs or CisGem, suggest that more active treatment combinations are needed to unlock an anti-cancer immune response. Combining atezolizumab with bevacizumab along with CisGem, all of which have immunomodulatory effects, is one such approach. This combination has yet to be evaluated in BTC.

Published Phase III data in other tumor types such as NSCLC support the rationale for the combination of platinum-based chemotherapy, atezolizumab and bevacizumab in BTC. In patients with metastatic non-squamous NSCLC, the addition of atezolizumab to bevacizumab plus chemotherapy significantly improved PFS and OS compared with bevacizumab plus chemotherapy (Socinski et al. 2018). Importantly, in a pre-specified analysis of patients with baseline liver metastases, atezolizumab plus bevacizumab and chemotherapy significantly improved OS and PFS in patients with liver metastases. Conversely, neither atezolizumab plus chemotherapy nor bevacizumab combined with chemotherapy prolonged OS or PFS in patients with liver metastases (Reck et al. 2019). This finding indicates that the dual targeting of PD-L1 and VEGF with a chemotherapy backbone may be needed to induce clinically meaningful antitumor immunity in hepatic tumors. These data provide clinical proof of principle to evaluate the atezolizumab, bevacizumab, and CisGem combination regimen in BTC.

On the basis of the compelling rationale described above and expected clinical benefit with the combination of atezolizumab, bevacizumab, and CisGem and the well-defined safety profile of each approved drug as single agent and in combination, the Sponsor believes that the potential benefits of the combination outweigh its risks in the treatment of advanced-stage BTC, which remains an incurable disease with a high unmet medical need.

The overall benefit–risk ratio for atezolizumab in combination bevacizumab and CisGem is expected to be acceptable in this setting.

1.5.4 Benefit-Risk Assessment during the COVID-19 Pandemic

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

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13; Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if the 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 IL-6, IL-10, IL-2, and interferon-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from SARS-CoV-2 infection.

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

Neutropenia and lymphopenia associated with chemotherapy may increase the risk of developing an infection in patients receiving atezolizumab in combination with chemotherapy.

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

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

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

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

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of atezolizumab with bevacizumab in combination with CisGem, compared with atezolizumab in combination with CisGem, in patients with advanced BTC (i.e., iCCA, eCCA, or GBC) who have not received prior systemic therapy. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

In this protocol, ″study treatment″ refers to the combination of treatments assigned to patients as part of this study. Patients will receive one of the following combinations of treatments (see Section 3.1 for details):

- Atezolizumab + Bevacizumab + chemotherapy (CisGem), followed by Atezolizumab + Bevacizumab
- Atezolizumab + Placebo + chemotherapy (CisGem), followed by Atezolizumab + Placebo

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of Atezo + Bev + CisGem compared with Atezo + PBO + CisGem	• PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 or death from any cause (whichever occurs first)
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of Atezo + Bev + CisGem compared with Atezo + PBO + CisGem	• OS, defined as the time from randomization to death from any cause • Confirmed ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1 • DOR, defined as the time from the first occurrence of a confirmed objective response to disease progression as determined by the investigator according to RECIST v1.1 or death from any cause (whichever occurs first) • DCR, defined as the proportion of patients with a CR or a PR on two consecutive occasions ≥ 4 weeks apart or SD with a minimum duration of 9 weeks, as determined by the investigator according to RECIST v1.1 • TTCD in patient-reported physical functioning, role functioning, and quality of life, as measured by the respective scales of the EORTC QLQ-C30 and/or EORTC IL77, and defined as the time from randomization to the first clinically meaningful deterioration that is either maintained for two consecutive assessments or followed by death from any cause within 3 weeks
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of Atez + Bev + CisGem compared with Atezo + PBO + CisGem	• PFS rates at specified timepoints (e.g., 6 months and 12 months), defined as the probability that a patient will be alive without experiencing disease progression, as determined by the investigator according to RECIST v1.1, at specified timepoints • OS rates at specific timepoints (e.g., 6 months and 12 months), defined as the probability that a patient will be alive at specified timepoints • Mean scores and changes in mean scores from baseline in all scales of the EORTC QLQ-C30, EORTC IL77, and EORTC QLQ-BIL21 • Proportion of responses on the PGI-CI and PGI-S

Table 1 Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of Atezo + Bev + CisGem compared with Atezo + PBO + CisGem	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Exploratory Safety Objective	**Corresponding Endpoints**
• To evaluate the treatment-related tolerability of Atezo + Bev + CisGem compared with Atezo + PBO + CisGem from the patient perspective	• Frequency, severity, interference, and/or presence of select symptomatic treatment toxicities, as determined through use of the PRO-CTCAE • Change from baseline in select symptomatic treatment toxicities, as determined by the PRO-CTCAE • Overall troublesomeness with treatment, as determined by the treatment side effects single item of the EORTC QLQ-BIL21
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the pharmacokinetics of atezolizumab when given in combination with bevacizumab and/or CisGem	• Serum concentration of atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to atezolizumab	• Prevalence of ADAs to atezolizumab at baseline and incidence of ADAs to atezolizumab during the study
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Biomarker Objective	Corresponding Endpoint
• To identify and/or evaluate biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	• Relationship between biomarkers in blood, serum, plasma, and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; Atezo = atezolizumab; Bev = bevacizumab; CisGem = cisplatin and gemcitabine; CR = complete response; DCR = disease control rate; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; IL = Item Library; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; PBO = placebo; PFS = progression-free survival; PGI-CI = Patient Global Impression of Change, Importance; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic; PR = partial response; PRO-CTCAE = Patient-Reported Outcome Common Terminology Criteria for Adverse Events; QLQ-BIL21 = Quality-of-Life Questionnaire for Cholangiocarcinoma and Cancer of the Gallbladder; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; TTCD = time to confirmed deterioration.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase II, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of atezolizumab with bevacizumab in combination with CisGem, compared with atezolizumab in combination with CisGem, in patients with advanced BTC (i.e., iCCA, eCCA, or GBC) who have not received prior systemic therapy.

The study will enroll globally approximately 150 patients, who will be randomized in a 1:1 ratio to one of two treatment arms. The number of patients with either eCCA or GBC will be capped at a maximum of 50% of the total number of patients enrolled.

Treatment will consist of a chemotherapy combination phase followed by a CIT/placebo phase as outlined in Table 2.

Table 2 Study Treatment

Treatment Arm	Dose, Route, and Regimen (Drugs Listed in Order of Administration)	
	Chemotherapy Combination Phase [a] Cycles 1–8 (21-Day Cycles)	**CIT/Placebo Phase Cycles 9 and Beyond (21-Day Cycles)**
Arm A	Atezo + Bev + CisGem • Atezolizumab 1200 mg IV on Day 1 • Bevacizumab 15 mg/kg IV on Day 1 • Cisplatin 25 mg/m^2 IV on Days 1 and 8 • Gemcitabine 1000 mg/m^2 IV on Days 1 and 8	Atezo + Bev • Atezolizumab 1200 mg IV on Day 1 • Bevacizumab 15 mg/kg IV on Day 1
Arm B	Atezo + PBO + CisGem • Atezolizumab 1200 mg IV on Day 1 • Placebo IV on Day 1 • Cisplatin 25 mg/m^2 IV on Days 1 and 8 • Gemcitabine 1000 mg/m^2 IV on Days 1 and 8	Atezo + PBO • Atezolizumab 1200 mg IV on Day 1 • Placebo IV on Day 1

Atezo = atezolizumab; Bev = bevacizumab; CisGem = cisplatin and gemcitabine; CIT = cancer immunotherapy; PBO = placebo.

[a] Treatment during the chemotherapy combination phase will be administered on a 21-day cycle until completion of 8 cycles, loss of clinical benefit, or unacceptable toxicity, whichever occurs first.

Randomization will be stratified according to the following stratification factors:

- Location of primary tumor (iCCA vs. eCCA vs. GBC)
- Metastatic disease (yes vs. no)
- Geographic region (Asia vs. rest of the world)

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for 1 re-screening opportunity (for a total of 2 screenings per participant) at the investigator's discretion. Patients are not required to re-sign the Informed Consent Form if they are re-screened within 60 days after previously signing the Informed Consent Form. The investigator will record reasons for screen failure in the screening log (see Section 4.5.1).

Patients will continue treatment as indicated in Table 2 until unacceptable toxicity or loss of clinical benefit, as determined by the investigator after an integrated assessment of radiographic and biochemical data and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). In the absence of unacceptable toxicity, patients who meet the criteria for disease progression (as assessed by the investigator according

to RECIST v1.1; see Appendix 5) while receiving atezolizumab will be permitted to continue the study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in 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

Patients who transiently withhold or permanently discontinue one component of their treatment (i.e., either atezolizumab, bevacizumab/placebo, or chemotherapy) because of toxicity may continue with the other components of study treatment, as long as the patients are experiencing clinical benefit in the opinion of the investigator. However, bevacizumab/placebo should not be continued as a single agent.

Patients will undergo tumor assessments every 9 (±1) weeks following treatment initiation, as outlined in Section 4.5.5 and Appendix 1. Sites will collect and send imaging used for tumor assessments to an IRF to enable potential centralized, independent review of response and progression endpoints.

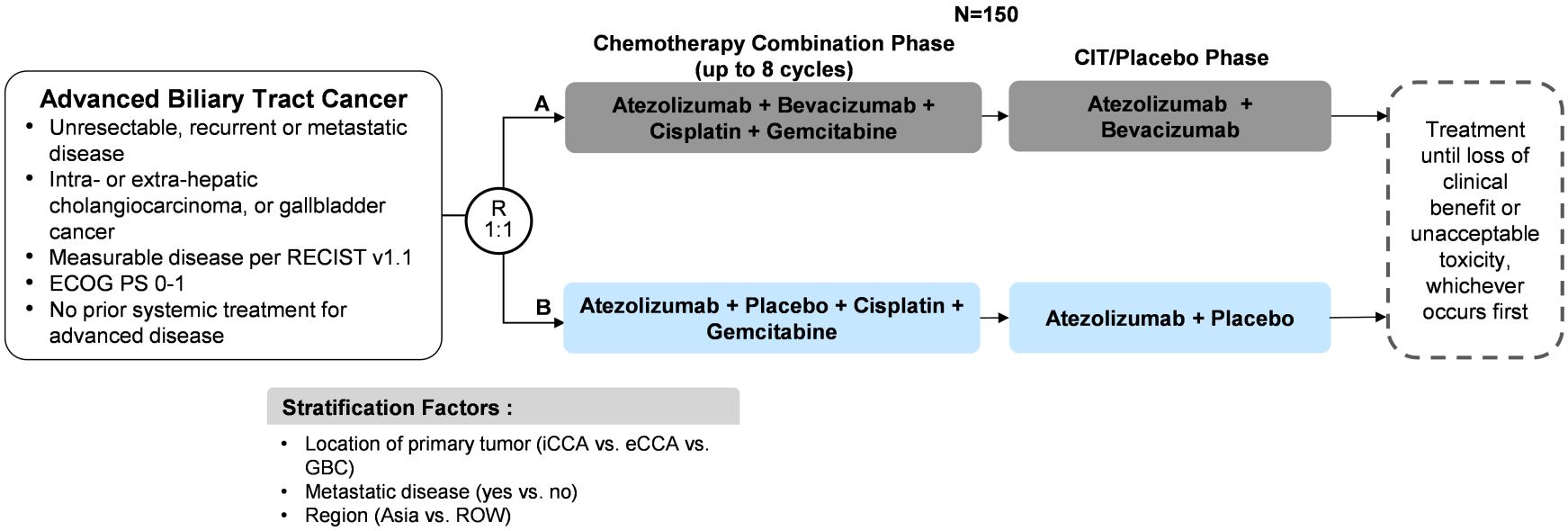
Following disease progression or loss of clinical benefit, patients will be followed for survival and subsequent anti-cancer therapies until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Patient-reported outcome (PRO) assessments will be completed before starting treatment, at specified timepoints during treatment, and at treatment discontinuation.

Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Serum samples will be collected to monitor the pharmacokinetics (PK) of atezolizumab when administered in combination with bevacizumab and/or CisGem. Patient samples, including archival of tumor tissues, as well as serum and plasma, will be collected for future exploratory biomarker assessments.

An overview of the study design is presented in Figure 1. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



CIT = cancer immunotherapy; eCCA = extrahepatic cholangiocarcinoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GBC = gallbladder cancer; iCCA = intrahepatic cholangiocarcinoma; R = randomization; RECIST = Response Evaluation Criteria in Solid Tumors; ROW = rest of the world.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date at which the last data required for study analysis are collected. The end of study will occur once the last patient, last visit occurs following the final OS analysis. The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3–5 years.

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

If the Sponsor decides to terminate the study, patients who are still receiving study treatment or undergoing survival follow-up may be enrolled in an extension study or a non-interventional study, if available.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab, as outlined in the prescribing information. Anti-tumor activity has been observed across doses, ranging from 1–20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical PK, efficacy, and safety data (see the Atezolizumab Investigator's Brochure for details).

3.3.2 Rationale for Bevacizumab Dose and Schedule

Bevacizumab will be administered at a dose of 15 mg/kg Q3W on Day 1 of each 21-day cycle, which is the approved dosage for bevacizumab (Avastin local labels). This dose schedule aligns with the atezolizumab dose schedule highlighted above and was the dose used in combination with atezolizumab in the GO30140, IMbrave150, and IMpower150 studies. In these studies, the combination of atezolizumab plus bevacizumab was generally safe and well-tolerated and no new safety signals related to the combination therapy were identified beyond the established safety profile for each individual agent. The results of the IMpower150 study showed that the addition of platinum-based chemotherapy to atezolizumab and bevacizumab was also generally safe, well-tolerated, and consistent with previously reported safety risks of the individual drugs.

3.3.3 Rationale for Patient Population

This study will enroll patients with advanced BTC who have not been previously treated for advanced disease. Consistent with other trials in BTC, the patient population will include patients with iCCA, eCCA and GBC. Patients with ampullary tumors will be excluded as these are thought to behave differently to other BTCs.

The prognosis for patients with advanced BTC is poor, with median survival rarely exceeding 1 year. As a result, a significant unmet need exists for new and effective treatments.

3.3.4 Rationale for Treatment Arms

The standard of care for first-line treatment for most patients with advanced BTC is CisGem. In this study, patients in both arms will receive this standard chemotherapy regimen in combination with either atezolizumab plus bevacizumab or atezolizumab plus placebo. Despite the failure of anti-VEGF agents combined with chemotherapy in advanced BTC, VEGF remains a rational target given its multifaceted role in maintaining an immunosuppressive TME. Immunotherapy with drugs targeting PD-1/PD-L1 has transformed cancer treatment, but this approach has not been well-studied in BTC. Preliminary data indicate limited clinical activity of single-agent anti–PD-1/PD-L1 antibodies, including atezolizumab, highlighting the need for combination regimens to augment anti-cancer immunity in patients with BTC. Biliary tract cancer has an unfavorable TME that is dominated by immunosuppressive elements, many of which are known to be regulated by VEGF. Collectively, these observations provide a compelling rationale to study atezolizumab in combination with bevacizumab and chemotherapy in patients with advanced BTC.

In this study, both treatment arms are considered experimental. This randomized Phase II study aims to assess the relative merits of both experimental regimens in order to inform the design of future studies in BTC.

The study does not include a CisGem-only treatment arm, given that this regimen has been well-characterized in previous randomized clinical trials (see Section 1.5.3).

3.3.5 Rationale for Continued Treatment of Atezolizumab/Bevacizumab and Atezolizumab/Placebo after Chemotherapy

The ability to treat patients on a continuous basis with platinum-based chemotherapy regimens is limited because of the risk of cumulative toxicity. In BTC, CisGem administration is typically limited to a maximum of 24 weeks or 8 cycles, and for most patients, clinical response is noted by 24 weeks (Furuse et al. 2011).

The toxicity profile and response for anti–PD-1/PD-L1 agents differ from chemotherapy and permit longer treatment durations. The incidence and nature of toxicities associated with immunotherapy is different from platinum-based chemotherapy regimens and PD-1/PD-L1 antibodies are generally considered to be more easily tolerated than chemotherapies. The combination of atezolizumab, bevacizumab, and carboplatin/paclitaxel was successfully evaluated by the Sponsor in patients with NSCLC adenocarcinoma in the IMpower150 Phase III study. This study protocol allowed for the continuation of atezolizumab, with or without bevacizumab, following the cessation of induction chemotherapy. In this study, the rate of serious adverse events with

atezolizumab either alone or in combination with bevacizumab during the maintenance phase were low and clinically manageable. Furthermore, the median durations of treatment with atezolizumab and bevacizumab were longer than the duration of chemotherapy; 8.2 months for atezolizumab (range: 0–26 months), 6.7 months for bevacizumab (range: 0–26 months), and 2.2 months for chemotherapy (range: 0–5 months; Socinski et al. 2018). The patterns of response to either PD-1 or PD-L1 inhibitors are different than that of chemotherapies, with clinical responses occurring in a delayed fashion or converting from either stable disease (SD) to RECIST-defined partial response (PR) or complete response (CR) or from PR to CR. Delayed initial anti-tumor response or late conversion to CR may occur sometime after stopping treatment with CisGem. For these reasons, continued treatment with atezolizumab or atezolizumab plus bevacizumab/placebo following cessation of chemotherapy may be clinically beneficial to patients with BTC.

3.3.6 Rationale for Progression-Free Survival as the Primary Endpoint

In this study, the primary efficacy endpoint will be investigator-assessed PFS. In BTC, PFS has been shown to strongly correlate with OS in a systematic review of data from 104 trials and is considered to be an appropriate surrogate endpoint of clinical benefit in BTC (Eckel and Schmid 2007). In addition, PFS is not generally confounded by subsequent therapies. Progression-free survival has been used successfully as a surrogate endpoint of benefit for advanced BTC to guide follow-on Phase III studies (Valle et al. 2009).

3.3.7 Rationale for Stratification Factors

Patients will be stratified according to anatomic subtype, presence of metastatic disease, and geographic region in order to balance key prognostic variables between treatment arms:

- Anatomic subtype: Each anatomic subtype of BTC has a distinct epidemiology, pathobiology, and prognosis (Rizvi et al. 2018). For example, iCCA has a better prognosis than other BTC subtypes, whereas GBC has a poorer prognosis (Furuse et al. 2011). Anatomic subtypes of BTC are also heterogeneous with respect to genetic background and TME composition, which may impact response to immunotherapy (Rizvi et al. 2018).
- Extent of disease: This study will enroll patients with either locally advanced tumors not amenable to surgical resection or metastatic disease. The presence of distant metastases is a poor prognostic factor (Park et al. 2009; Kim et al. 2017).

- Geographic region: Differences exist with respect to patient characteristics, treatment strategies, and clinical outcomes between Eastern and Western patients with BTC (Marcano-Bonilla et al. 2016; Olthof et al. 2019). The prevalence of risk factors such as fluke infestation and viral hepatitis varies by geographic region, which may contribute to a differential response to immunotherapy (Khan et al. 2019; Kelley et al. 2020).

3.3.8 Rationale for Atezolizumab Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, CR, PR, and SD 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 tumor-infiltrating immune cells and no viable cancer cells. Because of the potential for a response after pseudoprogression, this study will allow all patients to continue treatment after apparent radiographic progression per RECIST v1.1, provided the benefit–risk ratio is determined to be favorable by the investigator (for the criteria, see Section 3.1). Patients should be discontinued in the event of 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 for details).

3.3.9 Rationale for Biomarker Assessments

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 and anti–PD-L1 therapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). In this study, archival or newly collected tumor tissue will be obtained at baseline. If archival tumor tissue is not available, or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required, if deemed clinically feasible by the investigator. Archival or baseline tumor specimens will be tested for PD-L1 expression retrospectively by a central laboratory. In addition to the assessment of PD-L1 status, other exploratory biomarkers, such as potential predictive and prognostic biomarkers related to the clinical benefit of atezolizumab, bevacizumab, CisGem, and combinations of these therapies; or tumor immunobiology, mechanisms of resistance, or tumor type may be analyzed.

Tissue samples will be collected for DNA extraction to enable whole exome sequencing (WES) to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the

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

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

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

3.3.10 Rationale for Non-Standard Clinical Outcome Assessments

Patient experience with advanced BTC is complex and impacted by both disease- and treatment-related symptoms. Patients with advanced BTC present with a number of disease-related symptoms, which can differ according to the anatomic subtype and can include yellowing of the skin and eyes, itching, abdominal pain, appetite loss, weight loss, or fatigue, which negatively affect their daily functioning and health-related quality of life (Koeberle et al. 2008; Zabernigg et al. 2012). Such concepts are best documented through PRO instruments, which uniquely and directly capture patients' perspective of their disease, and ultimately provide clinicians with valuable information to support decision-making.

Cancer treatments, particularly combination therapies, can also produce significant symptomatic adverse events, some of which can overlap with disease-related symptoms. Recent research has shown that clinicians may underreport the incidence and severity of symptoms experienced by patients receiving treatment for cancer (Fromme et al. 2004; Trotti et al. 2007; Pakhomov et al. 2008; Basch 2010;

Quinten et al. 2011; Atkinson et al. 2012; Basch et al. 2014). Collecting adverse event information directly from patients can provide a better understanding of treatment characteristics and their effects. In order to evaluate the tolerability of the study treatments, patients will be asked to report on their experience related to four treatment-related symptoms selected from the validated PRO-Common Terminology Criteria for Adverse Events (PRO-CTCAE) item bank (see Appendix 11). Because there may be an overlap in these symptoms with those associated with advanced BTC, only symptoms that are uniquely associated with the study treatments were chosen from the PRO-CTCAE. The 4 symptoms were identified as being salient to patients' experience with the study treatments, on the basis of known adverse drug reactions, mechanism of action, and recent work to identify common adverse events associated with immunotherapies (King-Kallimanis et al. 2019; Hansen et al. 2020).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 150 patients with unresectable, recurrent or metastatic BTC will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at the time of signing the Informed Consent Form
- Ability to comply with the study protocol
- Considered to be eligible to receive platinum-based chemotherapy, in the investigator's judgment
- Documentation of recurrent/metastatic or locally advanced unresectable disease based on computed tomography (CT) or magnetic resonance imaging (MRI) scans (see Appendix 4)
- Histologically or cytologically confirmed diagnosis of iCCA, eCCA, or GBC
  - For patients with recurrent BTC, histologic confirmation of BTC at the time of resection is acceptable
- No prior systemic therapy (including systemic investigational agents) for advanced BTC
  - Prior chemotherapy or radiotherapy (with or without radio-sensitizing chemotherapy) in the neoadjuvant or adjuvant setting is permitted provided this is completed at least 6 months prior to Day 1 of Cycle 1
  - Prior treatment with gemcitabine administered as a radiation sensitizer in the neoadjuvant and adjuvant settings surrounding surgery, during and up to 4 weeks after radiation therapy is allowed, provided all toxicities have returned to baseline, or Grade 1 or better

- Previous use of herbal therapies and traditional Chinese medicines with anti-cancer activity included in the label is allowed, provided that these medications are discontinued prior to Day 1 of Cycle 1
- The following prior interventions are permitted, provided the patient has fully recovered:

  Surgery: Non-curative resection with macroscopic residual disease or palliative bypass surgery. Patients who have previously undergone curative surgery must have evidence of non-resectable disease requiring systemic chemotherapy.

  Photodynamic therapy: Prior photodynamic therapy for localized disease with no evidence of metastatic disease or for localized disease to relieve biliary obstruction in the presence of metastatic disease, provided patient has clear evidence of disease progression requiring systemic chemotherapy.

  Palliative radiotherapy: Palliative radiotherapy, provided that all adverse events have resolved and the patient has measurable disease outside the field of radiation.

- At least one measurable untreated lesion (per RECIST v1.1)
- Adequate biliary drainage with no evidence of ongoing infection
  - If applicable, treatable and clinically relevant biliary duct obstruction must be relieved by internal endoscopic drainage/stenting at least 2 weeks prior to Day 1 of Cycle 1 or by palliative bypass surgery or percutaneous drainage prior to Day 1 of Cycle 1, and the patient has no active or suspected uncontrolled infection
  - Patients fitted with a biliary stent should be clinically stable and free of signs of infection and have total bilirubin $\leq 2\times$ upper limit of normal (ULN) and AST/ALT $\leq 5\times$ ULN for ≥ 2 weeks prior to Day 1 of Cycle 1. Patients with improving biliary function who meet all other inclusion criteria may be re-tested during the screening window.
- Availability of a representative tumor specimen that is suitable for determination of PD-L1 status via central testing
  - A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 16 slides containing unstained, freshly cut, serial sections should be submitted along with an associated pathology report within 4 weeks of randomization
  - If FFPE specimens described above are not available, any type of specimen (including fine-needle aspiration, cell pellet specimens [e.g., from pleural effusion], and lavage samples) are also acceptable. This specimen should be accompanied by the associated pathology report.

    If archival tissue is either insufficient or unavailable, a core-needle biopsy specimen should be collected during the screening period, if clinically

feasible. Trans-jugular biopsy tissue sample collections for patients who are at high risk of bleeding may be allowed.

If archival tissue is either insufficient or unavailable and a fresh biopsy is not clinically feasible, the patient may still be eligible.

- Negative HIV test at screening with the following exception: Patients with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count $\geq 200/\mu L$, and have an undetectable viral load
- Documented virology status of hepatitis, as confirmed by screening hepatitis B virus (HBV) or hepatitis C virus (HCV) tests
  - For patients with active HBV: HBV DNA < 500 IU/mL during screening, initiation of anti-HBV treatment at least 14 days prior to Day 1 of Cycle 1 and willingness to continue anti-HBV treatment during the study (per local standard of care [e.g., entecavir])
  - Patients with HCV, either with resolved infection (as evidenced by detectable antibody) or chronic infection (as evidenced by detectable HCV RNA), are eligible
- Eastern Cooperative Oncology Group Performance Status of 0 or 1
- Life expectancy of > 3 months
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 7 days prior to Day 1 of Cycle 1 unless otherwise specified:
  - AST and ALT $\leq 2.5 \times$ ULN with the following exceptions:

    Patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN.
  - Serum bilirubin $\leq 2 \times$ ULN
  - Albumin ≥ 28 g/L (≥ 2.8 g/dL)
  - Creatinine clearance ≥ 60 mL/min (calculated using the Cockcroft-Gault formula)
  - Hemoglobin ≥ 90 g/L (≥ 9 g/dL)

    Patients may be transfused to meet this criterion.
  - Platelet count $\geq 100 \times 10^9$/L ($\geq 100{,}000/\mu L$) without transfusion
  - Lymphocyte count $\geq 0.5 \times 10^9$/L ($\geq 500/\mu L$)
  - ANC $\geq 1.5 \times 10^9$/L ($1500/\mu L$) without granulocyte colony-stimulating factor support
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 2 \times$ ULN
  - Proteinuria $< 2+$ on dipstick analysis (within 7 days prior to Day 1 of Cycle 1)

    Patients discovered to have $\geq 2+$ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection (or an alternative method such as protein: creatinine ratio, per local guidance) and must demonstrate < 1 g of protein in 24 hours.

- 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 while they are receiving atezolizumab and bevacizumab and for 5 months after the final dose of atezolizumab and for 6 months after the final dose of bevacizumab or CisGem, whichever is later. Women must refrain from donating eggs during this same period.
  - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
  - Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- For men: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:
  - With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of bevacizumab or CisGem, whichever is later, to avoid exposing the embryo. Men must refrain from donating sperm during this same period.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

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

- Recurrent disease $\leq$6 months after curative surgery or $\leq$6 months after the completion of adjuvant therapy (chemotherapy and/or radiation)
- Prior local regional therapy such as radioembolization
- Combined or mixed hepatocellular/CCA
- Clinically significant hepatic encephalopathy within the 12 months prior to Day 1 of Cycle 1
- National Cancer Institute Common Terminology Criteria for Adverse Events Grade $\geq$2 peripheral neuropathy
- Prior bleeding event due to untreated or incompletely treated esophageal and/or gastric varices within 6 months prior to Day 1 of Cycle 1

  Patients at high risk of esophageal varices are required to undergo an esophagogastroduodenoscopy (EGD) during screening or must have undergone an EGD within 6 months of Day 1 of Cycle 1. All size of varices (small to large) must be assessed and treated per local standard of care prior to Day 1 of Cycle 1. Patients at high-risk of esophageal varices who have had an EGD within 6 months of Day 1 of Cycle 1 do not need to repeat EGD at screening. Criteria for high-risk varices include at least one of the following:

  - Presence or history of cirrhosis
  - Presence or history of portal hypertension
  - Presence or history of primary biliary cirrhosis, or primary sclerosing cholangitis
  - HBV or HCV infection
  - Evidence of gross vascular invasion (portal vein, hepatic vein or collateral vessels)
  - Evidence of splenomegaly
  - Platelet count $<120\times10^9$/L (120,000/μL) and albumin $<$36 g/L (3.6 g/dL)
  - Evidence of portal vein occlusion due to malignant invasion or constriction
  - Evidence of varices by imaging
- Active or history of autoimmune disease or immune deficiency, including, but not limited to: myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, *granulomatosis with polyangiitis*, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 12 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study

- Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study
- Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  Rash must cover $<10\%$ of body surface area.

  Disease is well-controlled at baseline and requires only low-potency topical corticosteroids.

  There is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the 12 months prior to Day 1 of Cycle 1.

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to Day 1 of Cycle 1, unstable arrhythmia, or unstable angina
- History of malignancy other than BTC within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>90\%$), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Symptomatic, untreated, or actively progressing CNS metastases

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

  - Measurable disease, per RECIST v1.1, must be present outside the CNS.
  - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
  - Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
  - There is no evidence of interim progression between completion of CNS-directed therapy and initiation of study treatment.
  - The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, and neurosurgical resection within 28 days prior to initiation of study treatment.
  - The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anticonvulsant therapy at a stable dose is permitted.

  - Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.
- For patients with lung metastases, if one of the following criteria applies:
  - Large, centrally located pulmonary metastases
  - Clear tumor infiltration into the thoracic great vessels seen on imaging
  - Clear cavitation of pulmonary lesions seen on imaging
- Active tuberculosis
- Severe infection within 4 weeks prior to Day 1 of Cycle 1, 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 Day 1 of Cycle 1

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease [COPD] exacerbation) are eligible for the study, provided the signs of active infection have resolved
- Prior allogeneic stem cell or solid organ transplantation
- On the waiting list for liver transplantation
- 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 or within 5 months after the final dose of atezolizumab or within 6 months after the final dose of bevacizumab and/or CisGem
  - Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to Day 1 of Cycle 1
- Co-infection with HBV and HCV
  - Patients with a history of HCV infection but who are negative for HCV RNA by polymerase chain reaction will be considered to be negative for HCV infection
- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected serum calcium $>$ ULN)
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- History of allergic reactions to cisplatin or other platinum-containing compounds
- Known hypersensitivity to gemcitabine
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or bevacizumab formulations

- Treatment with a live, attenuated vaccine within 4 weeks prior to Day 1 of Cycle 1 or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Treatment with investigational therapy within 4 weeks prior to Day 1 of Cycle 1
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to Day 1 of Cycle 1
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to Day 1 of Cycle 1 or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
  - Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study
  - Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for COPD or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study
- Inadequately controlled arterial hypertension (defined as systolic blood pressure [BP] $>$150 mmHg and/or diastolic BP $>$100 mmHg), based on an average of at least 3 BP readings at 2 or more sessions
  - Anti-hypertensive therapy to achieve these parameters is allowed
- History of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1 of Cycle 1
- History of hemoptysis ($\geq$2.5 mL of bright red blood per episode) within 1 month prior to Day 1 of Cycle 1
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (within 10 days of Day 1 of Cycle 1) use of aspirin ($>$325 mg/day) or current or recent treatment with dipyridamole, ticlopidine, clopidogrel, and cilostazol
- Current or recent (within 10 days prior to Day 1 of Cycle 1) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose
  - Prophylactic anticoagulation for the patency of venous access devices is allowed provided the activity of the agent results in an INR $<$1.5$\times$ ULN and

aPTT is within normal limits (according to institutional standards) within 14 days prior to Day 1 of Cycle 1

  - Prophylactic use of low-molecular-weight heparin (i.e., 40 mg/day enoxaparin) is allowed. However, the use of direct oral anticoagulant therapies such as dabigatran (Pradaxa®) and rivaroxaban (Xarelto®) is not recommended due to bleeding risk

- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to Day 1 of Cycle 1
- History of abdominal or tracheoesophageal fistula, GI perforation, or intra-abdominal abscess within 6 months prior to Day 1 of Cycle 1
- 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
- Major surgical procedure within 4 weeks prior to Day 1 of Cycle 1 or anticipation of need for a major surgical procedure during the study
- History of clinically significant and uncontrolled intra-abdominal inflammatory disease within 6 months prior to Day 1 of Cycle 1, including, but not limited to, peptic ulcer disease, diverticulitis, or colitis
- Chronic daily treatment with a non-steroidal anti-inflammatory drug (NSAID)
  - Occasional use of NSAIDs for the symptomatic relief of medical conditions such as headache or fever is allowed
- Preexisting renal impairment, myelosuppression, or hearing impairment

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a randomized, double-blind study. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from the interactive voice or Web-based response system (IxRS).

Patients will be randomly assigned in a 1:1 ratio to one of two treatment arms:

- Arm A (Atezolizumab + Bevacizumab + CisGem)
- Arm B (Atezolizumab + Placebo + CisGem)

Randomization will occur through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified through an IxRS according to the stratification factors outlined in Section 3.1.

4.2.1 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the

exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, and IxRS service provider.

The Sponsor will remain blinded to treatment assignment until the time of the first interim analysis of PFS. Investigators and patients will remain blinded to treatment assignment until the time of the final analysis of OS, except in cases for which single-patient unblinding is necessary, as outlined below.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations. The investigator should inform the Medical Monitor that the treatment code has been broken.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. Unblinding may be permitted if an investigator is deciding whether a patient should withdraw from the study and initiate treatment with a proven therapy. However, unblinding will not be permitted if an investigator is deciding whether a patient should withdraw from the study and initiate treatment with an unproven therapy. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are atezolizumab and bevacizumab/placebo. Cisplatin and gemcitabine are considered non-IMPs.

4.3.1 Study Treatment Formulations and Packaging

4.3.1.1 Atezolizumab

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

4.3.1.2 Bevacizumab and Placebo

Bevacizumab will be supplied by the Sponsor as a sterile liquid in single-use, 16-mL, preservative-free glass vials that contain 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.

Matching placebo will be provided by the Sponsor. Placebo will be supplied as a sterile liquid in single-use, 16-mL, preservative-free glass vials that contain the vehicle without active ingredient. Further details are provided in the pharmacy manual.

4.3.1.3 Cisplatin and Gemcitabine

For information on the formulation and packaging of CisGem, see the local prescribing information for these drugs.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Treatment must be initiated no later than 3 business days after randomization, with the exception of the emergence of an adverse event for which dosing may be postponed.

If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule, with one exception:
If treatment was postponed for fewer than 3 days, the patient can resume the original schedule.

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

Details on treatment administration (e.g., dose and timing) 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.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 14 and Appendix 15.

4.3.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg Q3W on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, and clinical status (see Section 3.1 for details).

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

Table 3 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured 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 measured during the infusion and at 30 (±10) minutes after the infusion.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 14.

No dose modification for atezolizumab is allowed.

4.3.2.2 Bevacizumab and Placebo

Bevacizumab (Arm A) at a dose of 15 mg/kg or matching placebo (Arm B) will be administered after atezolizumab by IV infusion on Day 1 of each 21-day cycle. There will be a minimum 5-minute gap between administration of atezolizumab and bevacizumab/placebo. Treatment duration is described in Section 3.1.

The dose of bevacizumab will be based on the patient's weight (in kilograms) measured ≤14 days prior to Day 1 of Cycle 1 and will remain the same throughout the study unless there is a weight change of >10% from the baseline body weight, in which case the bevacizumab dose should be modified.

Administration of bevacizumab/placebo will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 13. Bevacizumab/placebo infusions will be administered per the instructions outlined in Table 4.

Table 4 Administration of First and Subsequent Bevacizumab/Placebo Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the bevacizumab/placebo infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Bevacizumab/placebo should be infused over 90 (±15) minutes. • Vital signs should be measured at the end of the infusion and 2 (±1) hours 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 measured within 60 minutes prior to the infusion. • Bevacizumab/placebo should be infused over 60 (±10) minutes if the previous 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/placebo may be infused over 30 (±15) minutes thereafter. • Vital signs should be measured at the end of the infusion and 2 (±1) hours after the infusion.

Guidelines for medical management of IRRs are provided in Appendix 14.

No dose modifications are permitted for bevacizumab/placebo aside from weight-based dose changes as outlined in the protocol.

4.3.3 Chemotherapy (Cisplatin and Gemcitabine)

Cisplatin will be administered by IV infusion at a dose of 25 mg/m^2 followed by gemcitabine at a dose of 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle.

Gemcitabine and cisplatin and accompanying supportive care will be administered according to the local prescribing information. In general, sites should also follow their institutional guidelines and local standard of care for determining dose adjustments in the event of changes in patient weight. Cisplatin will be administered after completion of the bevacizumab/placebo infusion, and gemcitabine will be administered after completion of the cisplatin infusion.

Dose modification guidelines are provided in Section 5.1.4 and Appendix 14.

4.3.4 Investigational Medicinal Product Handling and Accountability

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

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

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

Investigational medicinal products will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

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

4.3.5 Continued Access to Atezolizumab and Bevacizumab

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

A patient will be eligible to receive Roche IMPs (atezolizumab and bevacizumab) after completing the study if all of the following conditions are met:

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

A patient will not be eligible to receive Roche IMPs (atezolizumab and bevacizumab) after completing the study if any of the following conditions are met:

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

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available *from* the following website:

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

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to Day 1 Cycle 1 to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

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

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 4.1.1)
- Hormone-replacement therapy
- Prophylactic use of low-dose anti-coagulation, unfractionated heparin, or low molecular weight heparin (LMWH)
  - The preferred choice for anti-coagulation treatment is LMWH as per American Society of Clinical Oncology guidelines (Lyman et al. 2013)
- Vaccinations (such as influenza, COVID-19)
  - Live, attenuated vaccines are not permitted (see Section 4.4.3)
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) ≥ 7 days prior to Day 1 of Cycle 1 of the chemotherapy combination phase and during the CIT/placebo phase, as outlined below:
  - Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy. Bevacizumab/placebo must be held during palliative radiotherapy treatment. Upon completion of palliative radiotherapy treatment, continuation of bevacizumab/placebo treatment may be allowed.
- 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 3 or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole brain radiotherapy) and continue on study treatment, 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 and bevacizumab/placebo should be withheld during CNS-directed radiation therapy.

- Other local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:
  - Patients experiencing a mixed response requiring local therapy for control of 3 or fewer lesions may still be eligible to continue study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.
- Relief of biliary tract obstruction during study treatment
  - In the event of the development of obstructive jaundice due to biliary tract obstruction, appropriate measures will be undertaken to diagnose (e.g., by ultrasound and/or CT scan) and relieve the obstruction (e.g., by Endoscopic retrograde cholangiopancreatography [ERCP]/Percutaneous transhepatic cholangiography [PTC] $\pm$ stent insertion/drainage) in accordance with institutional standards of care.
  - Protocol treatment should be deferred until the liver function tests have sufficiently resolved to permit safely restarting study treatment in the opinion of the investigator.
  - Biliary tract obstruction by itself shall not constitute evidence of disease progression.
  - Imaging will be performed at the planned time points according to the protocol.
- On study tissue biopsies
  - The following precautions should be considered by the investigator with regard to the administration of bevacizumab or bevacizumab placebo after tumor biopsies; they are not expected to supersede institutional guidelines
    - Bevacizumab/placebo should not be administered until ≥ 3 days following the procedure and evidence of adequate wound healing is observed.
    - For patients undergoing needle biopsies of deep-seated lesions (e.g., liver or renal), hemoglobin, and hematocrit will be checked at the time of biopsy and prior to restarting bevacizumab/placebo, as clinically indicated.
    - Suggested post-biopsy hematocrit/hemoglobin thresholds include:

      For patients who have a < 2 unit decrease in hemoglobin (g/dL) or a $< 6\%$ decrease in hematocrit following the biopsy, bevacizumab may be restarted with appropriate clinical monitoring

      For patients who have a ≥ 2 but < 3 unit decrease in hemoglobin (g/dL) or a $\geq 6\%$ but $< 9\%$ decrease in hematocrit, bevacizumab may be restarted at the discretion of the investigator

      Patients who have a ≥ 3 unit decrease in hemoglobin (g/dL) or a $\geq 9\%$ decrease in hematocrit should be evaluated (e.g., by means of CT scan or

ultrasound), and bevacizumab may be restarted once the levels improve at the discretion of the investigator

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

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

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or 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 13).

4.4.2 Cautionary Therapy

4.4.2.1 Corticosteroids, Immunosuppressive Medications, and TNF-α Inhibitors

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

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (see Section 5.1 and Appendix 15 for details).

4.4.2.2 Herbal Therapies

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

4.4.3 Prohibited Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, is prohibited for various time periods prior to Day 1 of Cycle 1 (depending on the anticancer agent; see Section 4.1.2) and during study treatment until disease progression is documented and patient has discontinued study treatment. This includes, but is not limited to, the following:

- 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, 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 local therapy under certain circumstances (see Section 4.4.1 for details)
- Concomitant use of herbal therapies and traditional Chinese medicine with anti-cancer activity included in the label
- Investigational therapy within 4 weeks prior to Day 1 of Cycle 1 and during study treatment
- Live, attenuated vaccines (e.g., FluMist®) within 4 weeks prior to Day 1 of Cycle 1, during atezolizumab treatment, and for 5 months after the final dose of atezolizumab
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to Day 1 of Cycle 1 and during study treatment because these agents could potentially increase the risk of autoimmune conditions when given in combination with atezolizumab
- Current use of full dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purposes or anti-platelet therapy are prohibited within 10 days prior to Day 1 of Cycle 1 and during study treatment
  - Local label recommended doses for prophylactic use of anticoagulants or thrombolytic therapies are allowed.
  - Low-dose aspirin (<325 mg/day) is permitted. Coadministration of proton-pump inhibitors is strongly recommended to reduce potential GI damage.
  - If a patient experiences a venous thromboembolism event while still receiving study treatment, it may still be possible for the patient to continue study treatment despite anticoagulation treatment (see Section 4.1.2).

- Use of warfarin or warfarin-like products is not permitted (includes for prophylactic use)
- Concomitant chronic use of NSAIDs while receiving study treatment is prohibited, with the exception of chronic low-dose aspirin (<325 mg/day). However, for the symptomatic relief of medical conditions (e.g., headache, fever), sporadic or short-term intake of oral NSAIDs is allowed, when coadministered with proton-pump inhibitors to reduce potential GI damage

4.4.3.1 Prohibited and Cautionary Therapy for Gemcitabine-Treated Patients

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

4.4.3.2 Prohibited and Cautionary Therapy for Cisplatin-Treated Patients

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

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

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

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

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. The schedule of activities related to PRO assessments is provided in Appendix 2. All activities should be performed and documented for each patient.

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

4.5.1 Informed Consent Forms and Screening Log

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a detailed record of all patients screened and, to document eligibility or record reasons for screening failure, as applicable. Patients who do not initially meet all eligibility criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per patient) at the discretion of the investigator. Patients are not required to re-sign the Informed Consent Form if they are re-screened within 60 days after previously signing the Informed Consent Form. The investigator will record reasons for screen failure in the screening log.

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

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to Day 1 of Cycle 1 will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

4.5.3 Physical Examinations

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

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

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic BP, and temperature. Record abnormalities observed at baseline on the

General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Vital signs are to be measured before, during, and after infusions as outlined in Table 5, and at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

Table 5 Timing for Vital Sign Measurements for First and Subsequent Infusions

	Timing for Vital Sign Measurements	
Drug	**First Infusion**	**Subsequent Infusions**
Atezolizumab	• Within 60 minutes prior to the atezolizumab infusion • Record patient's vital signs during or after the infusion if clinically indicated	• Within 60 minutes prior to the atezolizumab infusion • Record patient's vital signs during or after the infusion if clinically indicated
Bevacizumab/ placebo	• Within 60 minutes prior to the bevacizumab/placebo infusion • At the end of infusion and 2 (±1) hours after the infusion	• Within 60 minutes prior to the bevacizumab/placebo infusion • At the end of infusion and 2 (±1) hours after the infusion

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline and every 9 (±1) weeks thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 or (for patients who continue atezolizumab plus bevacizumab or placebo, after radiographic disease progression) loss of clinical benefit, as determined by the investigator (see Section 3.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start a new anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to Day 1 of Cycle 1 do not have to be repeated at screening.

Screening assessments must include CT scans (with oral or IV contrast) or MRI scans 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 (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen and pelvis should be performed. A CT scan with contrast or MRI scan of the head must be done at screening to evaluate CNS metastasis in all

patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Bone scans and CT scans of the neck should also 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 (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

All measurable and evaluable lesions identified at baseline should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Objective response at a single timepoint will be determined by the investigator according to RECIST v1.1 (see Appendix 5). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology: RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils), and platelet count
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), magnesium, sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH
- Coagulation: INR and aPTT
- Thyroid-function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- HIV serology
- HBV serology: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody, total hepatitis B core antibody (HBcAb), and HBV DNA

  If a patient has a positive HBsAg test and/or a positive total HBcAb test at screening, an HBV DNA test and a quantitative HBsAg test must also be performed during screening to determine if the patient has an HBV infection, as well as at Cycles 5 and 9, and at the discontinuation visit. If local quantitative HBsAg test is not available, a qualitative HBsAg followed by a quantitative HBV DNA can be performed as an alternative.

- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- C-reactive protein
- CA19-9
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

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

- Serum samples for atezolizumab PK analysis through use of a validated assay
- Serum samples for assessment of anti-drug antibodies (ADAs) to atezolizumab through use of a validated assay
- Blood, serum, plasma, and peripheral blood mononuclear cell (PBMC) samples for exploratory research on biomarkers and biomarker assay development
- Whole metagenomics sequencing and comprehensive analysis of the microbiome will be performed on stool samples for exploratory microbiome research
- A representative tumor specimen that is suitable for determination of PD-L1 status via central testing

  A FFPE tumor specimen in a paraffin block (preferred) or at least 16 slides containing unstained, freshly cut, serial sections should be submitted along with an associated pathology report within 4 weeks of randomization

  If FFPE specimens described above are not available, any type of specimen (including fine-needle aspiration, cell pellet specimens [e.g., from pleural effusion], and lavage samples) are also acceptable. This specimen should be accompanied by the associated pathology report.

  If archival tissue is either insufficient or unavailable, a core-needle biopsy specimen should be collected during the screening period, if clinically feasible. Transjugular biopsy tissue sample collections for patients who are at high risk of bleeding may be allowed.

If archival tissue is either insufficient or unavailable and a fresh biopsy is not clinically feasible, the patient may still be eligible.

Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least 3 cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable.

If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required, if clinically feasible. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria.

Exploratory biomarker research may include, but will not be limited to, analysis of genes or gene signatures associated with tumor immunobiology, PD-L1, immune cell subpopulations, T cell–receptor repertoire, or cytokines associated with T-cell activation. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of next-generation sequencing of a comprehensive panel of genes. DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. Next-generation sequencing methods will include WES of tissue and blood samples, but WES of blood samples will be performed only at participating sites (see Section 4.5.9).

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

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

Biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Plasma and/or Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed
- Blood, plasma, serum, PBMC, and tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the Institutional Review Board (IRB)/Ethics Committee (EC)-approved Informed Consent Form and applicable laws (e.g., health authority requirements)
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database,

whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination

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

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

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

4.5.7 Electrocardiograms

An ECG is required at screening and when clinically indicated. Electrocardiograms for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. Electrocardiogram recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.8 Clinical Outcome Assessments

Patient-reported outcome instruments will be completed to more fully characterize the clinical profile of Atezolizumab + Bevacizumab + CisGem compared with Atezolizumab + Placebo + CisGem. Patient-reported outcome data will be collected through use of the following instruments:

- European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30)
- European Organisation for Research and Treatment of Cancer quality-of-life questionnaire for cholangiocarcinoma and cancer of the gallbladder (QLQ-BIL21)
- Selected items from the EORTC Item Library (IL) 77
- Patient Global Impression of Change and its Importance (PGI-CI)
- Patient Global Impression of Severity (PGI-S)
- Patient-Reported Outcome Common Terminology Criteria for Adverse Events (PRO-CTCAE)

4.5.8.1 Data Collection Methods for Clinical Outcome Assessments

Patient-reported outcome instruments will be completed at home or the clinic at specified timepoints during the study (see schedule of activities in Appendix 2). Instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

Patient-reported outcome instruments, translated into the local language as appropriate, will be completed during clinic visits through use of an electronic device provided by the Sponsor when possible. The device will be pre-programmed to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic device and instructions for completing the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel. In circumstances when the electronic device is not available (e.g., device failure or due to supply issues), a backup data collection method (e.g., web backup) will be used. Cycles 1–5 Day 15 PRO assessments will be completed at home via telephone interview with patient responses collected on the device (or web backup) by site staff.

Patients should be given the following instructions for completing PRO instruments at home:

- Patients should complete the instruments in a quiet area with minimal distractions and disruptions
- Patients should answer questions to the best of their ability; there are no right or wrong answers
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments

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

- Patients' health status should not be discussed prior to administration of the instruments
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 20 minutes at each specified visit
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers
- Site staff should not interpret or explain questions, but may read questions verbatim upon request

- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments

4.5.8.2 Description of Clinical Outcome Assessment Instruments

EORTC QLQ-C30

The EORTC QLQ-C30 is a validated and reliable self-reported measure (Aaronson et al. 1993; Fayers et al. 2001); see Appendix 6). It consists of 30 questions that assess 5 aspects of patient functioning (physical, emotional, role, cognitive, and social), Global Health Status and Quality of Life (GHS/QoL), and 9 symptoms (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. The functioning and symptoms items are scored on a 4-point scale that ranges from ″not at all″ to ″very much,″ and the GHS/QoL items are scored on a 7-point scale that ranges from ″very poor″ to ″excellent.″

EORTC QLQ-BIL21

The EORTC QLQ-BIL21 is a validated and reliable self-reported measure that serves as a modular supplement to the QLQ-C30 for use in patients with CCA and cancer of the gallbladder (Kaupp-Roberts et al. 2016; see Appendix 7). It consists of 21 questions that assess 8 symptoms (eating, jaundice, tiredness, pain, anxiety, treatment side effects, difficulties with draining bags/tube, and concerns regarding weight loss) with a recall period of the previous week. The scoring for the QLQ-BIL21 follows that of the QLQ-C30.

EORTC IL77

The EORTC IL77 is a reduced version of the QLQ-C30 that was created specifically for this study from the EORTC Quality of Life Group IIL (https://www.eortc.be/itemlibrary/). It consists of 12 questions that assess 2 aspects of patient functioning (physical and role), GHS/QoL, and 2 symptoms (nausea and vomiting, and appetite loss) with a recall period of the previous week (see Appendix 8). The scoring for the IL77 follows that of the QLQ-C30.

PGI-CI

The PGI-CI is a 2-item, self-reported measure used to assess patients' impression about changes to their overall health because of their cancer and the associated importance compared with when they began the study (see Appendix 9). In the first item, the PGI-CI utilizes a 7-point response scale that ranges from ″very much worse″ to ″very much improved″ (adapted from Guy et al. 1976). In the second item, the PGI-CI utilizes a 3-point response scale (″yes,″ ″no,″ and ″not applicable″) for patients to indicate if the change they experienced (and reported in the first item) was important to them.

PGI-S

The PGI-S is a 1-item, self-reported measure used to assess patients' impression about how severely their overall health has been impacted because of their cancer during the

preceding week (see Appendix 10). The PGI-S utilizes a 5-point response scale that ranges from ″very severe″ to ″none″ (adapted from Guy et al. 1976).

PRO-CTCAE

The PRO-CTCAE is a validated item bank that is used to characterize the presence, frequency of occurrence, severity, and/or degree of interference with daily function of 78 patient-reportable symptomatic treatment toxicities (Basch et al. 2014; Dueck et al. 2015). The PRO-CTCAE contains 124 questions that are rated either dichotomously (for determination of presence vs. absence) or on a 5-point Likert scale (for determination of frequency of occurrence, severity, and interference with daily function). Treatment toxicities can occur with observable signs (e.g., vomiting) or non-observable symptoms (e.g., nausea). The standard PRO-CTCAE recall period is the previous 7 days.

A subset of 4 symptoms deemed most applicable to the current treatments has been selected for this study (see Appendix 11). Symptoms have been selected on the basis of known adverse drug reactions, mechanism of action of the treatments under investigation, and recent work to identify common adverse events associated with immunotherapies (King-Kallimanis et al. 2019; Hansen et al. 2020).

4.5.9 Blood Samples for Whole Exome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WES to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WES is contingent upon the review and approval of the exploratory research by each site's IRB or EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WES, this section of the protocol (Section 4.5.9) will not be applicable at that site.

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

characterization of important biomarkers and pathways to support future drug development.

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

Blood samples collected for WES are to be stored no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

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

4.5.10 Optional Tumor Biopsies

Consenting patients will undergo optional tumor biopsies at 2–4 weeks after treatment initiation, at disease progression, and may undergo additional on-treatment biopsies at any other time at the investigator's discretion (if deemed clinically feasible by the investigator). Samples collected via resection, core-needle biopsy (at least 3 cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.6. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. See Section 4.5.6 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Stool Samples

Patients will be given the option of consenting to provide stool samples. Optional stool samples will be collected at baseline and one additional timepoint between Cycle 2 and Cycle 3.

The Informed Consent Form will contain a separate section that addresses optional stool samples. A separate, specific signature will be required to document a patient's agreement to provide optional stool samples. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Stool Sample Informed Consent eCRF.

The gut microbiome has been shown to be a key determinant in immune regulation in cancer, in part by influencing T-cell driven anti-tumor responses (Routy et al. 2018). For example, antibiotic treatment is associated with poor survival outcomes to anti–PD-1 therapy in NSCLC, RCC, and urothelial carcinoma (Elkrief et al. 2019). Conversely, the risk of colitis with CITs may be predicted based on a patient's pretreatment microbiome (Dubin et al. 2016; Chaput et al. 2017). Thus, heterogeneity in microbiome composition across patients may be a key driver of safety events in addition to efficacy. Whereas gut bacteria have been implicated in the development of liver cancer, their impact on the efficacy of CIT is still unknown.

This study will examine whether a patient's microbiome can determine response to a CIT combination, and conversely, whether a CIT combination can alter the microbiome to such an extent that on-treatment changes to the microbiome could be early predictors of adverse events, including colitis. Analyzing the microbiome in BTC may provide the opportunity to discover systemic effects on distal cancers.

Samples may be used for exploratory biomarker research as described in Section 4.5.6. See Section 4.5.6 for details on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

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

4.5.12 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (atezolizumab, bevacizumab/placebo, and chemotherapy) 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 determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- 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 for details)

If one component of study treatment is transiently withheld or permanently discontinued because of tolerability concerns, the patient may continue with the other components of study treatment until loss of clinical benefit, as long as the patients are experiencing

clinical benefit in the opinion of the investigator. However, bevacizumab/placebo should not be continued as a single agent.

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

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the final dose of study treatment. The visit at which response assessment shows progressive disease 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 (see Appendix 1).

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).

4.5.13 Patient Discontinuation from the Study

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

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

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

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

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

4.5.14 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.

4.5.15 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

The safety plan for patients in this study is based on clinical experience with atezolizumab and bevacizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections 5.1.1, 5.1.2, 5.1.3, and 5.1.4).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab and bevacizumab/placebo will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing patients who experience anticipated adverse events, including criteria for treatment interruption or discontinuation, are provided in Appendix 14, and Appendix 15. See Sections 5.2, 5.3, 5.4, 5.5, and 5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

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

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

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: 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, i*mmune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 15 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: GI perforations, hemorrhage, arterial thromboembolic events, fistulae, wound-healing complications, hypertension, venous thromboembolism, and proteinuria.

See Appendix 14 of the protocol and Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for bevacizumab.

5.1.3 Risks Associated with Combination Use of Atezolizumab and Bevacizumab

The risk of overlapping toxicities between atezolizumab and bevacizumab is anticipated to be minimal, based on the known safety profile of each agent and available data from clinical studies. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hemorrhage, hypothyroidism, and GI toxicity) may be ambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with bevacizumab could be exacerbated by the immunostimulatory activity of atezolizumab.

5.1.4 Risks Associated with Cisplatin or Gemcitabine

For adverse reactions, warnings, and precautions for CisGem, see the local prescribing information. See Section 5.1.5 for dose modifications and Appendix 14 for management of risks associated with CisGem.

5.1.5 Cisplatin and Gemcitabine Dose Modifications

The investigator may attribute toxicity to cisplatin or gemcitabine and use stepwise dose modifications according to Table 6. Dose modifications for hematologic toxicity will be based on blood counts obtained within 1 day prior to Days 1 and 8 of each cycle of therapy. Dose re-escalations are only permitted for the Day 8 gemcitabine dose adjustment for hematologic parameters. Treatment with filgrastim or pegfilgrastim may be used if needed. Investigators may follow institutional guidelines of local standard of care if they conflict with these recommendations, however treatment with sargramostim is not allowed.

Table 6 Dose-Modification Levels for Cisplatin and Gemcitabine

Treatment	Starting Dose	Dose Level –1	Dose Level –2	Dose Level –3	Dose Level –4
Cisplatin [a]	25 mg/m^2	20 mg/m^2	15 mg/m^2	Discontinue	–
Gemcitabine [b]	1000 mg/m^2	800 mg/m^2	600 mg/m^2	Discontinue	–

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

[b] Dose re-escalations are only permitted for the Day 8 gemcitabine dose adjustment for hematologic parameters.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

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

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

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

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

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

see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, IRRs, CRS, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- 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 arterial thromboembolic event
- Grade ≥3 venous thromboembolic event
- Any grade posterior reversible encephalopathy syndrome
- Grade ≥3 congestive heart failure
- *Myelitis*
- *Facial paresis*

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4, 5.5, and 5.6.

For each adverse event 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).

After initiation of study treatment on Day 1 of Cycle 1, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

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 (v5.0) 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 (v5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating ″yes″ or ″no″ accordingly. The following guidance should be taken into consideration (see also Table 8):

- 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 8 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 1 adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions and Cytokine Release Syndrome

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

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured on the Adverse Event eCRF as a diagnosis (e.g., ″infusion-related reaction″ or ″cytokine release syndrome″). Avoid ambiguous terms such as ″systemic reaction.″ Cases of late-onset CRS should be reported as ″cytokine release syndrome″ on the Adverse Event eCRF. Associated signs and symptoms of an IRR should be recorded on the dedicated Infusion-Related Reaction eCRF.

If a patient experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the

Adverse Event eCRF, with associated signs and symptoms of an IRR also recorded separately on the dedicated Infusion-Related Reaction eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 14.

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes

more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from ″non-serious″ to ″serious,″ providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.5 Abnormal Laboratory Values

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

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

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high BP), 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× ULN) in combination with either an elevated total bilirubin (>2× 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× ULN in combination with total bilirubin >2× ULN
- Treatment-emergent ALT or AST >3× ULN in combination with clinical jaundice

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

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of BTC 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 Biliary Tract Cancer

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 Cases of Accidental Overdose or Medication Error

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

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

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

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

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

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

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

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

As an example, an accidental overdose that resulted in a headache would require 2 entries on the Adverse Event eCRF, 1 entry to report the accidental overdose and 1 entry to report the headache. The ″Accidental overdose″ and ″Medication error″ boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO-CTCAE data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile patient reports of treatment-related symptoms (via the PRO-CTCAE) with investigator reports of adverse events. Sites are not expected to review the PRO-CTCAE data for adverse events.

5.3.5.14 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

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

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

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

5.4.1 Medical Monitors and Emergency Medical Contacts

Contact Information for Sites in North, South America and Europe

Medical Monitor/Roche Medical Responsible}: [redacted] M.D., Ph.D. (Primary)

Telephone No.: [redacted]

Mobile Telephone No.: +1 (650) 580-7063

Medical Monitor/Emergency Medical Contact: [redacted] Pharm.D. (Secondary)

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. 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 Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment on Day 1 of Cycle 1, serious adverse events and adverse events of special interest will be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab or 6 months after the final dose of bevacizumab or chemotherapy (CisGem). A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the final dose of bevacizumab or chemotherapy (CisGem). The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

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

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

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

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study 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).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

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

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

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

Drug	Document
Atezolizumab	Atezolizumab Investigator's Brochure
Bevacizumab	Bevacizumab 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 statistical considerations and analysis plan are summarized below.

Efficacy analyses will be performed based on the intent-to-treat (ITT) principle that all randomized patients, regardless of whether they receive the assigned treatment or not, will be included for analyses with patients grouped according to the treatment assigned at randomization. The ITT population will be used for the efficacy endpoints, including ORR, PFS, and OS. Duration of response (DOR) will be assessed in the DOR-evaluable population, a subset of the ITT population who achieve the best overall response as CR or PR. The PRO analyses of time to confirmed deterioration (TTCD) will be conducted based on the ITT population, and the remaining PRO analyses will be conducted in the PRO-evaluable population, which is a subset of the ITT patients with a non-missing baseline PRO assessment and at least 1 postbaseline PRO assessment.

Safety analyses will be conducted for all randomized patients who receive any amount of any component of study treatment, defined as safety-evaluable population, with patients grouped according to actual treatment received. The full set of the safety-evaluable patients will be included in analyses where applicable. For analyses that assess postbaseline changes compared with baseline values, a subset of the safety-evaluable population who do not have missing data at baseline and have at least one postbaseline value will be included for the analyses.

Pharmacokinetic and ADA analyses will be performed in all patients with at least 1 PK assessment and all patients with at least 1 postbaseline ADA assessment, respectively.

The final PFS analysis will be performed at the time when approximately 90 PFS events, as assessed by the investigator per RECIST v1.1, have been observed. The final OS

analysis will be performed when approximately 90 OS events have been observed or when all patients have been followed for a minimum of 2 years, whichever occurs first.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this Phase II study is estimation and hypothesis generation regarding the effect of atezolizumab with bevacizumab in combination with CisGem (Arm A) on PFS relative to atezolizumab in combination with CisGem (Arm B). Point and CI estimates of the true underlying HR of comparing PFS between Arm A and Arm B will be calculated. A total of approximately 150 patients will be randomized at a 1:1 randomization ratio to either Arm A or Arm B. It is assumed that the median duration of PFS in the control arm (Arm B) is 9 months. Operating characteristics (statistical power based on a two-sided significance level of 0.05 and expected total number of events) at the time of the final PFS analysis for true underlying HR values of 0.55, 0.60, and 0.70 are provided in Table 9. The final PFS analysis will occur when approximately 90 PFS events have been observed. The planned sample size of 150 patients, targeting approximately 90 PFS events at the time of the final PFS analysis, is considered to provide sufficient data and precision for the purpose of estimation of the HR point estimate and its 95% CI.

Table 9 Operating Characteristics for Proposed Study Design for Several Possible True Underlying PFS Hazard Ratio Values

	True Underlying HR		
	0.55	**0.60**	**0.70**
Expected number of events	90	90	90
Power [a]	81%	68%	39%
95% CI for true HR [b]	(0.36, 0.83)	(0.40, 0.91)	(0.46, 1.06)

HR = hazard ratio; PFS = progression-free survival.

Note: Operating characteristics are based on the following assumptions: PFS event times are exponentially distributed and median PFS in Arm B is 9 months.

[a] Two-sided $\alpha = 0.05$.

[b] Confidence intervals are based on the assumption that the PFS HR point estimate is equal to the true underlying value of the HR in each column.

It should be noted that the study is underpowered for detection of minimal clinically meaningful differences under an assumed true HR of 0.60 and above (see second and third columns of Table 9). Therefore, a clinically meaningful HR point estimate may not be statistically significant due to a low power.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study drug administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study drug discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

Descriptive statistics will be used in these summary tables. Continuous variables will be summarized using means, standard deviations, medians and ranges. Categorical variables will be summarized using counts and percentages.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity, stratification factors, etc.) will be summarized using means, standard deviations, medians, and ranges for continuous variables and counts and percentages for categorical variables, as appropriate. Summaries will be presented overall and by treatment arm.

6.4 EFFICACY ANALYSES

The primary analysis population for the efficacy analyses will be the ITT population and will consist of all randomized patients, with patients grouped according to their assigned treatment, regardless of whether they received any assigned study treatment or not.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is investigator-assessed PFS according to RECIST v1.1.

Investigator-assessed PFS is defined as the time from randomization to the occurrence of disease progression as determined by investigator according to RECIST v1.1, or death from any cause, whichever occurs first. Patients who have not experienced disease progression or death at the time of the clinical cutoff date will be censored at the time of the last tumor assessment at which they were known to be progression-free with radiographic evidence as of the clinical cutoff date. Patients with no postbaseline tumor assessment will be censored at the date of randomization.

A stratified Cox proportional-hazards model will be used to estimate the PFS HR and its 95% CI. A stratified two-sided log-rank test will be used to compare the investigator-assessed PFS between Arm A and Arm B at the two-sided significance level of 0.05. The stratification factors for these stratified analyses are location of primary tumor (iCCA vs. eCCA vs. GBC), metastatic disease (yes vs. no), and geographic region (Asia vs. rest of the world). However, if at least one stratum has fewer than 10 events at the time of analysis, the level of stratification factor that contains the smallest number of events will be combined with other levels of the same stratification factor for the stratified analysis. The final set of stratification factors used in the primary endpoint analysis will

be applied to all other endpoints where stratified analyses are performed.
The stratification information will be obtained from the IxRS at the time of randomization. Results from an unstratified analysis will also be provided. The Kaplan-Meier method will be used to estimate median PFS for each treatment arm. The Brookmeyer-Crowley methodology will be used to calculate the 95% CI for the median PFS of each treatment arm.

To assess the homogeneity of the treatment effect with respect to the primary efficacy endpoint of PFS, forest plots (including the estimated HRs) for clinically relevant subgroups will be provided.

To assess the robustness of the primary PFS analysis, a sensitivity analysis will be performed by incorporating an additional censoring rule for patients who take new anti-cancer therapy prior to occurrence of radiographic progression. These patients will be censored at the last tumor assessment before start of the new treatment, regardless of progression or death afterwards.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are OS, investigator-assessed confirmed ORR, DOR, and DCR, and TTCD in patient-reported physical functioning, role functioning, and quality of life.

6.4.2.1 Overall Survival

Overall survival is defined as the time from randomization to death from any cause. Data for patients who are not reported as having died at the time of the clinical cutoff date will be censored at the date last known to be alive. Data for patients who do not have postbaseline information will be censored at the date of randomization.

The analysis methods for OS will be similar to those described for PFS.

6.4.2.2 Confirmed Objective Response Rate

Confirmed ORR is defined as the proportion of patients with a CR or PR on two consecutive occasions $\geq$4 weeks apart, as determined by the investigator according to RECIST v1.1. Patients without any postbaseline tumor assessments will be considered as non-responders.

The confirmed ORRs for each treatment arm will be calculated based on the ITT population, and the respective 95% CIs will be estimated using the Clopper-Pearson method. The confirmed ORRs will be compared between Arm A and Arm B using the stratified Cochran-Mantel-Haenszel test, and the ORR difference between these 2 arms will be also calculated with 95% CI being computed using the normal approximation to the binomial distribution.

6.4.2.3 Duration of Response

Duration of response is defined as the time from the first occurrence of a confirmed objective response to disease progression as determined by the investigator according to RECIST v1.1 or death from any cause (whichever occurs first). Data for patients who are alive and who have not experienced disease progression at the time of the clinical cutoff date will be censored at the date of the last tumor assessment at which they were known to be progression-free.

The DOR will be analyzed for the subset of ITT patients who have the best confirmed response as PR or CR. The median DOR and its 95% CI for each treatment arm will be estimated by Kaplan-Meier methodology.

6.4.2.4 Disease Control Rate

Disease control rate is defined as the proportion of patients with CR or PR on two consecutive occasions $\geq$4 weeks apart, or SD with a minimum duration of 9 weeks, as determined by the investigator according to RECIST v1.1.

The DCR for each treatment arm will be calculated based on the ITT population, with the respective 95% CIs being estimated using the Clopper-Pearson method.

6.4.2.5 Time to Confirmed Deterioration

Time to confirmed deterioration in patient-reported physical functioning, role functioning, and quality of life, as measured by the respective scales of the EORTC QLQ-C30 and/or EORTC IL77, is defined as the time from randomization to the first clinically meaningful deterioration that is either maintained for two consecutive assessments or followed by death from any cause within 3 weeks. Clinically meaningful deterioration will be defined using anchor-based analyses, details for which will be pre-specified in a separate statistical analysis plan.

The TTCD analyses will be conducted in the ITT population, and the analysis methods will be similar to those described for PFS.

6.4.3 Exploratory Efficacy Endpoints

6.4.3.1 Exploratory Progression-Free Survival

Progression-free survival rates at specified timepoints (e.g., 6 and 12 months), defined as the probability that a patient will be alive without experiencing disease progression, as determined by the investigator according to RECIST v1.1, at specified timepoints. The PFS rates will be estimated using the Kaplan-Meier methodology.

6.4.3.2 Exploratory Overall Survival

Overall survival rates at specific timepoints (e.g., 6 months and 12 months), defined as the probability that a patient will be alive at specified timepoints will be estimated using the Kaplan-Meier methodology.

6.4.3.3 Exploratory Patient-Reported Outcome Endpoints

Completion rates and reasons for missing data will be summarized for the EORTC QLQ-C30, EORTC QLQ-BIL21, EORTC IL77, PGI-CI, and PGI-S at each treatment cycle by treatment arm and within the ITT population.

Visit mean summary and change from baseline analyses will be performed for all scales of the EORTC QLQ-C30, EORTC QLQ-BIL21, and EORTC IL77. Summary statistics (e.g., number of patients, mean, standard deviation, median, minimum, maximum, 95% CI) of linearly transformed scores (per the EORTC scoring manual) will be calculated at all assessment timepoints for each study arm. These analyses will be performed in the PRO-evaluable population.

Summary statistics (e.g., number of patients, proportions) will be calculated for the PGI-CI and PGI-S in the PRO-evaluable population.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received any amount of any component of study treatment, with patients grouped according to treatment received.

6.5.1 Analyses of Exposure, Adverse Event, Laboratory, Vital Sign, and ECG Data

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, number of cycles, and dose intensity) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment or worsen after the first dose of study treatment for existing baseline conditions (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, BP, 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 postbaseline severity grades. Changes in vital signs and ECGs will be summarized.

6.5.2 Exploratory Analyses of PRO-CTCAE Data

Patient-reported outcome-CTCAE analyses will be descriptive, with a focus on characterizing the pattern of symptomatic treatment toxicities over the course of the study. Results from these exploratory analyses will be presented separately from the other safety analyses. Patient-reported outcome-CTCAE data will be analyzed at the item level in line with current NCI CTCAE recommendations for data handling (Basch et al. 2014).

Patient-reported outcome-CTCAE data will be summarized over time. The proportion of missing data at each assessment timepoint will also be summarized to facilitate interpretation of data.

The number and percentage of patients reporting each symptom and the change from baseline by category (presence, frequency of occurrence, severity, interference) will be summarized at each assessment timepoint by treatment arm. For items that are rated on a 5-point Likert scale, the maximum postbaseline score and change from baseline will be summarized by treatment arm.

Graphical representation of PRO-CTCAE data over time may also be provided.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of all patients with at least 1 PK assessment.

Samples will be collected for PK analyses and serum concentrations of atezolizumab will be reported as individual values and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) by treatment arm and cycle, when appropriate and as data allow. Individual and median serum atezolizumab concentrations will be plotted for PK-evaluable patients by day.

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, as warranted by the data. Potential correlations of relevant PK parameters with dose, safety, efficacy, or biomarker outcomes may be explored.

Additional PK and pharmacodynamic analyses will be conducted as appropriate.

6.7 IMMUNOGENICITY ANALYSES

Immunogenicity analysis in this study will be based on ADAs to atezolizumab. The immunogenicity analysis population will consist of all patients with at least 1 postbaseline ADA assessment. Patients will be grouped according to treatment received.

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

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

6.8 BIOMARKER ANALYSES

Exploratory biomarker data may be analyzed in the context of this study and in aggregate with data from other studies.

6.9 INTERIM ANALYSES

6.9.1 Planned Interim Analysis

One interim analysis of PFS and ORR will be performed at the time when 100 patients have been followed for at least 6 months, and is estimated to occur at approximately 12 months after the first patient is enrolled. All of the planned 150 patients are expected to have been randomized in the study at the time of this planned interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel, who will have full access to unblinded data at the time of analysis. Access to treatment assignment information will follow the Sponsor's standard procedures and will not be given to the Sponsor until the first interim analysis within this study is being conducted.

6.9.2 Optional Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The optional interim analysis will be performed and interpreted by Sponsor study team personnel, who will have full access to unblinded data at the time of analysis. Access to treatment assignment information will follow the Sponsor's standard procedures and will not be given to the Sponsor until the first interim analysis within this study is being conducted.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

Electronic Case Report Forms 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

Electronic Case Report Forms 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. Electronic Case Report Forms 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. Electronic Case Report Forms should be reviewed and electronically signed and dated by the investigator or a designee.

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

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

An electronic device will be used to capture PRO data when possible (see Section 4.5.8.1). The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure method. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored

by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

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.

7.5 USE OF COMPUTERIZED SYSTEMS

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

trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

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

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters

(e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

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

Approximately 75 sites globally will participate to randomize approximately 150 patients. Screening and enrollment will occur through an IxRS.

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

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted 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 made available upon request. For more information, see 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.

9.7 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities

Day	Screening [a]	Treatment Cycles (21-Day Cycles) [b]			Treatment Discontinuation Visit [c] ≤30 Days after Final Dose	Follow-Up
		Chemotherapy Combination Phase (Cycles 1–8)		CIT/Placebo Phase (Cycles 9 and Beyond)		
Day	Days –28 to –1	Day 1	Day 8	Day 1		
(Window)		(±3 Days)				
Informed consent [d]	x					
Baseline tumor tissue sample [e]	x					
Demographic data	x					
Medical history, including cancer, and baseline conditions [f]	x					
PRO assessments [g]		See Appendix 2				
Vital signs [j]	x	x		x	x	
Weight [k]	x	x [k]	x [k]	x [k]		
Height	x					
Complete physical examination [l]	x					
Limited physical examination [l]		x [m]		x [m]	x	
ECOG Performance Status	x	x [m]		x [m]	x	
ECG [n]	x	If clinically indicated				
EGD [o]	x					
Hematology [p]	x [q]	x	x	x [m]	x	
Chemistry profile (serum or plasma) [r]	x [q]	x [m]		x [m]	x	

Appendix 1: Schedule of Activities

Day	Screening [a]	Treatment Cycles (21-Day Cycles) [b]			Treatment Discontinuation Visit [c] ≤30 Days after Final Dose	Follow-Up
		Chemotherapy Combination Phase (Cycles 1–8)		CIT/Placebo Phase (Cycles 9 and Beyond)		
	Days –28 to –1	Day 1	Day 8	Day 1		
(Window)		(±3 Days)				
Coagulation tests: INR and aPTT	x [q]				x	
Pregnancy test [s]	x	x		x	x	
TSH, free T3, and free T4 [t]	x	x [t]			x	
CA 19-9	x	x		x	x	
C-reactive protein		x		x	x	
HIV, HBV, HCV serology [u]	x					
Quantitative HBsAg, HBV DNA, HCV RNA [v]	x			x	x	
Urinalysis [w]	x	x [m]		x [m]		
Atezolizumab IV infusion [x]		x		x		
Bevacizumab/placebo IV infusion [x]		x		x		
Cisplatin and gemcitabine IV infusions [x]		x	x			
Concomitant medications [y]	x	x		x	x	
Tumor assessment [z, aa]	x [z]	x [aa]				
Adverse events [bb]		x	x	x	x	x
Serum sample for ADA and PK assessment [cc]		See Appendix 3				
Blood samples for biomarkers (central laboratory) [cc]		See Appendix 3				
Fresh tumor tissue biopsy sample (optional)		See Appendix 3				

Appendix 1: Schedule of Activities

Day	Screening [a]	Treatment Cycles (21-Day Cycles) [b]			Treatment Discontinuation Visit [c] ≤30 Days after Final Dose	Follow-Up
		Chemotherapy Combination Phase (Cycles 1–8)		CIT/Placebo Phase (Cycles 9 and Beyond)		
	Days –28 to –1	Day 1	Day 8	Day 1		
(Window)		(±3 Days)				
Stool sample (optional)	x	See Appendix 3				
Survival and anti-cancer therapy follow-up [dd]						x

Appendix 1: Schedule of Activities

ADA = anti-drug antibody; CIT = cancer immunotherapy; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EGD = esophagogastroduodenoscopy; EORTC = European Organisation for Research and Treatment of Cancer; FFPE = formalin-fixed, paraffin-embedded; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PK = pharmacokinetic; PRO = patient-reported outcome; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = free triiodothyronine; T4 = free thyroxine.

Notes: All assessments will be performed on the day of the specified visit unless a time window is specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule. If treatment was postponed for fewer than 3 days, the patient can resume the original schedule. Screening local laboratory assessments obtained ≤96 hours prior to the initiation of study treatment do not have to be repeated for Cycle 1.

[a] Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 of Cycle 1 may be used; such tests do not need to be repeated for screening.

[b] During the study treatment period, assessments scheduled on the days of study treatment infusions, should be performed before the infusion unless otherwise noted.

[c] Patients will be asked to return to the clinic no more than 30 days after the final dose of study treatment for a treatment discontinuation visit.

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Representative tumor specimens in formalin fixed paraffin-embedded (FFPE) blocks (preferred) or at least 16 unstained slides with an associated pathology report should be submitted within 4 weeks of randomization. A patient with insufficient or unavailable archival tissue or without a fresh biopsy sample may be eligible. See Section 4.1.1 for tissue sample requirements.

[f] Medical history, including clinically significant diseases, surgeries, reproductive status, smoking history, and use of alcohol, will be recorded at screening. Cancer history includes stage, date of diagnosis, and prior cancer therapies and procedures.

[g] The ±3-day window only applies to visit scheduling. PROs should be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments and prior to the administration of study treatment (−3-day window). In scenarios where laboratory assessments (e.g., blood draws) are done at a different location than the one providing treatment or when they are done on a different day than study treatment administration, laboratory assessments can be completed before the completion of PROs (−3 days) as long as results have not been discussed with patients.

[j] Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Vital signs should be recorded as described in Section 4.5.4.

[k] The dose of bevacizumab/placebo will be based on the patient's weight (in kilograms) measured ≤14 days prior to baseline (the initiation of study treatment) and will remain the same throughout the study unless there is a weight change of >10% from baseline body weight, in which case the bevacizumab dose should be modified. Body weight will be re-baselined at the time of dose change, and dose modifications should occur if the patient's weight changes >10% from the new baseline. In general, sites should also follow their institutional guidelines and local standard of care for determining chemotherapy dose adjustments in the event of changes in patient weight.

[l] Complete and limited physical examinations are defined in Section 4.5.3.

[m] ECOG Performance Status, limited physical examination, local laboratory assessments, and PRO assessments may be obtained ≤96 hours before Day 1 of each cycle.

[n] An ECG is required at screening and when clinically indicated. Electrocardiograms for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. Electrocardiogram recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

[o] Patients at high risk of esophageal varices are required to undergo an EGD during screening or must have undergone an EGD within 6 months of Day 1 of Cycle 1. Please refer to Section 4.1.2 for risk criteria.

[p] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils), and platelet count.

[q] At screening, patients must have adequate hematologic and end-organ function defined by laboratory results obtained within 7 days prior to Day 1 of Cycle 1, as described in Section 4.1.1. Screening local laboratory assessments obtained ≤96 hours prior to the initiation of study treatment do not have to be repeated for Cycle 1.

[r] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), magnesium, sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH.

[s] All women of childbearing potential (including those who have had a tubal ligation) must have a serum pregnancy test performed at screening and documented as negative within 14 days prior to Day 1 of Cycle 1. During the study, urine pregnancy tests will be performed on Day 1 of every cycle. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[t] TSH, free T3 (or total T3 at sites where free T3 is not performed), and free T4 will be collected at screening, on Day 1 of Cycle 1, and every fourth cycle thereafter (e.g., Cycles 1, 5, 9, 13, and so forth).

[u] During screening, patients will be tested for HIV, HBsAg, HBsAb, total HBcAb, and HCV antibody. HBV DNA test must be performed during screening in patients who have positive serology for HBsAg and/or positive serology for HBcAb. If a patient has a positive HCV antibody test during screening, an HCV RNA test must also be performed.

[v] If a patient tests positive for HBsAg and/or HBcAb, quantitative HBsAg and HBV DNA will be tested during screening, Day 1 of Cycles 5 and 9, and at the discontinuation visit. If a patient tests positive for HCV antibody during screening, quantitative HCV RNA must be tested locally during screening, on Day 1 of Cycles 5 and 9, and at the discontinuation visit. If local quantitative HBsAg test is not available, a qualitative HBsAg followed by quantitative HBV DNA can be performed as an alternative. Study treatment and procedures may proceed while HBV DNA is being processed, but results should be reviewed by the investigator as soon as they are available. If HBV DNA increases to ≥500 IU/mL, consultation with a hepatologist or gastroenterologist with specialty in HBV is recommended. The Medical Monitor is available to advise as needed.

[w] Urinalysis includes PH, specific gravity, glucose, protein, ketones, and blood. Dipstick is permitted. Urine dipstick for proteinuria at screening must be $<2+$ within 7 days prior to Day 1 of Cycle 1. Patients discovered to have $\geq 2+$ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate <1 g of protein in 24 hours. Urinalysis/urine dipstick should be repeated before every cycle during treatment.

[x] Atezolizumab will be administered prior to bevacizumab/placebo. Patients will receive atezolizumab by continuous IV infusion every 21 days on Day 1 of each 21-day cycle as indicated. For atezolizumab, the initial dose 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. Following atezolizumab, patients will receive bevacizumab/placebo by continuous IV infusion every 21 days on Day 1 of each 21-day cycle as indicated. The initial dose of bevacizumab/placebo will be delivered over 90 (± 15) minutes. Subsequent infusions will be delivered over 60 (± 10) minutes if the previous continuous IV infusion was tolerated without infusion-associated adverse events, or 90 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. 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. During the chemotherapy combination phase, patients will receive cisplatin at a dose of 25 mg/m^2 IV followed by gemcitabine at a dose of 1000 mg/m^2 by continuous IV infusion on Days 1 and 8 of each 21-day cycle. Cisplatin will be administered after completion of the bevacizumab/placebo infusion, and gemcitabine will be administered after completion of the cisplatin infusion. Dosing of all study drugs will occur only if the clinical assessment and local laboratory test results are acceptable. If a tumor assessment was performed, results must be reviewed by the investigator before dosing of study treatment.

[y] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to Day 1 of Cycle 1 should be documented until the treatment discontinuation visit. At study visits, changes to current medications or medications used since the last documentation will be recorded.

[z] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as a standard of care prior to obtaining informed consent and within 28 days prior to Day 1 of Cycle 1 do not have to be repeated at screening. Screening assessments must include CT scans (with oral or IV contrast) or MRI scans 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 (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen and pelvis should be performed. A CT scan with contrast or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Bone scans and CT scans of the neck should also 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.

[aa] Patients will undergo tumor assessments at baseline and every 9 (±1) weeks thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 or (for patients who continue atezolizumab plus bevacizumab or placebo, after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 3.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected. All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[bb] After informed consent has been obtained, but prior to Day 1 of Cycle 1, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment or until initiation of a new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. 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 adverse event should be reported (see Section 5.6).

[cc] See Appendix 3 for details of the PK, immunogenicity, and biomarker collection schedule. Blood samples may be processed at sites to obtain serum and plasma, as described in the laboratory manual.

[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.

Appendix 2
Schedule of Patient-Reported Outcome Assessments

	All Treatment Cycles (21-Day Cycles) [a]							Treatment Discontinuation Visit [b] ≤30 Days after Final Dose
	Chemotherapy Combination Phase						CIT/Placebo Phase	
	Cycles 1–2			Cycles 3–5		Cycles 6–8	Cycles 9 and Beyond	
Day	Day 1	Day 8	Day 15 [c]	Day 1	Day 15 [c]	Day 1	Day 1	
(Window)	(−3 Days)							
EORTC QLQ-C30	x						x (Cycles 9 and 11 only)	x
EORTC IL77				x		x	x (Odd cycles 13+ only)	
EORTC QLQ-BIL21	x			x		x	x (Odd cycles 9+ only)	x
PGI-CI				x (Cycle 3 only)		x (Cycle 6 only)	x (Cycle 9 only)	x
PGI-S	x			x (Cycle 3 only)		x (Cycle 6 only)	x (Cycle 9 only)	x
PRO-CTCAE	x	x	x [c]	x	x [c]	x	x (Odd cycles 9+ only)	x

Appendix 2 Schedule of Patient-Reported Outcome Assessments

CIT = cancer immunotherapy; EORTC = European Organisation for Research and Treatment of Cancer; IL = item library; PGI-CI = Patient Global Impression of Change and its Importance; PGI-S = Patient Global Impression of Severity; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcome Common Terminology Criteria for Adverse Events; QLQ-BIL21 = Quality-of-Life Questionnaire for Cholangiocarcinoma and Cancer of the Gallbladder.

[a] All PRO assessments will be completed at the clinic, except for the Day 15 PRO-CTCAE which will be completed from home. The ± 3-day window only applies to visit scheduling. PROs should be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment (– 3-day window). In scenarios where laboratory assessments (e.g., blood draws) are done at a different location than the one providing treatment or when they are done on a different day than study treatment administration, laboratory assessments can be completed before the completion of PROs (– 3 days) as long as results have not been discussed with patients.

[b] Patients will be asked to return to the clinic not more than 30 days after the final dose of study treatment for a treatment discontinuation visit.

[c] These PRO assessments will be completed at home via telephone call.

Appendix 3
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Visit	Timepoint	Sample Type
• Screening and between Cycle 2 and Cycle 3 (optional)		• Stool sample (optional)
• Day 1 of Cycle 1	• Prior to any drug administration	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Blood biomarker (PBMC) • Serum biomarker • Plasma biomarker • Blood (WES) [a]
	• 30 (±10) minutes after end of atezolizumab infusion	• Atezolizumab PK (serum)
• Day 1 of Cycles 2, 3, 4, 8, 12, and 16	• Prior to any drug administration	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Blood biomarker (PBMC) • Serum biomarker • Plasma biomarker
• 2–4 weeks after treatment initiation and at disease progression (optional)		• Fresh tumor tissue biopsy sample (optional) [b]
• Treatment discontinuation visit (≤30 days after final dose) [c]	• At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Blood biomarker (PBMC) • Serum biomarker • Plasma biomarker

ADA = anti-drug antibody; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; WES = whole exome sequencing.

[a] Blood sample for WES to be collected at Day 1 of Cycle 1, or as soon as possible after enrollment. Collection for participating sites only.

[b] For patients who consent to collection of optional biopsies, optional tumor biopsy samples may be collected by core-needle or excisional or punch biopsy at the investigator's discretion. Preferably, growing lesions should be selected.

[c] If biomarker samples have been collected or will be collected at a visit within 7 days of the biopsy procedure date, an additional biomarker sample collection is not required

Appendix 4
Staging Criteria for Advanced Biliary Cancers

BTC subtype	Locally advanced	Metastatic
Extrahepatic (Biliary confluence involvement)	• Bilateral extension to second-order biliary radicles • Encasement or occlusion of hepatic artery (or bilateral involvement of hepatic arteries) • Encasement or occlusion of portal vein • Atrophy of one liver lobe with contralateral portal branch or hepatic artery involvement • Extrahepatic adjacent local invasion (vessels or organs)	• Multifocal masses within different liver segments • Metastatic lymph nodes beyond the hepatoduodenal ligament • Extrahepatic disseminated disease (e.g., lung, bone, peritoneum)
Intrahepatic (Hepatic mass without biliary confluence involvement)	• Hepatic artery involvement • Multifocal masses within the same liver segment • Extrahepatic adjacent local invasion (vessels or organs)	
Gallbladder	• Large intrahepatic adjacent local invasion • Extrahepatic adjacent local invasion (vessels, bile ducts or organs)	

BTC = biliary tract cancer.

REFERENCE

Malka D, Cervera P, Foulon S, et al. Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial. Lancet Oncol 2014;15:819–828.

Appendix 5
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 ≤5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

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

[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) since they are, by definition, simple cysts
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if 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, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

Computed tomography 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 a 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. Magnetic resonance imaging 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 the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or

new lesions on a different modality, since 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 used 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 5 lesions total (and a maximum of 2 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 1 or 2 organ sites involved, a maximum of 2 lesions (1 site) and 4 lesions (2 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 should be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. 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 CR criteria are met, since 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 the 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 since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and ″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: Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response: 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 schedule of activities.

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

Table 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 3 measured lesions and during the study, only 2 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 ″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 1.

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

REFERENCE

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

Appendix 6
European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30)

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EORTC QLQ-C30 (version 3)

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

Please fill in your initials: ⌊ | | | ⌋
Your birthdate (Day, Month, Year): ⌊ | | | | | | | | ⌋
Today's date (Day, Month, Year): 31 ⌊ | | | | | | | | ⌋

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

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

Please go on to the next page

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

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 7
European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire for Cholangiocarcinoma and Cancer of the Gallbladder (EORTC QLQ-BIL21)

This document must not be reproduced. The Sponsor will provide a copy of the document upon request.

EORTC QLQ – BIL21

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

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had trouble with eating?	1	2	3	4
32.	Have you felt full up too quickly after beginning to eat?	1	2	3	4
33.	Have you had problems with your sense of taste?	1	2	3	4
34.	Were you restricted in the types of food you can eat as a result of your disease or treatment?	1	2	3	4
35.	Have your skin or eyes been yellow (jaundiced)?	1	2	3	4
36.	Have you had itching?	1	2	3	4
37.	Have you been worried about your skin being yellow?	1	2	3	4
38.	Have you been less active than you would like to be?	1	2	3	4
39.	Have you felt "slowed down"?	1	2	3	4
40.	Have you felt lacking in energy?	1	2	3	4
41.	Did you have pain during the night?	1	2	3	4
42.	Have you had pain in your stomach area?	1	2	3	4
43.	Have you had pain in your back?	1	2	3	4
44.	Did you have a bloated feeling in your abdomen?	1	2	3	4
45.	Have you felt stressed?	1	2	3	4
46.	Have you felt less able to enjoy yourself?	1	2	3	4
47.	Have you worried about your health in the future?	1	2	3	4
48.	Were you worried about your family in the future?	1	2	3	4
49.	To what extent have you been troubled with side-effects from your treatment?	1	2	3	4
50.	Have you had difficulties with drainage tubes/ bags?	1	2	3	4
51.	Have you worried about losing weight?	1	2	3	4

Appendix 8
European Organisation for Research and Treatment of Cancer Item Library 77 (EORTC IL77)

This document must not be reproduced. The Sponsor will provide a copy of the document upon request.

EORTC IL77

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

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

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Have you lacked appetite?	1	2	3	4
9. Have you felt nauseated?	1	2	3	4
10. Have you vomited?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

11. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

12. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 9
Patient Global Impression of Change and Its Importance (PGI-CI)

This document must not be reproduced. The Sponsor will provide a copy of the document upon request.

Patient Global Impression of Change and its Importance (PGI-CI)

1. Please choose the response below that best describes your overall health because of cancer **now compared with when you started the study**.

Very much improved	☐
Much improved	☐
Minimally improved	☐
No change	☐
Minimally worse	☐
Much worse	☐
Very much worse	☐

2. In the previous question, you reported the change you have experienced since the start of the study. Was this change important to you?

Yes	☐
No	☐
Not applicable (selected *No change*)	☐

Appendix 10
Patient Global Impression of Severity (PGI-S)

This document must not be reproduced. The Sponsor will provide a copy of the document upon request.

Patient Global Impression of Severity (PGI-S)

1. Please choose the response below that best describes how severely your overall health has been impacted because of cancer **over the past week**.

None	☐
Mild	☐
Moderate	☐
Severe	☐
Very severe	☐

Appendix 11
Patient-Reported Outcome Common Terminology Criteria for Adverse Events (PRO-CTCAE)

NCI PRO-CTCAE ™ ITEMS

Item Library Version 1.0

English

Form Created on 15 July 2020

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1a. In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
1b. In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

2a. In the last 7 days, did you have any RASH?	
O Yes	O No

3a. In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
3b. In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

4a. In the last 7 days, how OFTEN did you have a HEADACHE?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
4b. In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
4c. In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

Appendix 12
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

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

Appendix 13
Anaphylaxis Precautions

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

REQUIRED EQUIPMENT AND MEDICATION

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

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

PROCEDURES

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

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

Appendix 14
Overall Guidelines for Management of Patients Who Experience Adverse Events

DOSE MODIFICATIONS

There will be no dose modifications for atezolizumab. No dose modifications are permitted for bevacizumab/placebo aside from weight-based dose changes as outlined in the protocol.

Recommendations on dose modifications for cisplatin and gemcitabine (CisGem) are provided in the Safety Plan (Section 5.1.5).

TREATMENT INTERRUPTION

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

Bevacizumab/placebo treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If the event resolves to Grade ≤ 1, bevacizumab/placebo may be restarted at the same dose level. If bevacizumab/placebo is delayed due to toxicity for > 42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab/placebo. Bevacizumab/placebo can be resumed after being withheld for > 42 days if the patient is likely to derive clinical benefit.

Gemcitabine and cisplatin treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If gemcitabine or cisplatin have been withheld for > 42 days because of toxicity, the patient should be discontinued from gemcitabine or cisplatin.

Appendix 14: Overall Guidelines for Management of Patients Who Experience Adverse Events

Atezolizumab, bevacizumab/placebo, gemcitabine, or cisplatin treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The investigator will determine the acceptable length of treatment interruption. If atezolizumab, bevacizumab/placebo, gemcitabine, or cisplatin are transiently withheld or permanently discontinued, one or all of the other drugs can be continued as long as the patients are experiencing clinical benefit in the opinion of the investigator. However, bevacizumab/placebo should not be continued as a single agent. Recommendations on CisGem dose interruptions are provided in the Safety Plan (Section 5.1.5).

MANAGEMENT GUIDELINES

Guidelines for management of patients who experience specific adverse events are provided in Table 1. See both Table 1 and Table 2 for adverse events that occur during the chemotherapy combination phase. See Table 2 for adverse events that occur during the cancer immunotherapy (CIT)/placebo phase.

Specific adverse events associated with gemcitabine or cisplatin are provided below. For adverse events that are not listed herein, see guidelines in the applicable local prescribing information (if available) or Summary of Product Characteristics. For cases in which management guidelines are not covered in the protocol or prescribing information, patients should be managed as deemed clinically appropriate by the investigator.

Appendix 14: Overall Guidelines for Management of Patients Who Experience Adverse Events

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab plus Bevacizumab/Placebo with or without Cisplatin and Gemcitabine

Event	Action to Be Taken
IRRs, anaphylaxis, and hypersensitivity reactions	• Guidelines for management of IRRs for atezolizumab are provided in Appendix 15. • Guidelines for management of IRRs for bevacizumab/placebo are provided below. • For anaphylaxis precautions, see Appendix 13. • For hypersensitivity reactions and allergic reactions, permanently discontinue the causative agent.
IRR to bevacizumab/placebo, Grade 1	• Systemic intervention is not indicated. Continue bevacizumab/placebo.
IRR to bevacizumab/placebo, Grade 2	• Reduce infusion rate to ≤50% or interrupt infusion at the discretion of the investigator per medical judgment. • If the infusion is interrupted, it may be resumed at ≤50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.
IRR to bevacizumab/placebo, Grade 3 or 4	• Stop infusion and permanently discontinue bevacizumab/placebo. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen) if clinically indicated.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab plus Bevacizumab/Placebo with or without Cisplatin and Gemcitabine (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity	
GI perforation, any grade	• Withhold atezolizumab, gemcitabine, or cisplatin. • Permanently discontinue bevacizumab/placebo. • Initiate treatment per institutional guidelines. • If event improves, consider resuming atezolizumab. gemcitabine, or cisplatin If not, permanently discontinue atezolizumab, gemcitabine, or cisplatin. [a]
Bowel obstruction, Grade 2	• Atezolizumab, gemcitabine, or cisplatin. may be continued at the discretion of the investigator. • Withhold bevacizumab/placebo for partial obstruction requiring medical intervention. • Bevacizumab/placebo may be restarted upon complete resolution of event.
Bowel obstruction, Grade 3 or 4	• Atezolizumab, gemcitabine, or cisplatin may be continued at the discretion of the investigator. • Withhold bevacizumab/placebo until complete resolution. • If surgery is necessary, patient may restart bevacizumab/placebo after full recovery from surgery and at the investigator's discretion.
Posterior reversible encephalopathy syndrome	
Posterior reversible encephalopathy syndrome, any grade confirmed by magnetic resonance imaging	• Withhold atezolizumab and cisplatin. Permanently discontinue bevacizumab/placebo and gemcitabine. • If event improves, consider resuming atezolizumab and cisplatin. If not, permanently discontinue atezolizumab and cisplatin. [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab plus Bevacizumab/Placebo with or without Cisplatin and Gemcitabine (cont.)

Hypertension [a]	
General guidance	• Treat with antihypertensive medication as needed.
Hypertension, Grade 1	• Continue atezolizumab, bevacizumab/placebo, gemcitabine, or cisplatin. • Consider increased BP monitoring.
Hypertension, Grade 2	• Continue atezolizumab, gemcitabine, or cisplatin. • If asymptomatic, begin or modify baseline anti-hypertensive therapy and continue bevacizumab/placebo. • If symptomatic, start or adjust anti-hypertensive therapy.
Hypertension, Grade 3	• Continue atezolizumab, gemcitabine, or cisplatin. • Modify existing anti-hypertensive therapy (more than one drug or more intensive therapy than previously indicated). • Withhold bevacizumab/placebo until symptoms resolve and BP $<$ 160/90 mmHg.
Hypertension, Grade 4	• Atezolizumab, gemcitabine, or cisplatin may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab/placebo.
Hemorrhage	
Hemorrhage, Grade 3 or 4 (excluding cerebral hemorrhage)	• Continue atezolizumab. gemcitabine, or cisplatin. • Permanently discontinue bevacizumab/placebo.
CNS hemorrhage, any grade	• Atezolizumab, gemcitabine, or cisplatin may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab/placebo.
Grade $\geq$ 2 hemoptysis ($\geq$ 2.5 mL of bright red blood per episode)	• Continue atezolizumab, gemcitabine, or cisplatin. • Permanently discontinue bevacizumab/placebo.
Bleeding in patients on full-dose anticoagulant therapy	• Continue atezolizumab, gemcitabine, or cisplatin. • Permanently discontinue bevacizumab/placebo.

[a] Vascular disorders (including hypertension and hypotension) are possible adverse events of atezolizumab, considering the mechanism of action.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab plus Bevacizumab/Placebo with or without Cisplatin and Gemcitabine (cont.)

Event	Action to Be Taken
Thromboembolic events	
Venous thromboembolic event, Grade 3	• Atezolizumab, gemcitabine, or cisplatin may be continued at the discretion of the investigator. • Withhold bevacizumab/placebo treatment. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab/placebo should be withheld until the full-dose anticoagulation period is over. The use of direct oral anticoagulants is not recommended. • If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab/placebo may be resumed during full-dose anticoagulation if all of the criteria below are met: – The patient must not have pathological conditions that carry high risk of bleeding (e.g., tumor involving major vessels or other conditions). – The patient must not have had hemorrhagic events Grade >2 while in the study. – The patient must be on stable dose of heparin, low-molecular-weight heparin, or have an in-range INR (usually 2–3) on a stable dose of warfarin prior to restarting bevacizumab/placebo. • If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab/placebo.
Venous thromboembolic event, Grade 4	• Atezolizumab, gemcitabine, or cisplatin may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab/placebo.
Arterial thromboembolic event, any grade	• Atezolizumab, gemcitabine, or cisplatin may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab/placebo.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab plus Bevacizumab/Placebo with or without Cisplatin and Gemcitabine (cont.)

Event	Action to Be Taken
Proteinuria	
Proteinuria, Grade 1 (1+ by dipstick; urinary protein < 1.0 g/24 hours)	• Continue atezolizumab, bevacizumab/placebo, gemcitabine, and cisplatin.
Proteinuria, Grade 2 (2+ and 3+ by dipstick; urinary protein 1.0–3.4 g/24 hours)	• Continue atezolizumab, gemcitabine, or cisplatin. • For 2+ dipstick: Continue bevacizumab/placebo and collect 24-hour urine protein prior to subsequent bevacizumab/placebo administration. • For 3+ dipstick: Obtain 24-hour urine prior to administering bevacizumab/placebo. • Withhold bevacizumab/placebo for urinary protein ≥ 2 g/24 hours. • If bevacizumab is withheld and urine protein improves to < 2 g/24 hours ≤ 42 days after event onset, resume bevacizumab/placebo. If not, permanently discontinue bevacizumab/placebo.
Proteinuria, Grade 3 (4+ by dipstick; urinary protein ≥ 3.5 g/24 hours) with no diagnosis of nephrotic syndrome	• Atezolizumab, gemcitabine, or cisplatin may be continued at the discretion of the investigator. • Withhold bevacizumab/placebo. • If urine protein improves to < 2 g/24 hours ≤ 42 days after event onset, resume bevacizumab/placebo. If not, permanently discontinue bevacizumab/placebo.
Nephrotic syndrome, Grade 3 or 4	• Atezolizumab, gemcitabine, or cisplatin may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab/placebo.
Fistula	
Tracheoesophageal fistula and fistula formation involving an internal organ, any grade	• Withhold atezolizumab, gemcitabine, or cisplatin. • Permanently discontinue bevacizumab/placebo. • If event improves, consider resuming atezolizumab, gemcitabine, or cisplatin. If not, permanently discontinue atezolizumab. [a]
Fistula formation not involving an internal organ, Grade 4	• Withhold atezolizumab, gemcitabine, or cisplatin. • Permanently discontinue bevacizumab/placebo. • If event improves, consider resuming atezolizumab, gemcitabine, or cisplatin. If not, permanently discontinue atezolizumab, gemcitabine, or cisplatin. [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab plus Bevacizumab/Placebo with or without Cisplatin and Gemcitabine (cont.)

Event	Action to Be Taken
Wound dehiscence	
Wound dehiscence, any grade requiring medical or surgical therapy	• Atezolizumab, gemcitabine, or cisplatin may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab/placebo.
Congestive heart failure	
Congestive heart failure, Grade 3 or 4	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab/placebo, gemcitabine, or cisplatin.
Diarrhea	
Diarrhea, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 15. • Continue bevacizumab/placebo, gemcitabine and cisplatin.
Diarrhea, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 15. • Consider withholding bevacizumab/placebo. If event improves, resume bevacizumab/placebo. If not, permanently discontinue bevacizumab/placebo. • If event resolves to Grade 1 or better within 42 days, [b] resume gemcitabine and cisplatin with dose reduced by one level. [c, d] If not, permanently discontinue gemcitabine and cisplatin.
Pulmonary toxicity	
Pulmonary toxicity, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 15. • Continue gemcitabine and cisplatin.
Pulmonary toxicity, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 15. • Permanently discontinue gemcitabine. Withhold bevacizumab/placebo and cisplatin. • If event improves, resume bevacizumab/placebo and cisplatin at current dose. If not, permanently discontinue bevacizumab/placebo and cisplatin.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit.

[b] If the investigator believes the patient is likely to derive clinical benefit, can be resumed after being withheld for >42 days.

[c] Recommendations on dose modifications for gemcitabine and cisplatin are provided in the Safety Plan (Section 5.1.5).

[d] Cisplatin may be resumed at current dose if the investigator believes the patient is likely to derive clinical benefit.

Appendix 14: Overall Guidelines for Management of Patients Who Experience Adverse Events

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab plus Bevacizumab/Placebo with or without Cisplatin and Gemcitabine (cont.)

Dermatologic events	
Dermatologic event, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 15 Appendix 15. • Continue bevacizumab/placebo, gemcitabine, or cisplatin.
Dermatologic event, Grade 3	• Follow guidelines for atezolizumab in Appendix 15. • ·Withhold bevacizumab/placebo, gemcitabine, or cisplatin. • If event resolves to Grade 1 or better, resume {bevacizumab/placebo, gemcitabine, or cisplatin • Permanently discontinue bevacizumab/placebo, gemcitabine, or cisplatin if withheld for >42 days.
Dermatologic event, Grade 4	• Follow guidelines for atezolizumab in Appendix 15. • Permanently discontinue bevacizumab/placebo, gemcitabine, or cisplatin.
Neurologic toxicity	
Neurologic toxicity, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 15. • Continue bevacizumab/placebo, gemcitabine and cisplatin.
Neurologic toxicity, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 15. • Consider withholding bevacizumab/placebo. If event improves, resume bevacizumab/placebo. If not, permanently discontinue bevacizumab/placebo. • Withhold gemcitabine and cisplatin. • If event resolves to Grade 1 or better within 42 days, [b] resume gemcitabine and cisplatin with dose reduced by one level. [c, d] If not, permanently discontinue gemcitabine and cisplatin.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit.

[b] If the investigator believes the patient is likely to derive clinical benefit, can be resumed after being withheld for >42 days.

[c] Recommendations on dose modifications for gemcitabine and cisplatin are provided in the Safety Plan (Section 5.1.5).

[d] Cisplatin may be resumed at current dose if the investigator believes the patient is likely to derive clinical benefit.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab plus Bevacizumab/Placebo with or without Cisplatin and Gemcitabine (cont.)

Hepatic toxicity	
Hepatic toxicity, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 15. • Continue bevacizumab/placebo, gemcitabine and cisplatin.
Hepatic toxicity, Grade 3	• Follow guidelines for atezolizumab in Appendix 15. • Permanently discontinue gemcitabine. • Consider withholding bevacizumab/placebo. If event improves, resume bevacizumab/placebo. If not, permanently discontinue bevacizumab/placebo. • Withhold cisplatin. • If event resolves to Grade 1 or better within 42 days, [a] resume cisplatin with dose reduced by one level. [c, d] If not, permanently discontinue cisplatin.
Hepatic toxicity, Grade 4	• Follow guidelines for atezolizumab in Appendix 15. • Consider withholding bevacizumab/placebo. If event improves, resume bevacizumab/placebo. If not, permanently discontinue bevacizumab/placebo. • Permanently discontinue gemcitabine and cisplatin.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit.

[b] If the investigator believes the patient is likely to derive clinical benefit, can be resumed after being withheld for >42 days.

[c] Recommendations on dose modifications for gemcitabine and cisplatin are provided in the Safety Plan (Section 5.1.5).

[d] Cisplatin may be resumed at current dose if the investigator believes the patient is likely to derive clinical benefit.

Appendix 14: Overall Guidelines for Management of Patients Who Experience Adverse Events

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events with Atezolizumab plus Bevacizumab/Placebo with or without Cisplatin and Gemcitabine (cont.)

Bevacizumab-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab, bevacizumab/placebo, gemcitabine, and cisplatin.
Grade 3	• Continue atezolizumab, gemcitabine, and cisplatin. Withhold bevacizumab/placebo. • If event resolves to Grade 1 or better ≤42 days after event onset, resume bevacizumab/placebo. If not, permanently discontinue bevacizumab/placebo. [a]
Grade 4	• Withhold atezolizumab, bevacizumab/placebo, gemcitabine, and cisplatin. • If event improves, consider resuming atezolizumab, gemcitabine, and cisplatin. If not, permanently discontinue atezolizumab, gemcitabine, and cisplatin. [a] • If event resolves to Grade 1 or better ≤42 days after event onset, resume bevacizumab/placebo. If not, permanently discontinue bevacizumab/placebo. [a]
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 15. • Continue bevacizumab/placebo, gemcitabine, and cisplatin.
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 15. • Withhold bevacizumab/placebo, gemcitabine, and cisplatin. • If event resolves to Grade 1 or better ≤42 days after event onset, resume bevacizumab/placebo, gemcitabine, and cisplatin. If not, permanently discontinue bevacizumab/placebo, gemcitabine, and cisplatin. [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit.

[b] If the investigator believes the patient is likely to derive clinical benefit, can be resumed after being withheld for >42 days.

[c] Recommendations on dose modifications for gemcitabine and cisplatin are provided in the Safety Plan (Section 5.1.5).

[d] Cisplatin may be resumed at current dose if the investigator believes the patient is likely to derive clinical benefit.

Appendix 14: Overall Guidelines for Management of Patients Who Experience Adverse Events

Table 2 Guidelines for Management of Patients Who Experience Specific Adverse Events with Cisplatin and Gemcitabine

Hematologic toxicity on Day 1: ANC<$\times 10^9$/L (1500/μL) and/or platelet count <100$\times 10^9$/L (100,000/μL)	
Nadir [a] ANC $\geq 0.5 \times 10^9$/L (500/μL), absence of febrile neutropenia, and nadir platelet count $\geq 50 \times 10^9$/L (50,000/μL)	• Continue atezolizumab and bevacizumab/placebo. Withhold gemcitabine and cisplatin. • If ANC is $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count is $\geq 100 \times 10^9$/L (100,000/μL) within 42 days, [b] resume gemcitabine and cisplatin at current dose. [c] If not, permanently discontinue gemcitabine and cisplatin.
Nadir [a] ANC $< 0.5 \times 10^9$/L (500/μL) and nadir [a] platelet count $\geq 50 \times 10^9$/L (50,000/μL) **or** Febrile neutropenia **or** Nadir [a] platelet count $< 50 \times 10^9$/L (50,000/μL) without bleeding	• Withhold atezolizumab, bevacizumab/placebo, gemcitabine, and cisplatin. • If event improves, resume atezolizumab and bevacizumab/placebo. If not, permanently discontinue atezolizumab and bevacizumab/placebo. • If ANC is $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count is $\geq 100 \times 10^9$/L (100,000/μL) within 42 days, [b] resume gemcitabine and cisplatin dose reduced by one level. [c, d] If not, permanently discontinue gemcitabine and cisplatin.
Nadir [a] platelet count $< 50 \times 10^9$/L (50,000/μL) with bleeding	Any occurrence • Withhold atezolizumab and bevacizumab/placebo. • If event improves, resume atezolizumab and bevacizumab/placebo. If not, permanently discontinue atezolizumab and bevacizumab/placebo. First occurrence • Withhold gemcitabine and cisplatin. • If ANC is $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count is $\geq 100 \times 10^9$/L (100,000/μL) within 42 days, [b] resume gemcitabine and cisplatin with dose reduced by 2 levels. [c] If not, permanently discontinue gemcitabine and cisplatin. Second occurrence • Permanently discontinue gemcitabine and cisplatin.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit.

[b] If the investigator believes the patient is likely to derive clinical benefit, can be resumed after being withheld for >42 days.

[c] Recommendations on dose modifications for gemcitabine and cisplatin are provided in the Safety Plan (Section 5.1.5).

[d] Cisplatin may be resumed at current dose if the investigator believes the patient is likely to derive clinical benefit.

Table 2 Guidelines for Management of Patients Who Experience Specific Adverse Events with Cisplatin and Gemcitabine (cont.)

Hematologic toxicity on Day 8	
ANC $\geq 1.0 \times 10^9$/L (1000/μL), absence of febrile neutropenia, and platelet count $\geq 100 \times 10^9$/L (100,000/μL)	• Continue gemcitabine and cisplatin at current dose.
ANC 0.5–0.99 $\times 10^9$/L (500–999/μL) **or** Platelet count 50–99 $\times 10^9$/L (50,000–90,000/μL)	• Continue gemcitabine and cisplatin with dose reduced by one level. [c, d]
ANC $< 0.5 \times 10^9$/L (500/μL) **or** Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Withhold gemcitabine and cisplatin. • Treatment may be resumed on Day 1 of the next cycle if ANC is $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count is $\geq 100 \times 10^9$/L (100,000/μL).
Nephrotoxicity	
CrCl ≥ 60 mL/min at time of scheduled treatment	• Continue atezolizumab, bevacizumab/placebo, gemcitabine, and cisplatin.
CrCl < 60 mL/min at time of scheduled treatment	• Withhold cisplatin. Atezolizumab, bevacizumab/placebo and gemcitabine may be continued at the discretion of the investigator. If event improves to CrCl ≥ 60 mL/min within 42 days, [b] cisplatin may be resumed with dose reduced by one level [c] at the discretion of the investigator. If not, permanently discontinue cisplatin.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit.

[b] If the investigator believes the patient is likely to derive clinical benefit, can be resumed after being withheld for > 42 days.

[c] Recommendations on dose modifications for gemcitabine and cisplatin are provided in the Safety Plan (Section 5.1.5).

[d] Cisplatin may be resumed at current dose if the investigator believes the patient is likely to derive clinical benefit.

Table 2 Guidelines for Management of Patients Who Experience Specific Adverse Events with Cisplatin and Gemcitabine (cont.)

Mucositis	
Mucositis, Grade 1 or 2	• Continue atezolizumab, bevacizumab/placebo, gemcitabine, and cisplatin.
Mucositis, Grade 3 or 4	• Continue atezolizumab and bevacizumab/placebo. Withhold gemcitabine and cisplatin. • If event resolves to Grade 1 or better within 42 days, [b] resume gemcitabine and cisplatin with dose reduced by one level. [c, d] If not, permanently discontinue gemcitabine and cisplatin.
Hemolytic-uremic syndrome	
Hemolytic-uremic syndrome, any grade	• Permanently discontinue gemcitabine. Withhold atezolizumab, bevacizumab/placebo, and cisplatin. • If event improves, resume atezolizumab bevacizumab/placebo and cisplatin at current dose. If not, permanently discontinue atezolizumab, bevacizumab/placebo and cisplatin.
Capillary leak syndrome	
Capillary leak syndrome, any grade	• Permanently discontinue gemcitabine. Withhold atezolizumab, bevacizumab/placebo and cisplatin. • If event improves, resume atezolizumab, bevacizumab/placebo and cisplatin at current dose. If not, permanently discontinue atezolizumab, bevacizumab/placebo and cisplatin.
Ototoxicity	
	• If ototoxicity is suspected, audiometry will be performed to assess hearing.
For loss of greater than 25 decibels in two consecutive hearing frequencies	• Continue atezolizumab, bevacizumab/placebo and gemcitabine. • Withhold cisplatin for 1 week, and audiometry assessment will be repeated. If hearing loss is resolved, then the patient will be re-treated with a cisplatin dose that is one level lower than the prior cycle. [d] Patients will not undergo routine audiology monitoring for this study. If not, permanently discontinue cisplatin.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit.

[b] If the investigator believes the patient is likely to derive clinical benefit, can be resumed after being withheld for >42 days.

[c] Recommendations on dose modifications for gemcitabine and cisplatin are provided in the Safety Plan (Section 5.1.5).

[d] Cisplatin may be resumed at current dose if the investigator believes the patient is likely to derive clinical benefit.

Table 2 Guidelines for Management of Patients Who Experience Specific Adverse Events with Cisplatin and Gemcitabine (cont.)

Chemotherapy-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab, bevacizumab/placebo, gemcitabine, and cisplatin.
Grade 3	• Continue atezolizumab and bevacizumab/placebo. Withhold gemcitabine and cisplatin. • If event resolves to Grade 1 or better within 42 days, [b] resume gemcitabine and cisplatin with dose reduced by one level. [c, d] If not, permanently discontinue gemcitabine and cisplatin.
Grade 4	• Withhold atezolizumab, bevacizumab/placebo, gemcitabine, and cisplatin. • If event improves, resume atezolizumab and bevacizumab/placebo. If not, permanently discontinue atezolizumab and bevacizumab. • If event resolves to Grade 1 or better within 42 days, [a] resume gemcitabine and cisplatin with dose reduced by one level. [c, d] If not, permanently discontinue gemcitabine and cisplatin.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit.

[b] If the investigator believes the patient is likely to derive clinical benefit, can be resumed after being withheld for >42 days.

[c] Recommendations on dose modifications for gemcitabine and cisplatin are provided in the Safety Plan (Section 5.1.5).

[d] Cisplatin may be resumed at current dose if the investigator believes the patient is likely to derive clinical benefit.

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

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

- *Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.*
- *In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.*
- *Consider holding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5–1 mg/kg/day of prednisone or equivalent) may be administered.*
- *For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.*
- *Hold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1–2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.*
- *In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.*

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. *R*esumption of atezolizumab may be considered *in patients who are* deriving benefit and *have* fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's assessment of *the benefits and risks*

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

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 have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. *Coronavirus disease 2019 (COVID-19) evaluation should be performed per institutional guidelines where relevant.* Management guidelines for pulmonary events are provided in Table 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

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

	• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL = bronchoscopic alveolar lavage; *IV = Intravenous*

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

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

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

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

HEPATIC EVENTS

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

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

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

Table 2 Management Guidelines for Hepatic Events

Event	Management
Guidelines for patients without hepatocellular carcinoma	
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

LFT = liver function test.

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

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

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

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Guidelines for patients without hepatocellular carcinoma (cont.)	
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Guidelines for patients with hepatocellular carcinoma	
AST/ALT is within normal limits at baseline and increases to > 3 × ULN to ≤ 10 × ULN **or** AST/ALT is > ULN to ≤ 3 × ULN at baseline and increases to > 5 × ULN to ≤ 10 × ULN **or** AST/ALT is > 3 × ULN to ≤ 5 × ULN at baseline and increases to > 8 × ULN to ≤ 10 × ULN	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Monitor LFTs more frequently until return to baseline values. • For events of > 5 days' duration, consider initiating treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to baseline or to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to baseline or to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

AST = Aspartate transaminase; ALT = Alanine transaminase; LFT = liver function test; *ULN = upper limit of normal.*

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

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

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

Table 2 Management Guidelines for Hepatic Events (cont.)

Guidelines for patients with hepatocellular carcinoma (cont.)	
Event	**Management**
AST or ALT increases to >10×ULN or total bilirubin increases to >3×ULN	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to baseline, taper corticosteroids over ≥1 month.

AST = Aspartate transaminase; ALT = Alanine transaminase; LFT = liver function test*; ULN = upper limit of normal.*

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

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

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

GASTROINTESTINAL EVENTS

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

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

Appendix 15: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

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

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

GI = gastrointestinal.

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

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

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

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table 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 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 4 Management Guidelines for Endocrine Events

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

	• Permanently discontinue atezolizumab and contact *the* Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

Table 4 Management Guidelines for Endocrine Events (cont.)

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

Table 4 Management Guidelines for Endocrine Events (cont.)

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

MRI = magnetic resonance imaging.

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

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

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

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

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

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

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

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

IMMUNE-MEDIATED CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table 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., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis *or associated with pericarditis (see section on pericardial disorders below)* and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

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

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

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

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

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

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

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

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

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.

Infusion-related reactions are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

Cytokine release syndrome 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). Cytokine release syndrome 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.

Appendix 15: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with 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 7.

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

Appendix 15: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

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

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

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

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

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

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. National Cancer Institute CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

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

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

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

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

[f] See Riegler et al. (2019).

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 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

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

GI = gastrointestinal.

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

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

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

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

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

GI = gastrointestinal.

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

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

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

DERMATOLOGIC EVENTS

The majority of cases of rash *reported with the use of atezolizumab* were mild in severity and self-limited, 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 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

Table 9 Management Guidelines for Dermatologic Events (cont.)

Event	Management
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

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

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

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

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10*, with specific guidelines for myelitis provided in Table 1*.

Table 10 Management Guidelines for Neurologic Disorders

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

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

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

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

Table 1 Management Guidelines for Immune-Mediated Myelitis

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

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 .

Table ~~11~~*12* Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Refer patient to neurologist.

Event	Management
	• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

RENAL EVENTS

Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including 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 .

Table ~~12~~*13* Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor.[c] • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.

Event	Management
	• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

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

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

IMMUNE-MEDIATED MYOSITIS

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

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

Table *14* Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact *the* Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.

Appendix 15: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Event	Management
	• If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

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

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

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

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

Event	Management
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact *the* Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. *Permanently discontinue atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge

patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

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

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

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein 2014. A patient should be classified as having HLH if 5 of the following 8 criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (<100 g/L [10 g/dL] for infants $<$ 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

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

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq 181 \times 10^9$/L (181,000/μL)
  - AST ≥ 48 U/L

- Triglycerides > 1.761 mmol/L (156 mg/dL)
- Fibrinogen ≤ 3.6 g/L (360 mg/dL)

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

Table ~~13~~*15* Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

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

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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