PROTOCOL

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB COMPARED WITH SORAFENIB IN PATIENTS WITH UNTREATED LOCALLY ADVANCED OR METASTATIC HEPATOCELLULAR CARCINOMA**
PROTOCOL NUMBER:	YO40245
VERSION NUMBER:	6
EUDRACT NUMBER:	2017-003691-31
IND NUMBER:	135913
NCT NUMBER:	NCT03434379
TEST PRODUCTS:	Atezolizumab (RO5541267) Bevacizumab (RO4876646)
MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 18 October 2017
DATES AMENDED:	Version 2: 14 March 2018 Version 3: 15 September 2018 Version 4: 20 February 2019 Version 5: *15 January 2020* *Version 6: See electronic date stamp below.*

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
01-Feb-2021 17:34:51	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 6: RATIONALE

Protocol YO40245 has been amended primarily to align with updates in the Atezolizumab Investigator's Brochure, Version 17. Changes to the protocol, along with a rationale for each change, are summarized below.

- The descriptive and optional nature of subsequent overall survival (OS) analyses once statistical significance is reached at any of the pre-planned interim analyses of OS was clarified (Sections 6.1, 6.4.1.1, and 6.10)
- Severe Cutaneous Adverse Reactions (SCARs) were added as a risk associated with atezolizumab (Section 5.1.1) and a statement was added to Appendix 8 to communicate that caution should be used in patients who have previously experienced a severe or life-threatening atezolizumab skin adverse reaction
- The Management Guidelines for Dermatologic Events section of Appendix 12 was updated to include updated management guidelines for Grade 3 dermatologic events and new guidelines for Stevens-Johnson syndrome or toxic epidermal necrolysis of any grade were added
- Section 1.6.3, COVID-19 Considerations, has been added to describe COVID−19-related risks
- Exclusion criteria in Section 4.1.2 – Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia has been updated to include any active infection that, the opinion of the investigator, could impact patient safety
- COVID-19 risk language has been included in Section 5.1, Safety Plan, to state that patients with an active infection will be excluded from study participation
- The Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome were updated to include COVID-19 risk language
- The Management Guidelines for Hepatic Events for Patients with Hepatocellular Carcinoma section of Appendix 12 has been updated to align with the updated management guidelines in the Atezolizumab Investigator's Brochure v17

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 III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB COMPARED WITH SORAFENIB IN PATIENTS WITH UNTREATED LOCALLY ADVANCED OR METASTATIC HEPATOCELLULAR CARCINOMA**
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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

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IND NUMBER:	135913
NCT NUMBER:	NCT03434379
TEST PRODUCTS:	Atezolizumab (RO5541267) Bevacizumab (RO4876646)
PHASE:	III
INDICATION:	Metastatic hepatocellular carcinoma (HCC)
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of atezolizumab in combination with bevacizumab compared with sorafenib in patients with locally advanced or metastatic hepatocellular carcinoma (HCC) who have received no prior systemic treatment. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Efficacy Objective	Corresponding Endpoint
To evaluate the efficacy of atezolizumab + bevacizumab compared with sorafenib	• OS, defined as the time from randomization to death from any cause • PFS, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by an IRF according to RECIST v1.1
Secondary Efficacy Objectives	**Corresponding Endpoints**
To evaluate the efficacy of atezolizumab + bevacizumab compared with sorafenib	• OR, defined as a complete or partial response, as determined by the investigator according to RECIST v1.1 • PFS as determined by the investigator according to RECIST v1.1 • TTP, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1

Secondary Efficacy Objectives	Corresponding Endpoints
	• DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • Objective response as determined by an IRF according to RECIST v1.1 • TTP as determined by an IRF according to RECIST v1.1 • DOR as determined by an IRF according to RECIST v1.1 • Objective response as determined by an IRF according to HCC mRECIST • PFS as determined by an IRF according to HCC mRECIST • TTP as determined by an IRF according to HCC mRECIST • DOR as determined by an IRF according to HCC mRECIST
To evaluate the association of pre-specified biomarkers with efficacy of atezolizumab + bevacizumab compared with sorafenib	• PFS as determined by the investigator and by an IRF according to RECIST v1.1 and OS by baseline serum AFP level (< 400 ng/mL vs. ≥ 400 ng/mL)
To evaluate PROs of disease/treatment-related symptoms, GHS/QoL, and function experienced by patients on atezolizumab + bevacizumab versus sorafenib	• TTD, defined as the time from randomization to first deterioration (decrease from baseline of ≥ 10 points), maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks in the following EORTC QLQ-C30 subscales: – Physical functioning (PF) – Role functioning (RF) – GHS/QoL
Exploratory Efficacy Objectives	**Corresponding Endpoints**
To evaluate the efficacy of atezolizumab + bevacizumab compared with sorafenib	• Objective response as determined by the investigator according to imRECIST • PFS as determined by the investigator according to imRECIST • TTP as determined by the investigator according to imRECIST • DOR as determined by the investigator according to imRECIST

Exploratory Efficacy Objectives	Corresponding Endpoints
To evaluate PROs of disease/treatment-related symptoms (including abdominal pain and itching), GHS/QoL, and function experienced by patients on atezolizumab + bevacizumab versus sorafenib	• Mean and mean changes from baseline score (by cycle) in all the subscales of the EORTC QLQ-C30 and QLQ-HCC18 • Proportion of patients with clinically meaningful change in select scales of the QLQ-C30 (GHS/QoL, physical function, role function, appetite loss, diarrhea, fatigue, pain) and QLQ-HCC18 (fatigue, jaundice, pain) • TTD maintained for 2 consecutive timepoints, or 1 timepoint followed by death from any cause within 3 weeks, in select scales of the QLQ-C30 (appetite loss, diarrhea, fatigue, pain) and QLQ-HCC18 (jaundice, fatigue, pain) • TTD maintained for 2 consecutive timepoints, or 1 timepoint followed by death from any cause, within 3 weeks in HRQoL/GHS, physical function, and role function of the QLQ-C30 • Proportion of responses for abdominal pain item (of QLQ-HCC18 pain subscale) and itching item (of QLQ-HCC18 jaundice subscale)
Safety Objective	**Corresponding Endpoints**
To evaluate the safety of atezolizumab + bevacizumab compared with sorafenib	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v4.0 • Vital signs • Clinical laboratory test results
Pharmacokinetic Objective	**Corresponding Endpoint**
To characterize the PK profile of atezolizumab + bevacizumab	• Serum concentration of atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
To evaluate the immune response to atezolizumab	• Presence of ADAs to atezolizumab during the study relative to the presence of ADAs at baseline
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
To evaluate potential effects of ADAs to atezolizumab on the efficacy, safety, and pharmacokinetics of atezolizumab + bevacizumab	• Efficacy, safety, or PK endpoints by ADA status

Exploratory Biomarker Objective	Corresponding Endpoint
To identify tissue or blood-based biomarkers that are associated with response to atezolizumab + bevacizumab versus sorafenib, or can increase the understanding of HCC disease evolution under atezolizumab + bevacizumab treatment	• PFS as determined by the investigator according to RECIST v 1.1 and OS based on the following biomarkers in tumor tissue: – Baseline expression of T effector gene signature in tumor tissue – Baseline PD-L1 protein expression in tumor tissue – CD8 protein expression level or CD8+ T-cell localization – IHCs or genes/gene signatures (by gene expression profiling) related to tumor microenvironments – T cell receptor sequence profile in tumor-associated T cells • Objective response as determined by the investigator according to RECIST v1.1 and OS based on the following biomarkers in blood: – Immune-related biomarkers profiling in plasma and serum (e.g., interleukin 2, interferon-γ)
Exploratory Health Status Objective	**Corresponding Endpoint**
To evaluate health status experienced by patients on atezolizumab + bevacizumab versus sorafenib to generate utility scores for use in economic evaluations	• Health utility and VAS scores of the EQ-5D-5L questionnaire

ADA = anti-drug antibody; AFP = α-fetoprotein; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5-Dimension Questionnaire, 5-Level version; GHS = global health status; HCC = hepatocellular carcinoma; HCC mRECIST = modified RECIST for HCC; imRECIST = immune-modified RECIST; IRF = independent review facility; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PRO = patient-reported outcome; QLQ-C30 = quality-of-life questionnaire for cancer; QLQ-HCC18 = HCC disease-specific module; QoL = quality-of-life; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TTD = time to deterioration; TTP = time to progression; VAS = visual analog scale.

Study Design

Description of Study

This is a Phase III, randomized, multicenter, open-label, two-arm study designed to evaluate the efficacy and safety of atezolizumab and bevacizumab versus sorafenib in patients with locally advanced or metastatic HCC who have received no prior systemic treatment.

This study will enroll approximately 480 patients randomized in a 2:1 ratio to one of two treatment arms:

- Arm A (experimental arm): Atezolizumab 1200 mg IV infusion every 3 weeks (Q3W; dosed in 3-week cycles) and bevacizumab 15 mg/kg Q3W (dosed in 3-week cycles)
- Arm B (control arm): Sorafenib 400 mg by mouth, twice a day (BID), continuously

Randomization will be stratified according to the following stratification factors:

- Geographic region (Asia excluding Japan vs. rest of world)
- Macrovascular invasion and/or extrahepatic spread (presence vs. absence)
- Baseline α-fetoprotein (<400 vs. ≥400 ng/mL)

- Eastern Cooperative Oncology Group Performance Status (0 vs. 1)

Patients randomized to the atezolizumab and bevacizumab arm (Arm A) who transiently withhold or permanently discontinue either atezolizumab or bevacizumab may continue on single-agent therapy as long as the patients are experiencing clinical benefit in the opinion of the investigator and after discussion with the Medical Monitor (i.e., patients transiently withheld or permanently discontinued from bevacizumab treatment for adverse effects may continue atezolizumab monotherapy and vice versa).

Patients will receive atezolizumab and/or bevacizumab or sorafenib 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 per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 while receiving atezolizumab and/or bevacizumab or sorafenib 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

Tumor assessments will be performed at baseline and at regular intervals during study treatment. Additional scans will be performed as clinically indicated. Tumor assessments will continue until disease progression, regardless of whether treatment has been discontinued (e.g., for toxicity). Patients who meet RECIST v1.1 criteria for progression will undergo tumor assessments until disease progression (per immune-modified RECIST [imRECIST]) or loss of clinical benefit, whichever occurs later. In the absence of disease progression, tumor assessments should continue regardless of whether patients start new anti-cancer therapy, until consent is withdrawn, death, or the study is terminated by the Sponsor, whichever occurs first. Following disease progression, patients will be followed for survival and subsequent anti-cancer therapies until death, loss to follow-up, withdrawal of consent, or study termination by Sponsor, whichever occurs first.

Sites will provide imaging used for tumor assessments to an IRF to enable centralized, independent review of response and progression endpoints. These reviews will be performed prior to the pre-specified efficacy analyses. Independent Review Facility membership and procedures will be detailed in an IRF Charter.

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, v4.0 (NCI CTCAE v4.0). Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Serum samples will be collected to monitor the pharmacokinetics of atezolizumab when administered in combination with bevacizumab. Patient samples, including archival tumor tissues as well as serum and plasma, will be collected for future exploratory biomarker assessments.

Number of Patients

The study will enroll approximately 480 patients at approximately 120 study sites.
After completion of the global enrollment phase, additional patients may be enrolled in China in an extended China enrollment phase to ensure a total of approximately 135 patients from mainland China in a China subpopulation.

The Sponsor is targeting a total enrollment of approximately 135 patients from mainland China. After completion of the global enrollment phase, in the event that less than 135 patients from mainland China are enrolled, additional patients in China may be subsequently randomized into the two treatment arms in a 2:1 ratio in an extended China enrollment phase to ensure a total of approximately 135 patients from mainland China in a China subpopulation. The China

subpopulation will include all patients enrolled in China (i.e., during both the global enrollment phase and the extended China enrollment phase). The patients enrolled in the China extension phase will undergo the same schedule of activities and will receive atezolizumab and bevacizumab, or sorafenib as in the global study. The China subgroup analysis will be performed based on the China subpopulation.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Locally advanced or metastatic and/or unresectable HCC with diagnosis confirmed by histology/cytology or clinically by American Association for the Study of Liver Diseases (AASLD) criteria in cirrhotic patients

  Patients without cirrhosis require histological confirmation of diagnosis.
- Disease that is not amenable to curative surgical and/or locoregional therapies, or progressive disease after surgical and /or locoregional therapies
- No prior systemic therapy (including systemic investigational agents) for HCC

  Previous use of herbal therapies/traditional Chinese medicines with anti-cancer activity included in the label is allowed, provided that these medications are discontinued prior to randomization.
- At least 1 measurable (per RECIST 1.1) untreated lesion
- Patients who received prior local therapy (e.g., radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, transarterial embolization, etc.) are eligible provided the target lesion(s) have not been previously treated with local therapy or the target lesion(s) within the field of local therapy have subsequently progressed in accordance with RECIST v1.1
- Pretreatment tumor tissue sample (if available)

  If tumor tissue is available, a formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or approximately 10–15 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 specimens (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 tumor tissue is not available (e.g., depleted because of prior diagnostic testing), patients are still eligible.
- Eastern Cooperative Oncology Group Performance Status of 0 or 1 within 7 days prior to randomization
- Child-Pugh Class A within 7 days prior to randomization
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 7 days prior to randomization, unless otherwise specified:
- ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support
- Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - Platelet count $\geq 75 \times 10^9$/L (75,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9 g/dL)

    Patients may be transfused to meet this criterion.
  - AST, ALT, and alkaline phosphatase (ALP) $\leq 5 \times$ upper limit of normal (ULN)
  - Serum bilirubin $\leq 3 \times$ ULN

- Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq$ 50 mL/min (calculated using the Cockcroft-Gault formula)
- Serum albumin $\geq$ 28 g/L (2.8 g/dL) without transfusion
- For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 2 \times$ ULN
- Urine dipstick for proteinuria $< 2+$ (within 7 days prior to initiation of study treatment)

  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.

- Resolution of any acute, clinically significant treatment-related toxicity from prior therapy to Grade $\leq$ 1 prior to study entry, with the exception of alopecia
- Negative HIV test at screening
- Documented virology status of hepatitis, as confirmed by screening hepatitis B virus (HBV) and hepatitis C virus (HCV) serology test
- For patients with active HBV:

  HBV DNA $<$ 500 IU/mL obtained within 28 days prior to initiation of study treatment, and

  Anti-HBV treatment (per local standard of care; e.g., entecavir) for a minimum of 14 days prior to study entry and willingness to continue treatment for the length of the study
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $<$ 1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab, 6 months after the last dose of bevacizumab, or 6 months after the last dose of sorafenib. 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 has not undergone surgical sterilization (removal of ovaries and/or uterus).

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<$ 1% per year during the treatment period and for 6 months after the last dose of bevacizumab or 3 months after the last dose of sorafenib. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of bevacizumab or 3 months after the last dose of sorafenib to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For the extended China enrollment phase: Chinese ancestry and residence in Mainland China, Hong Kong, or Taiwan with enrollment at sites recognized by the China Center for Drug Evaluation

Exclusion Criteria

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

- History of leptomeningeal disease
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, 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
  – No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Known active tuberculosis
- 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 initiation of study treatment), unstable arrhythmia, or unstable angina
- History of congenital long QT syndrome or corrected QT interval >500 ms (calculated with use of the Fridericia method) at screening
- History of uncorrectable electrolyte disorder affecting serum levels of potassium, calcium, or magnesium
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- History of malignancy other than HCC 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
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia*, or any active infection that, in the opinion of the investigator, could impact patient safety*
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Prior allogeneic stem cell or solid organ 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

- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or bevacizumab formulation
- Pregnant or breastfeeding, or intention of becoming pregnant during study treatment or within at least 5 months after the last dose of atezolizumab, 6 months after the last dose of bevacizumab, or 6 months after the last dose of sorafenib

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
- Untreated or incompletely treated esophageal and/or gastric varices with bleeding or high risk for bleeding

  Patients must undergo an esophagogastroduodenoscopy (EGD), and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment. Patients who have undergone an EGD within 6 months of prior to initiation of study treatment do not need to repeat the procedure.
- A prior bleeding event due to esophageal and/or gastric varices within 6 months prior to initiation of study treatment
- Moderate or severe ascites
- History of hepatic encephalopathy
- Coinfection of HBV and HCV

  Patients with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV.
- 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, whole-brain radiotherapy, and/or neurosurgical resection within 28 days prior to initiation of study treatment.
  - The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. 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.
- Uncontrolled tumor-related pain

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

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

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with

spinal cord compression) should be considered for locoregional therapy if appropriate prior to enrollment.

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

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN)
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Treatment with strong CYP3A4 inducers within 14 days prior to initiation of study treatment, including rifampin (and its analogs) or St. John's wort
- 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 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, 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 after Medical Monitor approval has been obtained.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (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 blood pressure > 100 mmHg), based on an average of ≥ 3 BP readings on ≥ 2 sessions

  Anti-hypertensive therapy to achieve these parameters is allowable.
- Prior history of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of study treatment
- History of hemoptysis (≥ 2.5 mL of bright red blood per episode) within 1 month prior to initiation of study treatment
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (within 10 days of first dose of study treatment) use of aspirin (> 325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and cilostazol
- Current or recent (within 10 days prior to study treatment start) use of full-dose oral or parenteral anti-coagulants 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× ULN and aPTT is within normal limits within 14 days prior to initiation of study treatment.

  For prophylactic use of anti-coagulants or thrombolytic therapies, local label approved dose levels may be used.
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to the first dose of bevacizumab
- History of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months prior to initiation of study treatment

- History of intestinal obstruction and/or clinical signs or symptoms of GI obstruction including sub-occlusive disease related to the underlying disease or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding prior to initiation of study treatment

  Patients with signs/symptoms of sub-/occlusive syndrome/intestinal obstruction at time of initial diagnosis may be enrolled if they had received definitive (surgical) treatment for symptom resolution.
- Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Metastatic disease that involves major airways or blood vessels, or centrally located mediastinal tumor masses (< 30 mm from the carina) of large volume

  Patients with vascular invasion of the portal or hepatic veins may be enrolled.
- History of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including but not limited to active peptic ulcer disease, diverticulitis, or colitis
- Radiotherapy within 28 days and abdominal/ pelvic radiotherapy within 60 days prior to initiation of study treatment, except palliative radiotherapy to bone lesions within 7 days prior to initiation of study treatment
- Local therapy to liver (e.g., radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, transarterial embolization, etc.) within 28 days prior to initiation of study treatment or non-recovery from side effects of any such procedure
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to initiation of study treatment, or abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 60 days prior to initiation of study treatment or anticipation of need for major surgical procedure during the course of the study or non-recovery from side effects of any such procedure
- Chronic daily treatment with a nonsteroidal anti-inflammatory drug (NSAID)

  Occasional use of NSAIDs for the symptomatic relief of medical conditions such as headache or fever is allowed.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs (i.e., last patient in the global and extended China enrollment phases combined) or safety follow-up is received from the last patient (global and extended China enrollment phases combined), whichever occurs later.

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

Investigational Medicinal Products

Patients will receive treatment as outlined below 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).

Arm	Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)	Infusion Rate
A [a]	21 days	Atezolizumab 1200 mg IV on Day 1	Over 60 (±15) minutes (for the first infusion); 30 (±10) minutes for subsequent infusions if tolerated
		Bevacizumab 15 mg/kg IV on Day 1	Over 90 (±15) minutes (for the first infusion); shortening to 60 (±10) then 30 (±10) minutes for subsequent infusions if tolerated
B	21 days	Sorafenib 400 mg BID, by mouth, continuously	Not applicable

BID = twice per day.

[a] For patients randomized to Arm A, on Day 1 of each cycle, atezolizumab will be administered first, followed by bevacizumab, with a minimum of 5 minutes between dosing.

Statistical Methods

Primary Analysis

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab in combination with bevacizumab compared with sorafenib on the basis of the co-primary efficacy endpoints of OS and IRF-assessed PFS according to RECIST v1.1.

Overall survival and PFS will be tested initially in parallel with the overall type I error controlled at a 2-sided significance level of 0.05, where OS will be tested at a 2-sided significance level of 0.048 and PFS will be tested at a 2-sided significance level of 0.002.

Overall Survival

Overall survival is defined as the time from the date of randomization to the date of death from any cause. Patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Patients with no post-baseline information will be censored at the date of randomization.

The 2-sided log-rank test, stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline α-fetoprtein (AFP; <400 vs. ≥ 400 ng/mL), will be used as the primary analysis to compare OS between the two treatment arms. The results from the unstratified log-rank test will also be provided as a sensitivity analysis to check the robustness of the results of the stratified log-rank test.

The Kaplan-Meier method will be used to estimate median OS for each treatment arm. Brookmeyer-Crowley methodology will be used to calculate the 95% CI for the median OS for each treatment arm. Stratified Cox proportional-hazards models will be used to estimate the hazard ratio (HR) and its 95% CIs. The stratification factors will be the same as those used for the primary stratified log-rank test. The unstratified HR will also be provided.

A group sequential design will be used for testing the co-primary efficacy endpoint OS to account for the conduct of 2 interim analyses. An α-spending with use of the Lan-De Mets method approximating O'Brien-Fleming boundaries will be utilized to control the overall type I error rate of 0.048 for the OS co-primary efficacy endpoint. The first interim OS analysis will be conducted at time of the co-primary analysis of IRF-assessed PFS. The second interim OS analysis *is planned to* be conducted when approximately 243 OS events have been observed. *The final analysis of OS is expected to occur after approximately 312 deaths have occurred. If statistical significance is reached at one of the pre-planned interim analyses of OS, then that interim OS analysis will be regarded as the definitive analysis of OS and subsequent analyses of OS, including the final OS analysis, will be descriptive and considered as optional.*

IRF-Assessed Progression-Free Survival

Independent Review Facility-assessed PFS is defined as the time from randomization to the occurrence of disease progression as determined by the IRF 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 on or prior to the clinical cutoff date. Patients with no post-baseline tumor assessment will be censored at the date of randomization.

Methods for PFS analyses are similar to those described for the OS endpoint.

Determination of Sample Size

A total of approximately 480 patients will be randomized in the global enrollment phase of this study, with use of a 2:1 randomization ratio to allocate patients to either the atezolizumab and bevacizumab arm (Arm A) or the sorafenib arm (Arm B). The final OS analysis will be conducted at approximately 33 months after the first patient is randomized (first patient in [FPI]). *The final OS analysis will be descriptive and considered as optional if statistical significance is achieved at one of the pre-planned interim analyses of OS.*

The co-primary efficacy endpoints for this study are as follows:

- OS, defined as the time from randomization to death from any cause
- IRF-assessed PFS, defined as the time from randomization to the occurrence of disease progression per RECIST v1.1 or death from any cause, whichever occurs first.

The overall type I error rate for this study will be controlled at a 2-sided significance level of 0.05 by a graphical approach (i.e., α-splitting and recycling). The overall 2-sided significance level of 0.05 will be split into a 2-sided significance level of 0.048 for the testing of OS and a 2-sided significance level of 0.002 for the testing of PFS as a first step.

The sample size of the study was determined based on the number of deaths required to demonstrate efficacy in terms of OS. To detect an improvement in OS using a log-rank test at a 2-sided significance level of 0.048, approximately 312 deaths will be required to achieve 80% overall power assuming a target HR of 0.71 (median OS improvement vs. control is 4.9 months). The minimum detectable difference (MDD) of OS is an HR of 0.783 (median OS improvement is 3.3 months). *Three-hundred and twelve deaths are* expected to occur approximately 33 months after FPI.

The calculation of sample size and estimates of the OS analysis timelines are based on the following assumptions:

- Patients will be randomized to the atezolizumab + bevacizumab and sorafenib arms in a 2:1 ratio.
- OS follows a one-piece exponential distribution.
- The median OS in the control arm is 12 months.
- The stopping boundaries of the interim and final analyses of OS use the O'Brien-Fleming boundaries approximated using the Lan-DeMets method.
- The dropout rate is 5% for the atezolizumab + bevacizumab arm and 10% for the sorafenib arm over 12 months for OS.
- The recruitment of approximately 480 patients will take place over approximately 10 months

Interim Analysis

No interim analysis is planned for PFS in this study.

Two interim analyses of OS *are planned to* be performed. The first interim analysis will be performed at the time of the primary PFS analysis, estimated to occur at approximately 16 months after FPI. It is anticipated that at this time approximately 172 deaths will have been observed. The respective MDD OS HR is 0.633 (median OS improvement is 6.9 months). The second OS interim analysis is planned to be conducted when approximately 243 deaths are accumulated, estimated to occur at approximately 24 months after FPI. The respective MDD OS HR is 0.728 (median OS improvement is 4.6 months).

To control the 2-sided significance level at 0.048 for the interim and final OS analyses, the Lan-DeMets method will be used to approximate the O'Brien-Fleming boundaries.

The planned interim analyses for OS will be conducted by the Sponsor.

Analysis Timing	Planned Information Fraction	Required Events/ Analysis timing (estimated)	Stopping Boundary (2-Sided p-value)	
			α can be recycled to OS (i.e., OS α=0.05)	**α cannot be recycled to OS (i.e., OS α=0.048)**
1st OS interim analysis	55%	172/16 months	MDD.HR ≤ 0.636 (p-value ≤ 0.005)	MDD.HR ≤ 0.633 (p-value ≤ 0.005)
2nd OS interim analysis	78%	243/24 months	MDD.HR ≤ 0.73 (p-value ≤ 0.021)	MDD.HR ≤ 0.728 (p-value ≤ 0.02)
OS final analysis	100%	312/33 months	MDD.HR ≤ 0.784 (p-value ≤ 0.043)	MDD.HR ≤ 0.783 (p-value ≤ 0.041)

HR = hazard ratio; MDD = minimum detectable difference; OS = overall survival; PFS=progression-free survival.

Analysis timing shown in the table is projected based on protocol assumptions. Actual timing depends on the exact time that the required events have accrued.

The 1st OS interim analysis will be conducted when approximately 308 PFS events have happened. *If statistical significance is reached at one of the pre-planned interim analyses of OS, then that interim OS analysis will be regarded as the definitive analysis of OS and subsequent analyses of OS, including the final OS analysis, will be descriptive and considered as optional.*

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
16W-DCR	disease-control rate at 16 weeks
AASLD	American Association for the Study of Liver Diseases
ADA	anti-drug antibody
AFP	α-fetoprotein
APASL	Asian-Pacific Association for the Study of the Liver
ASCO	American Society of Clinical Oncology
BID	twice a day
BP	blood pressure
CDE	Center of Drug Evaluation (China)
COPD	chronic obstructive pulmonary disease
CR	complete response
CRC	carcinoma of the colon or rectum
CSR	Clinical Study Report
CT	computed tomography
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGD	esophagogastroduodenoscopy
EOC	epithelial ovarian cancer
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire
FDA	(U.S.) Food and Drug Administration
FPI	first patient in
FFPE	formalin-fixed, paraffin-embedded
FTC	fallopian tube cancer
GBM	glioblastoma multiforme
GHS	global health status
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Definition
HR	hazard ratio
HRQoL	health-related quality-of-life
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IL-2	interleukin-2
IMP	investigational medicinal product
imRECIST	immune-modified RECIST
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRF	Independent Review Facility
IRR	infusion-related reaction
ITT	intent-to-treat
IxRS	interactive voice or Web-based response system
LMWH	low molecular weight heparin
LPLV	last patient, last visit
MDD	minimum detectable difference
MID	minimally important differences
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NGS	next-generation sequencing
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small-cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PPC	primary peritoneal cancer
PR	partial response
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks

Abbreviation	Definition
QLQ-C30	quality-of-life questionnaire for cancer
QLQ-HCC18	quality-of-life questionnaire for cancer – HCC disease-specific module
QoL	quality-of-life
RBR	Research Biosample Repository
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SD	stable disease
SHARP	Sorafenib HCC Assessment Randomized Protocol (trial)
TTD	time to deterioration
TTP	time to progression
UC	urothelial carcinoma
ULN	upper limit of normal
VAS	visual analog scale
VEGF	vascular endothelial growth factor
VTE	venous thromboembolism
WES	whole-exome sequencing
WGS	whole-genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the sixth most common cancer globally and is the second most deadly cancer (International Agency for Research on Cancer 2012). There are over 700,000 new cases diagnosed each year worldwide with large geographic variation in both risk factors and incidence (Ferlay et al. 2010; El-Serag 2011). The majority (>80%) of cases occur in sub-Saharan Africa and eastern Asia, and China alone accounts for 55% of cases worldwide. Hepatitis B virus (HBV) infection is the main risk factor for HCC in Asia and Africa, while in Western countries and Japan, the main risk factor is hepatitis C virus (HCV) infection and excessive alcohol intake, along with other causes of cirrhosis.

Hepatocellular carcinoma is a highly lethal disease with the highest mortality-to-incidence rate ratio of 0.98 of any solid tumor (Kamangar et al. 2006). Up to 80% of patients first presenting with HCC have advanced unresectable or metastatic disease because of the late appearance of symptoms. It is a medically complex and difficult to treat disease because the majority of patients with HCC have underlying cirrhosis requiring management of both the malignancy and the cirrhosis. In the United States, at 5 years, the overall survival (OS) rate of patients with HCC is 17% and falls substantially to only 3% if present with distant metastasis (Siegel et al. 2016). In China, at 5 years, the OS rate of patients with HCC is 10.1% (Chen et al. 2016).

1.2 CURRENT SYSTEMIC TREATMENT FOR ADVANCED HEPATOCELLULAR CARCINOMA

Prior to the approval of sorafenib (Nexavar®), there was no globally approved systemic treatment for patients presenting with unresectable advanced or metastatic HCC. Doxorubicin was the most widely used cytotoxic agent, and is reported to have an 11%–15% response rate (Mok et al. 1999; Zhu 2006; Lind et al. 2007). More aggressive combinations of cytotoxic chemotherapy have not been shown to increase OS rates and have been associated with considerable toxicity (Yeo et al. 2005).

Sorafenib, an oral multi-kinase inhibitor, was first approved in 2007 by the U.S. Food and Drug Administration (FDA) and is currently considered the global standard of care for the first-line treatment of patients with advanced HCC. The efficacy of sorafenib has been demonstrated in 2 large multicenter, randomized, double-blind, placebo-controlled Phase III trials: the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial and a trial conducted in the Asia-Pacific region. Both studies demonstrated a survival benefit of sorafenib versus placebo. In the SHARP trial, median OS was 10.7 months with sorafenib versus 7.9 months with placebo (hazard ratio [HR]=0.69 [95% CI: 0.55, 0.87]); in the Asia-Pacific trial, median OS was 6.5 months versus 4.2 months (HR=0.68 [95% CI: 0.50, 0.93]). Benefit in median time to radiographic progression was also demonstrated: 5.5 months versus 2.8 months in the SHARP trial (HR=0.58 [95% CI: 0.5, 0.7]) and 2.8 months versus 1.4 months in the Asia-Pacific trial

(HR = 0.6 [95% CI: 0.4, 0.8]). The objective response rate (ORR; per RECIST v1.0) was 2.3% (7 of 299 patients) in the SHARP trial and 3.3% (5 of 150 patients) in the Asia-Pacific trial. The numerically shorter OS and duration of benefit in the Asia-Pacific trial may be largely attributed to the fact that patients had more advanced disease at the time of recruitment, and potentially also to the regional difference in etiology and supportive care (Llovet et al. 2008; Cheng et al. 2009).

Despite the survival benefit reported from these 2 Phase III studies, the overall benefit-risk ratio of sorafenib is modest given the known toxicity. Adverse events commonly reported across both sorafenib studies included hand–foot skin reaction, diarrhea, hypertension, weight loss, fatigue, anorexia, alopecia, nausea, and rash/desquamation. Drug-related adverse events reported were predominantly Grade 1 or 2 in severity. The drug discontinuation rate in patients receiving sorafenib was 38% in the SHARP trial compared with 20% in the Asia-Pacific trial. The frequency of dose reductions due to adverse events was similar between the 2 studies (26% in SHARP and 30.9% in the Asia-Pacific trial; Llovet et al. 2008; Cheng et al. 2009). Despite additional clinical experience with the use of sorafenib, the GIDEON study, which evaluated sorafenib in the real-world setting, showed the drug discontinuation rates due to adverse events in patients starting at the label-recommended dose of 800 mg was 27%, indicating that tolerability has not improved. Moreover, GIDEON showed that in real-life practice, the starting dose of 800 mg daily (400 mg twice a day [BID]) is halved to 400 mg daily in over 22% of patients (Lencioni et al. 2014).

Since the approval of sorafenib, there have been a number of Phase III trial failures in first-line HCC in head-to-head comparisons with sorafenib, including sunitinib, brivanib, and linifanib (Cheng et al. 2013; Johnson et al. 2013; Cainap et al. 2015). Recently, front-line treatment with lenvatinib, a multi-targeted receptor tyrosine kinase inhibitor, was shown to be non-inferior to sorafenib in terms of OS (lenvatinib vs. sorafenib: median OS 13.6 months vs. 12.3 months; HR = 0.92 [95% CI: 0.79, 1.06]; Cheng et al. 2017) though a clinically meaningful difference in OS from the accepted standard of care remains elusive. Therefore, there remains an ongoing high unmet medical need for patients with advanced unresectable HCC, requiring further evaluation of treatment with novel, more efficacious, and less toxic agents.

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 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 in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

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

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

1.4 BACKGROUND ON BEVACIZUMAB

Avastin® (bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in in vitro and in vivo assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF, and has an approximate molecular weight of 149 kD. Bevacizumab is produced in a mammalian Chinese hamster ovary cell line.

Bevacizumab was first granted marketing approval in the United States on 26 February 2004 (international birth date) in combination with IV 5-fluorouracil (5-FU)–based chemotherapy for the first-line treatment of patients with metastatic carcinoma of the colon or rectum (CRC). As of November 2016, bevacizumab has been approved for use in over 100 countries worldwide in a variety of indications, including locally recurrent or metastatic breast cancer; advanced, metastatic, or recurrent NSCLC; advanced and/or metastatic renal cell cancer (RCC); newly diagnosed glioblastoma multiforme (GBM) and GBM after relapse or disease progression; persistent, recurrent, or metastatic cervical cancer; front-line treatment of epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC); and treatment of platinum-sensitive and platinum-resistant recurrent EOC, PPC, or FTC.

1.5 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM IN HEPATOCELLULAR CARCINOMA

1.5.1 Atezolizumab Monotherapy

A comprehensive overview of atezolizumab efficacy across all indications is provided in the Atezolizumab Investigator's Brochure. This section provides an overview of the available efficacy data in patients with HCC treated with atezolizumab as a monotherapy. To date, atezolizumab used as a single agent has shown minimal activity in the treatment of patients with HCC with similar characteristics as those that would be included in this study. Safety findings in the HCC cohort are in line with expectations for an HCC population and with the atezolizumab safety profile observed in the overall study

population across multiple tumor types. No new safety signals related to atezolizumab monotherapy were observed in the HCC population.

Study PCD4989g

Study PCD4989g is a Phase Ia, multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion every 3 weeks (Q3W) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.
The largest cohorts enrolled into this trial consisted of patients with NSCLC, RCC, and UC. Expansion cohorts have included patients with CRC, melanoma, NSCLC, pancreatic cancer, UC, breast cancer, esophageal cancer, prostate cancer, small-cell lung cancer, malignant lymphoma, multiple myeloma, HCC, and other less common tumor types.

In the analysis of Study PCD4989g (clinical cutoff date of 31 December 2016) conducted in 15 patients with first- and later-line HCC, the median duration of treatment was 2.0 months (range: 0.7–6.3 months). At the time of the clinical cutoff date, 1 patient remained on treatment, 12 patients had discontinued treatment due to disease progression, 1 patient discontinued because of an adverse event, and 1 patient was discontinued as per the physician's decision.

Of the 15 response-evaluable patients, none had an objective response (confirmed complete response [CR] or partial response [PR] as assessed by the investigator per the Response Evaluation Criteria in Solid Tumors [RECIST] v1.1). Four patients (33.3%) had stable disease (SD) $<$24 weeks. No patients had SD $\geq$24 weeks.
Median progression-free survival (PFS) per the investigator assessment per RECIST v1.1 was 2.3 months (95% CI: 1.3, 3.4) and median OS was 5.3 months (95% CI: 2.4, NE).

Study YO29233

Study YO29233 is a Phase I, open-label, multicenter study evaluating the pharmacokinetics, safety, and preliminary anti-tumor activity of atezolizumab as a monotherapy in Chinese patients with locally advanced or metastatic gastric cancer, nasopharyngeal carcinoma, esophageal cancer, HCC and other solid tumors, and the safety and preliminary anti-tumor activity of atezolizumab in combination with gemcitabine and cisplatin in Chinese patients with Stage IV, treatment-naive NSCLC. For monotherapy cohorts, atezolizumab is administered as a single agent at a dose of 1200 mg IV Q3W.

Based on a clinical cutoff date of 1 April 2018, 21 patients with HCC had received atezolizumab monotherapy. At the time of the clinical cutoff date, 7 patients remained on treatment (3 first-line patients with HCC), while 7 patients had discontinued treatment due to disease progression, 2 patients discontinued treatment due to an adverse event,

2 patients discontinued treatment due to non-compliance with study drug, and 1 patient each discontinued treatment due to a protocol deviation, physician decision, and death due to progression of disease.

Of the 21 efficacy-evaluable patients (first-line and second-line or greater), 2 patients (9.5% [95% CI: 1.17%, 30.38%]) had a confirmed objective response and 11 patients (52.4% [95% CI: 29.78%, 74.29%]) had the best response of SD. Median PFS was 2.8 months (95% CI: 1.4, 7.8) and median OS was 11.1 months (95% CI: 4.7 months, NE).

1.5.2 Bevacizumab Monotherapy

A comprehensive overview of bevacizumab efficacy across all indications is provided in the Bevacizumab Investigator's Brochure. This section provides an overview of the available efficacy data in patients with HCC treated with bevacizumab as a monotherapy. Overall, bevacizumab as a single agent demonstrated minimal activity in HCC, and is unlikely to demonstrate a meaningful clinical benefit over the current standard of care (sorafenib) based on the survival data observed. Bevacizumab monotherapy was generally safe and well-tolerated in the HCC population, and safety findings were consistent with the HCC population and the established safety profile of bevacizumab. No new safety signals related to bevacizumab monotherapy were observed in this patient population.

Phase II Study of Bevacizumab in Unresectable Hepatocellular Carcinoma

This study was a Phase II, single-center, single-arm trial designed to evaluate the clinical and biological effects of bevacizumab in unresectable HCC (Siegel et al. 2008). Adult patients with organ-confined HCC, an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–2, and compensated liver function (Child-Pugh Class A or B7), received bevacizumab 5 mg/kg or 10 mg/kg every 2 weeks (Q2W) until disease progression or treatment-limiting toxicity. Of note, patients with extrahepatic disease or tumor invasion of the main portal vein or inferior vena cava were excluded. Given the known prognostic value of these factors, the study likely enrolled a population with a more favorable prognosis and treatment outcome compared with a population that would typically be enrolled in a first-line HCC study. The primary objective was to determine whether bevacizumab improved the 6-month PFS rate from 40% to at least 60%. Overall, 46 patients were enrolled, including 12 patients who received bevacizumab 5 mg/kg and 34 patients who received bevacizumab 10 mg/kg Q2W.

Clinical activity of bevacizumab was observed in patients with non-metastatic HCC. Of the 46 patients, 6 patients (13%) had objective responses (95% CI: 3%, 23%), and 65% (95% CI: 51%, 79%) of patients were progression-free at 6 months. Median PFS was 6.9 months (95% CI: 6.5, 9.1) and median OS was 12.4 months (95% CI: 9.4, 19.9). No significant changes were seen with respect to dose and outcome. The response rates for the 5 mg/kg and 10 mg/kg groups were 8.3% and 14.7%, respectively

(p = 0.99 by Fisher's exact test). Median OS times for patients receiving 5 mg/kg and 10 mg/kg were 15.1 months and 12.2 months, respectively (p = 0.64 by the log-rank test; Siegel et al. 2008).

Phase II Study of Bevacizumab in Advanced Hepatocellular Carcinoma

This study was a Phase II, single-center, single-arm trial designed to evaluate the efficacy, safety, and potential biomarkers of the activity of bevacizumab in patients with advanced HCC (Boige et al. 2012). Patients with histologically-confirmed advanced HCC that was not amenable to curative-intent therapies (e.g., resection, liver transplantation, or percutaneous ablation) received bevacizumab 5 mg/kg or 10 mg/kg Q2W until disease progression or unacceptable toxicity. The primary objective was to determine the disease-control rate at 16 weeks (16W-DCR) defined as the proportion of patients with a CR, PR, or SD at 16 weeks after study entry, according to RECIST v1.0.

Overall, 48 patients were enrolled, of which 25 patients were planned to receive bevacizumab 5 mg/kg and 23 patients were planned to receive bevacizumab 10 mg/kg, Q2W. Of the 48 patients enrolled, 43 patients received at least 1 dose of bevacizumab.

Among the 38 response-evaluable patients, 6 patients achieved a PR (intent-to-treat [ITT] ORR, 14% [95% CI: 4%, 24%]); the median duration of response (DOR) was 148 days (range, 55–362 days); 18 patients had SD (DCR, 56%), including 12 patients who experienced SD for ≥ 16 weeks. The 16W-DCR was 42% (95% CI: 27%, 57%) in the overall population, 39% (95% CI: 19%, 59%) in patients treated with 5 mg/kg bevacizumab, and 45% (95% CI: 23%, 67%) in those treated at the 10 mg/kg dose. In the overall population (N = 43), median PFS was 3 months (95% CI: 2, 4); median OS was 8 months (95% CI: 4, 9; Boige et al. 2012).

1.6 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.6.1 Rationale for the Combination of Anti-PD-L1 and Anti-VEGF Therapy in Hepatocellular Carcinoma

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

It is known that HCC is a highly vascularized tumor, and that several pro-angiogenic factors play a role in HCC pathogenesis. For example, in HCC, increased VEGF correlates with vascular density, tumor invasiveness and metastasis, and poor prognosis (Boige et al. 2012; Frenette 2012). The VEGF pathway also plays a crucial role in exerting and maintaining an immunosuppressive tumor microenvironment through several mechanisms. For instance, VEGF-A has been shown to induce FasL expression on endothelial cells, which have the ability to kill effector CD8+ T cells, but not T-reg cells. Administration of anti-VEGF-A attenuated tumor endothelial FasL expression and produced a significant increase in the influx of tumor-rejecting CD8+ over FoxP3+ T cells, which was FasL-dependent, and led to CD8-dependent tumor growth

suppression (Motz et al. 2014). Furthermore, bevacizumab can restore and/or maintain the antigen presentation capacity of dendritic cells, leading to enhanced T-cell infiltration in tumors (Oelkrug and Ramage 2014; Wallin et al. 2016). In addition to increased trafficking of T cells into tumors (Manning et al. 2007), several publications have illustrated that anti-VEGF therapies can also reduce the frequency of myeloid-derived suppressor cells, decrease production of suppressive cytokines, and lower the expression of inhibitory checkpoints on CD8+ T cells in tumors (Roland et al. 2009; Voron et al. 2015). Therefore, the immunomodulatory effect of bevacizumab is expected to increase CD8+ T-cell recruitment and relieve intra-tumoral immunosuppression, thereby boosting the effects of atezolizumab.

1.6.2 Clinical Data of Atezolizumab in Combination with Bevacizumab in Hepatocellular Carcinoma

Preliminary data from Study GO30140 indicates substantial numerical improvement in ORR for the combination of atezolizumab and bevacizumab compared with sorafenib, the current global standard of care, in patients with locally advanced or metastatic HCC, supporting the hypothesis of a synergistic/complementary effect of atezolizumab and bevacizumab.

Efficacy: Study GO30140

Study GO30140 is a Phase Ib, multicenter study of atezolizumab in combination with bevacizumab and/or first-line chemotherapy for patients with metastatic cancer. Arm A is designed to test the combination of atezolizumab and bevacizumab in patients with locally advanced or metastatic HCC who have not received prior systemic therapy. Patients received 1200 mg of atezolizumab and 15 mg/kg of bevacizumab on Day 1 of every 21-day cycle (Q3W).

Based on a clinical cutoff date of 26 July 2018, 103 patients (recruited from the United States and South Korea) with HCC received atezolizumab and bevacizumab combination therapy. All patients received atezolizumab and bevacizumab as first-line therapy. At the time of the clinical cutoff date, 70 patients remained on treatment, 18 patients had discontinued treatment due to disease progression, 2 patients discontinued treatment due to symptomatic deterioration, 6 patients discontinued treatment due to an adverse event, 4 patients discontinued treatment due to death, and 3 patients discontinued treatment due to patient decision or for other reasons.

Efficacy analyses were performed in the efficacy-evaluable population, defined as all patients who received any amount of the combination treatment and have been followed in the study for at least 16 weeks. Based on a clinical cutoff date of 26 July 2018, 73 patients enrolled into Arm A were efficacy-evaluable with a median duration of survival follow-up of 7.2 months.

Based on IRF-assessment per RECIST v1.1, the confirmed ORR was 27.4% (95% CI: 17.6, 39.1). Among the 20 responders, 4 patients (20%) achieved a CR and

the remaining 16 patients (80%) achieved a PR. The ORR based on the investigator's assessment per RECIST v1.1 was numerically similar to the ORR based on the IRF-assessment per RECIST v1.1. According to the investigator assessment per RECIST v1.1, 23 of 73 efficacy-evaluable patients (31.5% [95% CI: 21.1, 43.4]) achieved confirmed objective responses, with 1 patient (1.4%) achieving a CR. When tumor scans were assessed by the IRF according to HCC modified RECIST (mRECIST) criteria, 25 of 73 efficacy-evaluable patients (34.2% [95% CI: 23.5, 46.3]) achieved a confirmed objective response, 8 of those 25 responders (32%) achieved a best overall response of CR, and 17 of 25 responders (68%) achieved a best overall response of PR. Importantly, responses were observed in all assessed patient subgroups, including etiology, region, baseline α-fetoprotein (AFP), and tumor burden.

At the time of the clinical cutoff date, 80% (16 of 20 patients) of the IRF-assessed responses per RECIST v1.1 were ongoing, with durations ranging from 1.6+ to 22.0+ months (+denotes censored data). Nine patients had responses of 6 months or longer per IRF-assessment by RECIST v1.1.

The median DOR has not been reached by IRF-assessment (per RECIST v.1.1 or HCC mRECIST) or investigator assessment (per RECIST v1.1), nor has the median OS been reached. The median PFS by IRF-assessment per RECIST v1.1 and per HCC mRECIST was 7.5 months (95% CI: 5.4–14.9) and the median PFS by investigator assessment per RECIST v1.1 was 14.9 months (95% CI: 7.4–NE). The 6-month PFS rate was 56% by IRF-assessment per RECIST v1.1, 65% by investigator assessment per RECIST v1.1, and 58% by IRF-assessment per HCC mRECIST. These estimates of median PFS are considered to be unstable and expected to change with longer follow-up.

Safety: Study GO30140

In the analysis of safety data from Study GO30140 (clinical cutoff date 26 July 2018) in 103 patients with HCC (median treatment duration with atezolizumab was 3.5 months [range: 0–24 months]; median treatment duration with bevacizumab was 3.5 months [range: 0–23 months]), the combination of atezolizumab and bevacizumab was generally safe and well-tolerated; no new safety signals related to the combination therapy were identified beyond the established safety profile for each individual agent. Furthermore, no unexpected adverse events were observed.

Overall, 95 patients (92.2%) experienced at least 1 adverse event. The most common adverse events (≥20%) were decreased appetite (28.2%) and fatigue, pyrexia, and rash (20.4% each). Forty-one patients (39.8%) experienced a Grade 3–4 adverse event, with the most common Grade 3–4 adverse events (≥4%) being hypertension (11.7%) and increased AST (4.9%). Treatment-related Grade 3–4 adverse events were reported in 28 patients (27.2%), the most common being hypertension (9.7%) and neutrophil count decreased (2.9%).

A total of 36 patients (35%) experienced serious adverse events. Treatment-related serious adverse events occurred in 19 patients (18.4%), most of which were a single occurrence except colitis, esophageal varices hemorrhage and pneumonitis (1.9% each).

Five patients (4.9%) experienced Grade 5 adverse events, of which 2 patients (1.9%) experienced Grade 5 treatment-related adverse events.

Six patients (5.8%) discontinued both atezolizumab and bevacizumab treatment due to adverse events. Eight patients (7.8%) discontinued atezolizumab and 10 patients (9.7%) discontinued bevacizumab due to adverse events. All adverse events leading to any atezolizumab and/or bevacizumab discontinuation were single occurrences except for esophageal varices hemorrhage in 2 patients (1.9%), which led to discontinuation of bevacizumab only.

1.6.3 *COVID-19 Considerations*

In the setting of the 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 COVID-19. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of COVID-19.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13; Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from COVID-19 is altered by cancer immunotherapy.

Severe COVID-19 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 COVID-19.

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 COVID–19-related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

1.6.4 Summary

Overall, the combination of atezolizumab and bevacizumab may be a promising treatment option for patients with HCC. To address the ongoing high unmet medical need for patients with HCC, Study YO40245 aims to evaluate the efficacy and safety of atezolizumab and bevacizumab against the current standard of care, sorafenib, in patients with locally advanced or metastatic HCC.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of atezolizumab in combination with bevacizumab compared with sorafenib in patients with locally advanced or metastatic HCC who have received no prior systemic treatment. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the treatments assigned to patients as part of this study (i.e., atezolizumab and bevacizumab, or sorafenib).

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
To evaluate the efficacy of atezolizumab + bevacizumab compared with sorafenib	• OS, defined as the time from randomization to death from any cause • PFS, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by an IRF according to RECIST v1.1

Table 1 Objectives and Corresponding Endpoints (cont.)

Secondary Efficacy Objectives	Corresponding Endpoints
To evaluate the efficacy of atezolizumab + bevacizumab compared with sorafenib	• OR, defined as a complete or partial response, as determined by the investigator according to RECIST v1.1 • PFS as determined by the investigator according to RECIST v1.1 • TTP, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1 • DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • Objective response as determined by an IRF according to RECIST v1.1 • TTP as determined by an IRF according to RECIST v1.1 • DOR as determined by an IRF according to RECIST v1.1 • Objective response as determined by an IRF according to HCC mRECIST • PFS as determined by an IRF according to HCC mRECIST • TTP as determined by an IRF according to HCC mRECIST • DOR as determined by an IRF according to HCC mRECIST
To evaluate the association of pre-specified biomarkers with efficacy of atezolizumab + bevacizumab compared with sorafenib	• PFS as determined by the investigator and by an IRF according to RECIST v1.1 and OS by baseline serum AFP level ($<$ 400 ng/mL vs. $\geq$ 400 ng/mL)
To evaluate PROs of disease/treatment-related symptoms, GHS/QoL, and function experienced by patients on atezolizumab + bevacizumab versus sorafenib	• TTD, defined as the time from randomization to first deterioration (decrease from baseline of $\geq$ 10 points), maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks in the following EORTC QLQ-C30 subscales: – Physical functioning (PF) – Role functioning (RF) – GHS/QoL

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objectives	Corresponding Endpoints
To evaluate the efficacy of atezolizumab + bevacizumab compared with sorafenib	• Objective response as determined by the investigator according to imRECIST • PFS as determined by the investigator according to imRECIST • TTP as determined by the investigator according to imRECIST • DOR as determined by the investigator according to imRECIST
To evaluate PROs of disease/treatment-related symptoms (including abdominal pain and itching), GHS/QoL, and function experienced by patients on atezolizumab + bevacizumab versus sorafenib	• Mean and mean changes from baseline score (by cycle) in all the subscales of the EORTC QLQ-C30 and QLQ-HCC18 • Proportion of patients with clinically meaningful change in select scales of the QLQ-C30 (GHS/QoL, physical function, role function, appetite loss, diarrhea, fatigue, pain) and QLQ-HCC18 (fatigue, jaundice, pain) • TTD maintained for 2 consecutive timepoints, or 1 timepoint followed by death from any cause within 3 weeks, in select scales of the QLQ-C30 (appetite loss, diarrhea, fatigue, pain) and QLQ-HCC18 (jaundice, fatigue, pain) • TTD maintained for 2 consecutive timepoints, or 1 timepoint followed by death from any cause, within 3 weeks in HRQoL/GHS, physical function, and role function of the QLQ-C30 • Proportion of responses for abdominal pain item (of QLQ-HCC18 pain subscale) and itching item (of QLQ-HCC18 jaundice subscale)
Safety Objective	**Corresponding Endpoints**
To evaluate the safety of atezolizumab + bevacizumab compared with sorafenib	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v4.0 • Vital signs • Clinical laboratory test results
Pharmacokinetic Objective	**Corresponding Endpoint**
To characterize the PK profile of atezolizumab + bevacizumab	• Serum concentration of atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
To evaluate the immune response to atezolizumab	• Presence of ADAs to atezolizumab during the study relative to the presence of ADAs at baseline

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Immunogenicity Objective	Corresponding Endpoint
To evaluate potential effects of ADAs to atezolizumab + bevacizumab on the efficacy, safety, and pharmacokinetics of atezolizumab + bevacizumab	• Efficacy, safety, or PK endpoints by ADA status
Exploratory Biomarker Objective	**Corresponding Endpoint**
To identify tissue or blood-based biomarkers that are associated with response to atezolizumab + bevacizumab versus sorafenib, or can increase the understanding of HCC disease evolution under atezolizumab + bevacizumab treatment	• PFS as determined by the investigator according to RECIST v 1.1 and OS based on the following biomarkers in tumor tissue: – Baseline expression of T effector gene signature in tumor tissue – Baseline PD-L1 protein expression in tumor tissue – CD8 protein expression level or CD8+ T-cell localization – IHCs or genes/gene signatures (by gene expression profiling) related to tumor microenvironments – T cell receptor sequence profile in tumor-associated T cells • Objective response as determined by the investigator according to RECIST v1.1 and OS based on the following biomarkers in blood: – Immune-related biomarkers profiling in plasma and serum (e.g., interleukin-2, interferon-γ)
Exploratory Health Status Objective	**Corresponding Endpoint**
To evaluate health status experienced by patients on atezolizumab + bevacizumab versus sorafenib to generate utility scores for use in economic evaluations	• Health utility and VAS scores of the EQ-5D-5L questionnaire

ADA = anti-drug antibody; AFP = α-fetoprotein; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5-Dimension Questionnaire, 5-Level version; GHS = global health status; HCC = hepatocellular carcinoma; HCC mRECIST = modified RECIST for HCC; imRECIST = immune-modified RECIST; IRF = independent review facility; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PRO = patient-reported outcome; QLQ-C30 = quality-of-life questionnaire for cancer; QLQ-HCC18 = HCC disease-specific module; QoL = quality-of-life; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TTD = time to deterioration; TTP = time to progression; VAS = visual analog scale.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase III, randomized, multicenter, open-label, two-arm study designed to evaluate the efficacy and safety of atezolizumab and bevacizumab versus sorafenib in patients with locally advanced or metastatic HCC who have received no prior systemic treatment.

This study will enroll approximately 480 patients randomized in a 2:1 ratio to one of two treatment arms:

- Arm A (experimental arm): Atezolizumab 1200 mg IV infusion Q3W (dosed in 3-week cycles) and bevacizumab 15 mg/kg Q3W (dosed in 3-week cycles)
- Arm B (control arm): Sorafenib 400 mg by mouth, BID, continuously

Randomization will be stratified according to the following stratification factors:

- Geographic region (Asia excluding Japan vs. rest of world)
- Macrovascular invasion and/or extrahepatic spread (presence vs. absence)
- Baseline AFP ($<$400 vs. $\geq$400 ng/mL)
- ECOG Performance Status (0 vs. 1)

The study schema is shown in Figure 1.

Patients randomized to the atezolizumab and bevacizumab arm (Arm A) who transiently withhold or permanently discontinue either atezolizumab or bevacizumab may continue on single-agent therapy as long as the patients are experiencing clinical benefit in the opinion of the investigator and after discussion with the Medical Monitor (i.e., patients transiently withheld or permanently discontinued from bevacizumab treatment for adverse effects may continue atezolizumab monotherapy and vice versa).

Patients will receive atezolizumab and/or bevacizumab or sorafenib 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 per RECIST v1.1 while receiving atezolizumab and/or bevacizumab or sorafenib 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 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

Tumor assessments will be performed at baseline and at regular intervals during study treatment (see Section 4.5.5 and Appendix 1). Additional scans will be performed as clinically indicated. Tumor assessments will continue until disease progression, regardless of whether treatment has been discontinued (e.g., for toxicity). Patients who meet RECIST v1.1 criteria for progression will undergo tumor assessments until disease progression (per immune-modified RECIST [imRECIST]) or loss of clinical benefit, whichever occurs later. In the absence of disease progression, tumor assessments should continue regardless of whether patients start new anti-cancer therapy, until consent is withdrawn, death, or the study is terminated by the Sponsor, whichever occurs first. Following disease progression, patients will be followed for survival and subsequent anti-cancer therapies until death, loss to follow-up, withdrawal of consent, or study termination by Sponsor, whichever occurs first.

Sites will provide imaging used for tumor assessments to an IRF to enable centralized, independent review of response and progression endpoints. These reviews will be performed prior to the pre-specified efficacy analyses. Independent Review Facility membership and procedures will be detailed in an IRF Charter.

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, v4.0 (NCI CTCAE v4.0). Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Serum samples will be collected to monitor the pharmacokinetics of atezolizumab when administered in combination with bevacizumab. Patient samples, including archival tumor tissues as well as serum and plasma, will be collected for future exploratory biomarker assessments.

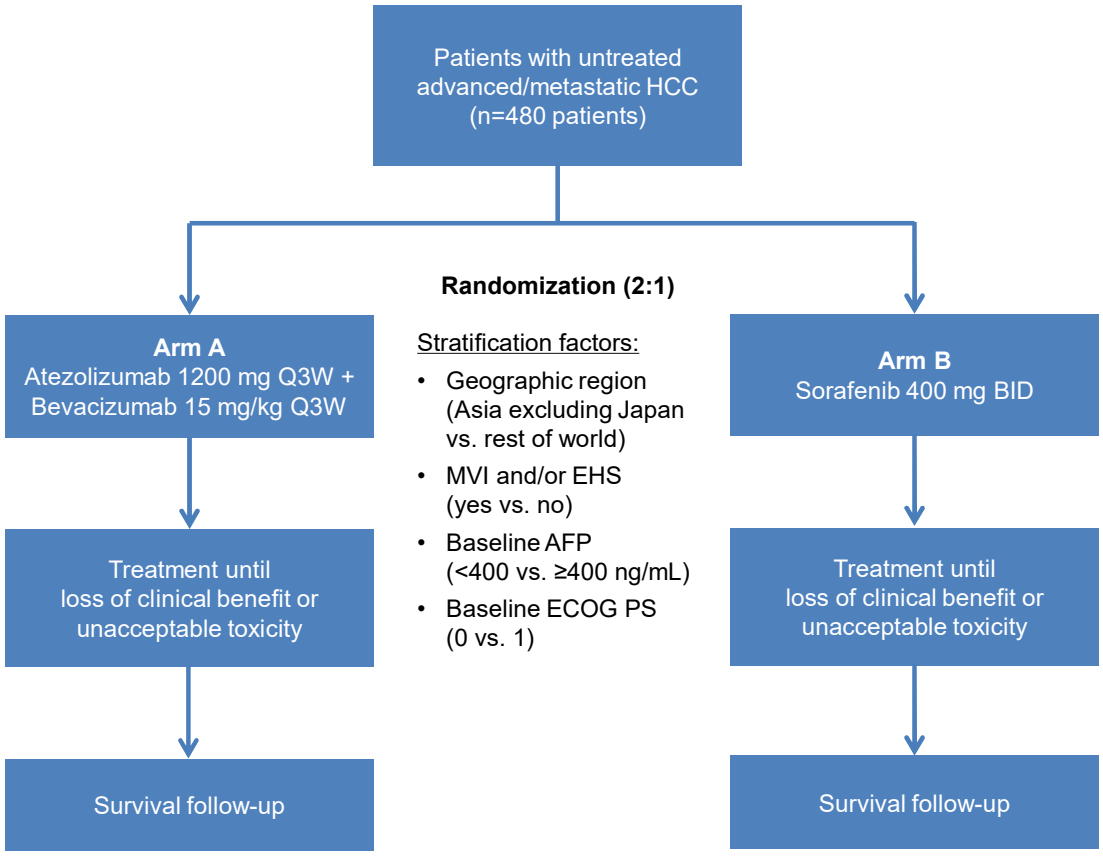
This study will initially enroll approximately 480 patients across all sites in a global enrollment phase.

The Sponsor is targeting a total enrollment of approximately 135 patients from mainland China. After completion of the global enrollment phase, in the event that less than 135 patients from mainland China are enrolled, additional patients in China may be subsequently randomized into the two treatment arms in a 2:1 ratio in an extended China enrollment phase to ensure a total of approximately 135 patients from mainland China in a China subpopulation. The China subpopulation will include all patients enrolled in China (i.e., during both the global enrollment phase and the extended China enrollment phase). The patients enrolled in the China extension phase will undergo the same schedule of activities and will receive atezolizumab and bevacizumab, or sorafenib

as in the global study. The China subgroup analysis will be performed based on the China subpopulation.

Figure 1 presents an overview of the study design. The schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



AFP = α-fetoprotein; BID = twice a day; ECOG = Eastern Cooperative Oncology Group; EHS = extrahepatic spread; HCC = hepatocellular carcinoma; MVI = macrovascular invasion; PS = Performance Status; Q3W = every 3 weeks.

3.1.2 Independent Data Monitoring Committee

An external independent Data Monitoring Committee (iDMC) will evaluate safety data during the study on a periodic basis—approximately every 6 months—until the time of the co-primary efficacy PFS final analysis and the first OS interim analysis. No efficacy interim analyses are planned to be conducted by the iDMC.

Staff at an independent Data Coordinating Center will prepare all safety analyses for iDMC review. The safety summaries will include demographic data, adverse events, serious adverse events, and relevant laboratory data.

Following the data review, the iDMC will provide a recommendation to the Sponsor whether to continue the study, amend the protocol, or stop the study. The final decision will rest with the Sponsor. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the Institutional Review Boards (IRBs)/Ethics Committees (ECs). Members of the iDMC will be external to the Sponsor. An iDMC charter will outline roles and responsibilities of the iDMC members as well as the policies and procedures to be followed by the iDMC.

3.2 END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs (i.e., last patient in the global and extended China enrollment phases combined) or safety follow-up is received from the last patient (global and extended China enrollment phases combined), whichever occurs later.

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

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 Q3W (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq®). 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 (refer to the Atezolizumab Investigator's Brochure for details).

3.3.2 Rationale for Bevacizumab Dose and Schedule

Bevacizumab will be administered at a fixed dose of 15 mg/kg Q3W on Day 1 of each 21-day cycle, which is the approved dosage for bevacizumab. This dose schedule aligns with the atezolizumab dose schedule highlighted above and is the dose used in combination with atezolizumab in Study GO30140. In this study, the combination of atezolizumab and 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.

3.3.3 Rationale for Patient Population

This study will enroll patients with untreated locally advanced or metastatic HCC, regardless of PD-L1 expression or HCC etiology. The broad patient population selected is similar to the population enrolled in Study GO30140, the initial study testing this combination first-line in patients with HCC.

Although sorafenib is approved for the first-line treatment of patients with advanced HCC, the prognosis of these patients remains poor with a median OS reported of 6.5–10.7 months. Treatment with sorafenib is also associated with significant toxicity including hand-foot skin reaction, diarrhea, hypertension, weight loss, fatigue, anorexia, alopecia, nausea, and rash/desquamation, all of which negatively impact the quality-of-life. Therefore, there is a continuing need for more efficacious, better tolerated treatments for the first-line treatment of patients with locally advanced or metastatic HCC.

Patients accrued on the study are also required to have adequate liver function, defined as Child-Pugh Class A. Patients with a Child-Pugh Class B or C rating have an increased risk of death due to underlying cirrhosis, which could potentially confound the appropriate evaluation of treatment-related anti-tumor efficacy; these patients are thus, excluded from the study. The proposed study population is the recommended patient population in the initial study of a new agent or combination of agents for HCC, as noted by an expert panel convened by the American Association for the Study of Liver Diseases (AASLD; Llovet et al. 2008).

3.3.4 Rationale for Control Arm

Patients in the control arm will receive sorafenib. Sorafenib is the only globally approved targeted therapy for patients with unresectable HCC who have not received prior systemic therapy and is considered the acceptable standard of care globally.
The survival benefit of sorafenib was demonstrated in 2 randomized Phase III trials versus placebo, one in a Western population and one in an Asian-Pacific population as discussed in Section 1.2. Sorafenib is the standard of care and the NCCN-, European Association for the Study of the Liver (EASL)-, and Asian-Pacific Association for the Study of the Liver (APASL)-recommended initial therapy regimen for patients with HCC (Omata et al. 2010; EASL-EORTC 2012; NCCN 2017). As such, this study will utilize sorafenib 400 mg BID continuously, the approved dose and schedule.

While lenvatinib recently demonstrated non-inferiority versus sorafenib in terms of OS in patients with advanced HCC (13.6 months for lenvatinib versus 12.3 months for sorafenib) in a randomized Phase III trial (Cheng et al. 2017), it has not been approved globally for this indication. Therefore, the Sponsor believes that the choice of using sorafenib as control treatment is appropriate.

3.3.5 Rationale for Open-Label Study

An open-label study design was chosen for this Phase III study given the unique toxicity profiles of the treatments in each study arm; patients as well as physicians may be capable of identifying treatment assignment if the treatment was assigned blinded. Furthermore, a blinded study would require patients randomized to sorafenib to receive placebo infusions of atezolizumab and bevacizumab which the Sponsor believes would impose unnecessary burden and excessive risk to patients.

As part of the study design, adequate steps have been taken to ensure the validity of the data in this open-label study (i.e., IRF-assessed PFS co-primary objective and IRF-assessed ORR as secondary endpoints).

3.3.6 Rationale for Overall Survival and Progression-Free Survival as Co-Primary Endpoints

In this study, the co-primary efficacy endpoints will be OS and IRF-assessed PFS.

Overall survival was chosen as one of the co-primary endpoints for this study because the measurement of this endpoint is clearly defined, and patients can be evaluated objectively.

Progression-free survival was chosen as a co-primary endpoint for this study because PFS is an important, clinically meaningful metric to demonstrate the efficacy of anti-cancer regimens in many first-line disease settings, particularly where additional lines of therapy are common. In addition, data from several tumor types have suggested a strong correlation between PFS and OS, thus supporting PFS as a robust surrogate predictor of OS and clinical benefit (Adunlin et al. 2015; Dabbous et al. 2017).

3.3.7 Rationale for Stratification

To balance the disease-related prognostic factors across treatment arms, randomization of patients into the study will be stratified. The proposed stratification factors are the following:

- Geographic region (Asia excluding Japan vs. rest of world)
- Macrovascular invasion and/or extrahepatic spread (presence vs. absence)
- Baseline AFP ($<$400 vs. $\geq$400 ng/mL)
- ECOG Performance Status (0 vs. 1)

3.3.7.1 Geographic Region

Although HCC is a global disease, there is significant geographic heterogeneity in terms of efficacy outcomes. In the SHARP trial, which recruited patients from Europe, Australia, and the Americas, median OS in the sorafenib and placebo–treated arm was 10.7 and 7.9 months, respectively (Llovet et al. 2008). In the Asia-Pacific trial, which recruited patients from China, South Korea, and Hong Kong, the median OS in the sorafenib and placebo–treated arm was 6.5 and 4.2 months, respectively (Cheng et al. 2009). In a subgroup analyses of Phase III trials evaluating sorafenib versus other multi-kinase inhibitors (sunitinib, brivanib, and linifanib), similar trends of differences in median OS were observed consistently between the 2 regions (sunitinib study: median OS 7.9 months [Asia] vs. 15.3 months [non-Asia]; brivanib study: median OS 8.7 months [Asia] vs. 10.9 months [non-Asia]; linifanib study: median OS 8.2 months [Asia] vs. 11.3 months [non-Asia]; Cheng et al. 2013; Johnson et al. 2013; Cainap et al. 2015).

These differences in outcome may be attributed to several potential causes that include regional differences in etiology and clinical practice patterns. Hepatitis B virus infection is the main risk factor for HCC in Asia (>70%), while in Western countries and Japan, the main risk factor is HCV infection (50%–70%) and excessive alcohol intake (20%), along with other causes of cirrhosis (10%), and literature has long cited that clinicopathologic features and prognoses differ among the different etiologies of HCC (Llovet et al. 2003; Sanyal et al. 2010; Nault 2014). Furthermore, even with the same etiology, the OS of patients differs, which can be attributed to the difference in clinical practice between the 2 regions (Cheng et al. 2013). Patients recruited from Asian regions, who may be considered ineligible for surgery or other localized treatments because of extent of disease, may have been treated more aggressively, with more transarterial chemoembolization and surgical treatment than patients recruited from other regions. Therefore, Asian-region patients recruited into clinical trials for first-line treatment may have more advanced disease and thus, worse outcomes than patients from other regions (Cheng et al. 2009).

Given this geographic heterogeneity, randomization into the study will be stratified by geographic region (Asia excluding Japan vs. rest of world). The median OS of advanced HCC for patients in Japan more closely resembles those of Western countries, and; therefore, Japan will not be included in the Asia region subgroup (Kudo et al. 2016).

3.3.7.2 Macrovascular Invasion and/or Extrahepatic Spread (Presence vs. Absence)

Randomization of patients will be stratified by presence or absence of extrahepatic spread or macrovascular invasion because these 2 factors have been shown to be strong independent prognostic factors associated with shorter OS. Patients with extrahepatic spread and/or macrovascular invasion have a worse prognosis than patients without either of these 2 factors, and stratification by these 2 variables has been recommended by an expert panel convened by the AASLD (Llovet et al. 2008; Bruix et al. 2012; Cheng et al. 2012; Bruix et al. 2017).

3.3.7.3 Baseline α-Fetoprotein(<400 ng/mL vs. ≥400 ng/mL)

Very high serum AFP level (≥400 ng/mL) is a strong prognostic factor of shorter OS time for patients with HCC, including those receiving sorafenib (Bronowicki et al. 2015; Bruix et al. 2017). Though serum AFP level may be an indirect measure of tumor burden, multivariate analysis has shown that even when tumor morphology is accounted for, AFP levels greater than 400 ng/mL still have independent prognostic value, suggesting that it could be a marker of a biologically more aggressive phenotype (Cancer of the Liver Italian Program Investigators 1998). Therefore, given the prognostic impact of serum AFP level, randomization of patients in this study will be stratified by their baseline serum AFP level (<400 ng/mL vs. ≥400 ng/mL).

3.3.7.4 Eastern Cooperative Oncology Group Performance Status (0 vs. 1)

Eastern Cooperative Oncology Group performance status is regarded as an acceptable and comprehensive parameter to determine the degree of health status in patients with cancer. In patients with HCC, a poor performance status is associated with larger tumor burden and more severe cirrhosis and is an indispensable surrogate to reflect the general condition of patients. Deterioration of performance status was identified as an independent predictor of decreased survival, and patients with a performance status of 1 had a 34% increased risk of mortality compared with patients with a performance status of 0 (Hsu et al. 2013). In the Phase III trials evaluating linifanib, brivanib, and most recently levatinib, patients with a performance status of 1 had a decreased medial OS compared with patients with a performance status of 0 in both the experimental and control arms (Johnson et al. 2013; Cainap et al. 2015; Cheng et al. 2017). Stratification by ECOG Performance Status has also been recommended by an expert panel convened by the AASLD (Llovet et al. 2008).

3.3.8 Rationale for Study 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 immune cells and no viable cancer cells. For sorafenib treatment, as noted in the prescribing information, it can be continued until the patient is no longer clinically benefitting from therapy or until unacceptable toxicity occurs. Therefore, this study will allow all patients to continue their assigned treatment after apparent radiographic progression per RECIST v1.1, provided the benefit-risk ratio is judged to be favorable by the investigator (see criteria in Section 3.1). Patients should be discontinued for unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, and clinical status (see Section 3.1 for details).

3.3.9 Rationale for Biomarker Assessments

Several exploratory biomarkers may correlate with clinical response of atezolizumab in combination with bevacizumab. Since the VEGF pathway plays a crucial role in exerting and maintaining an immunosuppressive tumor microenvironment through several mechanisms, the abundance of preexisting CD8+T-cell infiltrates, the expression of PD-L1 in tumors, or gene signatures related to the tumor stromal environment may be important determinants of clinical responses. In the current study, archival or baseline tumor specimens will be collected from patients and tested retrospectively with protein or genomic/transcriptomic platforms to explore the potential relationship to clinical

responses. In addition to the assessment of PD-L1 expression and CD8 T-cell status, other exploratory biomarkers, such as potential predictive and prognostic biomarkers related to the clinical benefit of atezolizumab in combination with bevacizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may be analyzed.

Archival tumor tissue will be collected at baseline if available. These baseline tissues will enable exploratory analysis of tumor tissue biomarkers related to clinical response, resistance, or disease progression.

Plasma and serum samples will be collected at baseline and during the study to evaluate changes in peripheral biomarkers such as immune-related biomarkers (e.g., interleukin-2 [IL-2], interferon-γ). Changes in biomarkers may provide evidence of biologic activity of atezolizumab in combination with bevacizumab in humans. Correlations between these biomarkers and safety and efficacy endpoints will be explored to identify blood-based biomarkers that might predict which patients are more likely to benefit from atezolizumab and bevacizumab combination therapy.

Tumor tissue and blood samples will be analyzed through use of next-generation sequencing (NGS), and/or additional protein detection methods to identify signatures and/or other biomarkers that are predictive of response to the combination, are associated with progression to a more severe disease state, are associated with acquired resistance to the combination, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology.

3.3.10 Rationale for Patient-Reported Outcomes Assessments

Both cancer- and treatment-related symptoms and the associated impact on health-related quality-of-life (HRQoL) in patients with HCC are complex. Historically, hepatobiliary cancers have been associated with poor prognosis and HRQoL (Heffernan et al. 2002). Patients with HCC have reported worsened physical, psychological, functional well-being, and hepatobiliary symptoms (pain, fatigue, anorexia/weight loss, obstructive jaundice/ascites) compared with the general population. Similarly, patients with HCC have reported worsened physical well-being and overall HRQoL compared with patients who have chronic liver disease (Fan et al. 2010). While there have been many advances in HCC treatment, and survival data and information about side effects of treatment are becoming more readily available, much less is known about the impact HCC treatments have on the patients' HRQoL.

Patient-reported information regarding treatment-related symptoms and other aspects of quality-of-life are valuable for both patients and clinicians in decision-making and may also predict survival. Common patient-reported symptoms of disease in this patient population include abdominal pain, fatigue, weight loss, poor appetite, and jaundice (Sun et al. 2008). The concepts of symptom burden and HRQoL are best documented

through standardized patient-reported outcomes (PROs), and validated measures will be used to assess these aspects at pre-specified timepoints in the study (see Appendix 1).

The European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30; see Section 4.5.8.1) and its HCC disease–specific module (EORTC QLQ-HCC18; see Section 4.5.8.2) have been selected on the basis of their content validity, performance, and breadth of concepts measured.

In addition, the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L; see Section 4.5.8.3) will be completed to inform pharmacoeconomic models and, as such, will not be included in the Clinical Study Report (CSR).

4. MATERIALS AND METHODS

4.1 PATIENTS

The study will enroll approximately 480 patients at approximately 120 study sites. After completion of the global enrollment phase, additional patients may be enrolled in China in an extended China enrollment phase to ensure a total of approximately 135 patients from mainland China in a China subpopulation.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing the Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Locally advanced or metastatic and/or unresectable HCC with diagnosis confirmed by histology/cytology or clinically by AASLD criteria (see Appendix 13) in cirrhotic patients

  Patients without cirrhosis require histological confirmation of diagnosis.
- Disease that is not amenable to curative surgical and/or locoregional therapies, or progressive disease after surgical and/or locoregional therapies
- No prior systemic therapy (including systemic investigational agents) for HCC

  Previous use of herbal therapies/traditional Chinese medicines with anti-cancer activity included in the label is allowed, provided that these medications are discontinued prior to randomization.
- At least 1 measurable (per RECIST v1.1) untreated lesion
- Patients who received prior local therapy (e.g., radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, transarterial embolization, etc.) are eligible provided the target lesion(s) have not been previously treated with local therapy or the target lesion(s) within the field of local therapy have subsequently progressed in accordance with RECIST v1.1

- Pretreatment tumor tissue sample (if available)

  If tumor tissue is available, a formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or approximately 10–15 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 specimens (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 (see Section 4.5.6 for further details).

  If tumor tissue is not available (e.g., depleted because of prior diagnostic testing), patients are still eligible.
- Eastern Cooperative Oncology Group performance status of 0 or 1 within 7 days prior to randomization
- Child-Pugh Class A (see Appendix 10) within 7 days prior to randomization
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 7 days prior to randomization, unless otherwise specified:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - Platelet count $\geq 75 \times 10^9$/L (75,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9 g/dL)

    Patients may be transfused to meet this criterion.
  - AST, ALT, and ALP $\leq 5 \times$ upper limit of normal (ULN)
  - Serum bilirubin $\leq 3 \times$ ULN
  - Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min (calculated with use of the Cockcroft-Gault formula)
  - Serum albumin ≥ 28 g/L (2.8 g/dL) without transfusion
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 2 \times$ ULN
  - Urine dipstick for proteinuria $< 2+$ (within 7 days prior to initiation of study treatment)

    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.
- Resolution of any acute, clinically significant treatment-related toxicity from prior therapy to Grade ≤ 1 prior to study entry, with the exception of alopecia
- Negative HIV test at screening

- Documented virology status of hepatitis, as confirmed by screening HBV and HCV serology test
- For patients with active HBV:

  HBV DNA $<$ 500 IU/mL obtained within 28 days prior to initiation of study treatment, and

  Anti-HBV treatment (per local standard of care; e.g., entecavir) for a minimum of 14 days prior to study entry and willingness to continue treatment for the length of the study
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $<$ 1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab, 6 months after the last dose of bevacizumab, or 6 months after the last dose of sorafenib. 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 has not undergone surgical sterilization (removal of ovaries and/or uterus).

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<$ 1% per year during the treatment period and for 6 months after the last dose of bevacizumab or 3 months after the last dose of sorafenib. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of bevacizumab or 3 months after the last dose of sorafenib to avoid exposing the embryo.

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

- For the extended China enrollment phase: Chinese ancestry and residence in Mainland China, Hong Kong, or Taiwan with enrollment at sites recognized by China's Center of Drug Evaluation (CDE)

4.1.2 Exclusion Criteria

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

- History of leptomeningeal disease
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 8 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
  – No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Known active tuberculosis
- 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 initiation of study treatment), unstable arrhythmia, or unstable angina
- History of congenital long QT syndrome or corrected QT interval >500 ms (calculated with use of the Fridericia's formula) at screening
- History of uncorrectable electrolyte disorder affecting serum levels of potassium, calcium, or magnesium

- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- History of malignancy other than HCC 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
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia*, or any active infection that, in the opinion of the investigator, could impact patient safety*
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease [COPD] exacerbation) are eligible for the study.
- Prior allogeneic stem cell or solid organ 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
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or bevacizumab formulation
- Pregnant or breastfeeding, or intention of becoming pregnant during study treatment or within at least 5 months after the last dose of atezolizumab, 6 months after the last dose of bevacizumab, or *6* month*s* after the last dose of sorafenib

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
- Untreated or incompletely treated esophageal and/or gastric varices with bleeding or high risk for bleeding

  Patients must undergo an esophagogastroduodenoscopy (EGD), and all size of varices (small to large) must be assessed and treated per local standard of care

prior to enrollment. Patients who have undergone an EGD within 6 months of prior to initiation of study treatment do not need to repeat the procedure.

- A prior bleeding event due to esophageal and/or gastric varices within 6 months prior to initiation of study treatment
- Moderate or severe ascites
- History of hepatic encephalopathy
- Coinfection of HBV and HCV

  Patients with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV.

- 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, whole-brain radiotherapy, and/or neurosurgical resection within 28 days prior to initiation of study treatment
  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. 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.
- Uncontrolled tumor-related pain

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

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

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

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

  Patients with indwelling catheters (e.g., PleurX®) are allowed.

- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL or corrected serum calcium $>$ ULN)
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Treatment with strong CYP3A4 inducers within 14 days prior to initiation of study treatment, including rifampin (and its analogs) or St. John's wort
- 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 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, 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 after Medical Monitor approval has been obtained.

  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] $\geq$ 150 mmHg and/or diastolic BP $>$ 100 mmHg), based on an average of $\geq$ 3 BP readings on $\geq$ 2 sessions

  Antihypertensive therapy to achieve these parameters is allowable.
- Prior history of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of study treatment
- History of hemoptysis ($\geq$ 2.5 mL of bright red blood per episode) within 1 month prior to initiation of study treatment
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (within 10 days of first dose of study treatment) use of aspirin ($>$ 325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and cilostazol
- Current or recent (within 10 days prior to study treatment start) use of full-dose oral or parenteral anti-coagulants 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 within 14 days prior to initiation of study treatment.

For prophylactic use of anti-coagulants or thrombolytic therapies, local label approved dose levels may be used.

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

  Patients with signs/symptoms of sub-occlusive syndrome/intestinal obstruction at time of initial diagnosis may be enrolled if they had received definitive (surgical) treatment for symptom resolution.
- Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Metastatic disease that involves major airways or blood vessels, or centrally located mediastinal tumor masses (< 30 mm from the carina) of large volume

  Patients with vascular invasion of the portal or hepatic veins may be enrolled.
- History of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including but not limited to active peptic ulcer disease, diverticulitis, or colitis
- Radiotherapy within 28 days and abdominal/pelvic radiotherapy within 60 days prior to initiation of study treatment, except palliative radiotherapy to bone lesions within 7 days prior to initiation of study treatment
- Local therapy to liver (e.g., radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, transarterial embolization, etc.) within 28 days prior to initiation of study treatment or non-recovery from side effects of any such procedure
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to initiation of study treatment, or abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 60 days prior to initiation of study treatment or anticipation of need for major surgical procedure during the course of the study or non-recovery from side effects of any such procedure
- Chronic daily treatment with a nonsteroidal anti-inflammatory drug (NSAID)

  Occasional use of NSAIDs for the symptomatic relief of medical conditions such as headache or fever is allowed.

4.2 METHOD OF TREATMENT ASSIGNMENT

4.2.1 Treatment Assignment

This is a randomized, open-label 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 randomized to one of two treatment arms, atezolizumab and bevacizumab or sorafenib, according to a 2:1 randomization ratio with use of a permuted-block randomization method. Randomization will be stratified according to the following stratification factors:

- Geographic region (Asia excluding Japan vs. rest of world)
- Macrovascular invasion and/or extrahepatic spread (presence vs. absence)
- Baseline AFP ($<$400 vs. $\geq$400 ng/mL)
- ECOG Performance Status (0 vs 1)

Patients should receive their first dose of study drug on the day of randomization if possible. If this is not possible, the first dose should occur within 3 business days after randomization, with the exception of the emergence of an adverse event, for which dosing may be postponed.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are atezolizumab, bevacizumab, and sorafenib.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab

The atezolizumab Drug Product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

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

4.3.1.2 Bevacizumab

The bevacizumab Drug Product will be supplied by the Sponsor as a sterile liquid in single-use 100-mg and 400-mg preservative-free glass vials to deliver 4 mL or 16 mL of bevacizumab (25 mg/mL). The vial contains approximately 4 mL or 16 mL of bevacizumab solution.

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

4.3.1.3 Sorafenib

Sorafenib tablets will be supplied by the Sponsor (where required by local health authority regulations) in a wallet containing 28 tablets.

For further details on the formulation, packaging, and handling, refer to the local prescribing information for sorafenib.

4.3.2 Study Treatment Dosage, Administration, and Compliance

Patients will receive treatment as outlined 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; see Section 3.1 for details). 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. If treatment was postponed for fewer than 3 days, the patient can resume the original schedule.

After 6 complete cycles, 1 of 3 cycles may be delayed by 1 week (28 days instead of 21 days for 1 cycle) to allow for vacations/holidays. Following the delay, the next cycle visit must be 21 days from the previous Day 1 visit: 2 consecutive 28 cycles are not permitted.

Table 2 Study Treatment Regimens

Arm	Cycle Length	Dose, Route, and Regimen [a]	Infusion Rate
A [b]	21 days	Atezolizumab 1200 mg IV on Day 1	Over 60 (±15) minutes (for the first infusion); 30 (±10) minutes for subsequent infusions if tolerated
		Bevacizumab 15 mg/kg IV on Day 1	Over 90 (±15) minutes (for the first infusion); shortening to 60 (±10) then 30 (±10) minutes for subsequent infusions if tolerated
B	21 days	Sorafenib 400 mg BID, by mouth, continuously	Not applicable

BID = twice per day.

[a] Drugs listed in order of administration.

[b] For patients randomized to Arm A, on Day 1 of each cycle, atezolizumab will be administered first, followed by bevacizumab, with a minimum of 5 minutes between dosing.

Any overdose or incorrect administration of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

No safety data related to overdosing of atezolizumab and bevacizumab are available to date.

Guidelines for treatment interruption or discontinuation and dosage modification (sorafenib arm only) for patients who experience adverse events are provided in Appendix 11 and Appendix 12.

Patients who are still receiving study treatment at the time of the end of this study will continue to be offered study treatment until disease progression or unacceptable toxicity. Patients may receive study treatment as part of an open-label extension study, if eligible.

4.3.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle 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 9. 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 • 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, anti-pyretics, 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

Table 3 Administration of First and Subsequent Atezolizumab Infusions (cont.)

First Infusion	Subsequent Infusions
	• 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

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

Guidelines for medical management of infusion-related reactions (IRRs) are provided in the Atezolizumab Investigator's Brochure.

No dose modification for atezolizumab is allowed.

4.3.2.2 Bevacizumab

Bevacizumab will be administered by IV infusion at a fixed dose of 15 mg/kg on Day 1 of each 21-day Cycle (see Table 2).

Administration of bevacizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 9. Bevacizumab infusions will be administered per the instructions outlined in Table 4. Guidelines for dosage modification and treatment interruption or discontinuation because of toxicities are provided in Appendix 11.

Table 4 Administration of First and Subsequent Bevacizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the Bevacizumab infusion • Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion • Bevacizumab should be infused over 90 (±15) minutes • Vital signs should be at the end of infusion and 2 (±1) hours after the infusion	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, anti-pyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator • Vital signs should be recorded within 60 minutes prior to the infusion

Table 4 Administration of First and Subsequent Bevacizumab Infusions (cont.)

First Infusion	Subsequent Infusions
• Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms	• Bevacizumab 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 may be infused over 30 (±15) minutes thereafter. • Vital signs should be at the end of infusion and 2 (±1) hours after the infusion

4.3.2.3 Sorafenib

A dose of 400 mg sorafenib (2×200 mg tablets) will be given by mouth BID, starting on Cycle 1, Day 1. Tablets should be taken with approximately 240 mL (1 cup or 8 ounces) of water, without food (at least 1 hour before or 2 hours after a meal). The evening dose should be taken approximately 12 hours after the morning dose.

Guidelines for dose modification and study treatment interruption or discontinuation are provided in Appendix 11.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab, bevacizumab, sorafenib) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor with use of the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

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 (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 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 HCC
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for HCC
- 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 at the following website:

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

4.4 CONCOMITANT THERAPY (PROHIBITED FOOD AND OTHER RESTRICTIONS)

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment 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
- Hormone replacement therapy
- Inactivated influenza vaccinations
- 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
- Low-dose aspirin ($<$ 325 mg/day) is permitted. Co-administration of proton pump inhibitors is strongly recommended to reduce potential GI damage
- Prophylactic use of low-dose anticoagulation, unfractionated heparin, or low molecular weight heparin (LMWH) is permitted. The preferred choice for anticoagulation treatment should be LMWH as per American Society of Clinical Oncology (ASCO) guidelines (Lyman et al. 2015).
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy. Bevacizumab or sorafenib treatment must be held during palliative radiotherapy treatment. Upon completion of palliative radiotherapy treatment, continuation of bevacizumab or sorafenib treatment may be allowed after Medical Monitor approval has been obtained.
- 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 radiation therapy) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy
  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.
  – Anti-convulsant therapy, if required, is administered at a stable dose

Note: Treatment with atezolizumab and bevacizumab 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 non-target lesions may still be eligible to continue study treatment after Medical Monitor approval has been obtained.

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

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.2.2) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 9).

4.4.2 Cautionary Therapy

4.4.2.1 Herbal Therapies

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

4.4.2.2 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.2.3 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 Appendix 12 and the Atezolizumab Investigator's Brochure for details).

4.4.2.4 Cautionary Therapy for Sorafenib-Treated Patients

Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

In vitro data suggest that sorafenib inhibits CYP2B6 and CYP2C8. Systemic exposure to substrates of CYP2B6 and CYP2C8 is expected to increase when co-administered with sorafenib. Therefore, the medications listed below should be avoided. If use of one of these medications is necessary, the risks and benefits should be discussed with the Medical Monitor prior to concomitant administration with sorafenib.

- CYP2B6 substrates, including, but not limited to, bupropion and efavirenz
- CYP2C8 substrates, including, but not limited to, repaglinide, montelukast, pioglitazone, and rosiglitazone

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

UGT1A1 and UGT1A9 Substrates

Caution is recommended when administering sorafenib with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (e.g., irinotecan). Sorafenib inhibits glucuronidation by the UGT1A1 and UGT1A9 pathways. Systemic exposure to substrates of UGT1A1 and UGT1A9 may increase when co-administered with sorafenib. For additional detail, see local prescribing information.

Anti-Arrhythmic Medications or Other Medications that Lead to QT Prolongation

Sorafenib has been shown to prolong the QT/QTc interval, which may lead to an increased risk of ventricular arrhythmia. Caution is recommended when administering sorafenib with certain anti-arrhythmic medicines or other medicinal products that lead to QT prolongation.

Strong CYP3A4 Inducers

Inducers of CYP3A4 may increase metabolism of sorafenib and thus decrease the systemic exposure to sorafenib. Caution is recommended for concomitant use of strong CYP3A4 inducers (including, but not limited to, phenytoin, St. John's Wort, dexamethasone, carbamazepine, rifampin, rifabutin, and phenobarbital) with sorafenib. For additional details, see local prescribing information.

4.4.3 Prohibited Therapy

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

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease 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)
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the last dose of atezolizumab
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 *drug-elimination* half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab
- Current use of full-dose anti-coagulants, thrombolytic therapy at therapeutic doses, or anti-platelet therapy are prohibited

  Local label-recommended doses for prophylactic use of anti-coagulants or thrombolytic therapies is 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 (VTE) event while still receiving study drug treatment, it may still be possible for the patient to remain on study medication despite anticoagulation treatment (see Section 4.1.2).
- Use of warfarin or Coumadin-like products (includes for prophylactic use) is prohibited

  Prophylactic use of low-dose anticoagulation, unfractionated heparin or LMWH is permitted. The preferred choice for anticoagulation treatment should be LMWH as per ASCO guidelines (Lyman et al. 2015).
- Concomitant chronic use of NSAIDs while receiving study drugs 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) intermittent or

short-term intake of oral NSAIDs is allowed, when co-administered with proton pump inhibitors to reduce potential GI damage.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. The schedule of biomarker, PK, and immunogenicity sampling is provided in Appendix 2. All activities must be performed and documented for each patient.

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. If treatment was postponed for fewer than 3 days, the patient can resume the original schedule.

After 6 complete cycles, 1 of 3 cycles may be delayed by 1 week (28 days instead of 21 days for 1 cycle) to allow for vacations/holidays. Following the delay, the next cycle visit must be 21 days from the previous Day 1 visit: 2 consecutive 28 cycles are not permitted.

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 screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. Patients who fail their first screening for study eligibility may qualify for 1 re-screening opportunity (for a total of 2 screenings per patient) at the investigator's discretion. All re-screening requests will require approval by the Medical Monitor or designee.

4.5.2 Medical History, 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 initiation of study treatment will be recorded. At the time of each follow-up physical

examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

4.5.3 Physical Examinations

A complete physical examination, performed at screening, 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 post-baseline 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.

As part of the tumor assessment, physical examinations should include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic BP, and temperature.

Vital signs are to be measured before, during, and after infusions for Arm A 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 in Arm A

	Drug	Timing for Vital Sign Measurements	
		First Infusion	Subsequent Infusions
Arm A	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	• Within 60 minutes prior to the bevacizumab infusion • At the end of infusion and 2 (±1) hours after the infusion	• Within 60 minutes prior to the bevacizumab 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, then every 6 weeks (±1 week) for the first 54 weeks following treatment initiation, and every 9 weeks (±1 week) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 or (for patients who continue treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 3.1 for details).
Patients who meet RECIST v1.1 criteria for progression will undergo tumor assessments until disease progression per imRECIST or loss of clinical benefit, whichever occurs later. In the absence of disease progression, tumor assessments should continue regardless of whether patients start new anti-cancer therapy, until consent is withdrawn, death, or the study is terminated by the Sponsor, whichever occurs first. 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 initiation of study treatment do not have to be repeated at screening.

Screening assessments must include CT scans (with oral or IV contrast) or magnetic resonance imaging (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 and MRI scans of the abdomen and pelvis should be performed. If a CT scan with contrast is not contraindicated, it is mandatory to obtain a multi-phase imaging of the liver, and every effort should be made to time the contrast administration so that high-quality arterial-phase imaging is obtained throughout the liver on the first run, and high-quality portal venous-phase imaging is obtained throughout the liver on the second run. 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. Patients with a history of irradiated brain metastases and without measurable brain lesion at screening are not required to undergo brain scans at subsequent tumor evaluations, unless scans are clinically indicated per local standard of care.

Bone scans or PET 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 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).

Response will be assessed by the investigator with use of RECIST v1.1 (see Appendix 3) and imRECIST (see Appendix 4). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

Scans will be submitted to an IRF for central review for evaluation of secondary progression and response efficacy endpoints.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

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

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

  If a patient has a positive HBsAg test and/or a positive total HBcAb test at screening, an HBV DNA test should be performed at screening.
- 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 active HCV infection.
- 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 has not undergone surgical sterilization (removal of ovaries and/or uterus).

- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

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

- Pharmacokinetic assays

  Serum samples will be assayed for atezolizumab concentration with use of validated immunoassays.

- Anti-drug antibody (ADA) assays

  Serum samples will be assayed for the presence of ADAs to atezolizumab with use of validated immunoassays.

- Quantitative HBsAg
- Serum and plasma samples for exploratory research on biomarkers

  Exploratory biomarker research may include, but not be limited to, analysis of genes or gene signatures associated with tumor immunobiology, PD-L1, or cytokines associated with T-cell activation and may involve extraction of circulating tumor DNA, or RNA, analysis of somatic mutations by NGS.

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.10), biological samples will be destroyed when the final CSR has been completed, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final CSR has been completed
- Serum, plasma, and tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final CSR has been completed
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if

samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

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 Patient-Reported Outcomes

To more fully characterize the clinical profile of atezolizumab in combination with bevacizumab, PRO data will be obtained through use of the following instruments: the EORTC QLQ-C30, HCC disease-specific treatment questionnaire (EORTC QLQ-HCC18), and the EQ-5D-5L. The questionnaires will be translated as appropriate (if necessary) in the country language(s) and as feasible in the local language.

To ensure instrument validity and that data standards meet health authority requirements, questionnaires must be completed by the patient during a clinic visit before discussion of the patient's health state, laboratory results, or health record, before administration of study treatment, and/or prior to any other study assessment(s).

Patients will complete paper versions of the EORTC QLQ-C30, EORTC QLQ-HCC18, and EQ-5D-5L questionnaires at the clinic site on Cycle 1, Day 1 and Day 1 of every cycle thereafter until the treatment discontinuation visit (included); after treatment discontinuation or disease progression, whichever comes first, questionnaires will be completed every 3 months (for 1 year), unless the patient withdraws consent or the Sponsor terminates the study as is denoted in Appendix 1. Paper PRO questionnaires will be provided and collected by site staff. Questionnaires should be self-administered, or they can be interviewer-administered by staff prior to other study assessments.

Study personnel should review all questionnaires for completeness before a patient leaves the investigational site. Patients for whom PRO questionnaires are not available in their native language or who are deemed by the investigator incapable of completing their PRO assessment may be exempt from all PRO assessments. In the event that

PRO questionnaires are not administered, site staff will record the reasons for why the measure was not completed in the eCRF.

4.5.8.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a validated, reliable self-reported measure (Aaronson et al. 1993; Fitzsimmons et al. 1999; see Appendix 5). It consists of 30 questions that assess 5 aspects of patient functioning (physical, emotional, role, cognitive, and social), 3 symptom scales (fatigue, nausea and vomiting, pain), global health/QoL, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week.
The EORTC QLQ-C30 module takes approximately 10 minutes to complete. Each score is transformed on to a 0 to 100–point scale. In the 5 functional scales and the Global Health Status (GHS) scale, a high score means a "high level of functioning or global health status." For the symptom scales and single items scales, a higher score implies a "high level of symptoms or problems." Previously published minimally important differences will be used to identify meaningful changes from baseline in each treatment group on the disease and treatment-related symptom scales (Osoba et al. 1998).

4.5.8.2 EORTC QLQ-HCC18

The EORTC QLQ-HCC18 is a disease-specific measure designed for use along with the EORTC QLQ-C30 in patients with HCC (Blazeby et al. 2004; Chie et al. 2012).
It contains 6 multi-item symptom scales (fatigue, body image, jaundice, nutrition, fevers, and pain), and 2 single-item scales (abdominal swelling and sexual interest) for a total of 18 questions with a recall period the past week. The EORTC QLQ-HCC18 module takes approximately 5 minutes to complete. All item responses are scored according to the EORTC guidelines for scoring and the supplementary manuscript on the QLQ-HCC18 module (Fayers et al. 2001; Chie et al. 2012).

4.5.8.3 EQ-5D-5L

The EQ-5D-5L is a validated self-reported health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013; see Appendix 7). There are 2 components to the EQ-5D-5L: a 5-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale (VAS) that measures health state. Published weighting systems allow for creation of a single composite score of a patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete.
The EQ-5D-5L will be included to derive utility to inform pharmacoeconomic models.

4.5.9 Tumor Samples at Screening

If available, archival tissue samples will be obtained at baseline for exploratory research on biomarkers.

Although any available tumor tissue sample can be submitted, sites are strongly encouraged to submit a representative FFPE tumor specimen in a paraffin block (preferred) or approximately 10−15 slides containing unstained, freshly cut, serial sections along with an associated pathology report. Samples collected via resection, core-needle biopsy, or excisional, incisional, punch, or forceps biopsy are preferred. However, all specimen types (e.g., fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples) are acceptable.

Exploratory biomarker research may include, but not be limited to, analysis of genes or gene signatures associated with tumor immunobiology, PD-L1, or cytokines associated with T-cell activation and may involve extraction of circulating tumor DNA, or RNA, analysis of somatic mutations by NGS.

If there is no available archival tissue sample at baseline, an optional screening biopsy may be performed. The Informed Consent Form will contain a separate section that addresses this optional screening biopsy. 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.

See Section 4.5.6 for details on sample storage, use of samples after patient withdrawal, and confidentiality standards for data.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

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

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

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology

- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (see Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

In addition to the RBR plasma sample collected during treatment, the following samples will also be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to atezolizumab and bevacizumab combination or HCC:

- Serum and plasma samples collected at Day 1 of Cycles 1, 2, and 4 and at time of radiographic progression
- Archival tumor tissue samples (e.g., from an earlier biopsy) collected at screening
- Tumor tissue samples collected on treatment at the investigator's discretion during the study
- Tumor tissue samples from biopsies collected after disease progression at the investigator's discretion during the study
- Leftover serum, plasma, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy, EGD, colonoscopy) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole-genome sequencing (WGS), whole-exome sequencing (WES), NGS, or other genomic analysis methods.

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

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

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

4.5.10.4 Confidentiality

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

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

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

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

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

4.5.10.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. A patient's withdrawal from Study YO40245 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study YO40245.

If a patient wishes to withdraw consent to the testing of his or her specimens after closure of the site, the investigator must inform the Sponsor by e-mailing the study number and patient number to the following e-mail address:

global_rcr-withdrawal@roche.com

4.5.10.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy

- 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) (see Section 3.1 for details)

Arm A patients: If one component of study treatment is discontinued permanently 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 and after discussion with the Medical Monitor if agreed upon by the investigator and patient.

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 $\leq$30 days after the last 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 and PRO assessments as outlined in the schedule of activities (see Appendix 1).

After treatment discontinuation, information on survival status 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).

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

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

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. 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.

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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, close monitoring of patients during the study, and regular monitoring by the iDMC (see Section 3.1.2). Administration of atezolizumab and bevacizumab 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 anticipated adverse events, including criteria for treatment interruption or discontinuation and dosage modification (sorafenib only), are provided in Appendix 11 and Appendix 12. See Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

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

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

5.1.1 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, meningoencephalitis, nephritis, myocarditis, myositis*, and severe cutaneous adverse reactions*. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab). See Appendix 12 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, VTE, and proteinuria.

Refer to Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for bevacizumab.

5.1.3 Risks Associated with Sorafenib

The most common side effects reported in patients receiving sorafenib include diarrhea, nausea, weight loss, hand-foot skin reaction, alopecia, anorexia, and voice changes. The most common Grade 3 or higher adverse reactions include diarrhea, hand-foot skin reaction, hypertension, abdominal pain, cardiac ischemia and/or infarction, hemorrhage, hypertension, hand-foot skin reactions and rash, and GI perforation.

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

5.1.4 Risks Associated with Combination Use of Atezolizumab and Bevacizumab

The risk of overlapping toxicities between atezolizumab and bevacizumab is anticipated to be minimal. 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 not be unambiguous 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.

Toxicities should initially be managed according to the recommendations in Appendix 11 with dose holds and modifications (if applicable) applied to the component of the study treatment judged to be the primary cause. If individual component causality for the toxicity cannot be adequately determined, then the most conservative management recommendation should be applied (in addition to Appendix 11, refer to adverse event management guidelines in Appendix 12 and in the most recent version of the Atezolizumab and Bevacizumab Investigator's Brochures).

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 elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, CRS, influenza--like illness, and systemic inflammatory response syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Grade ≥ 3 hypertension
- Grade ≥ 3 proteinuria

- Any grade GI perforation, abscesses, or GI fistulae
- Grade ≥2 non-GI fistula or abscess
- Tracheoesophageal fistula
- 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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse 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, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: 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 7):

- 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 7 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

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

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

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 1 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 3 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 ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). The patient population for this study consists of patients with decreased hepatic function who may exhibit abnormal liver function test results, some of which may meet Hy's law criteria prior to enrollment in the trial. The following modified Hy's law criteria are for the purpose of determining what may constitute a drug-induced liver injury for this trial population and define those cases which require expedited reporting to the health authorities in relation to Hy's law. Investigators must report as an adverse event the occurrence of either of the following:

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

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

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of HCC 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). An iDMC will monitor the frequency of deaths from all causes.

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Hepatocellular Carcinoma

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

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

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

  The patient has not experienced an adverse event.
- Hospitalization due solely to progression of the underlying cancer

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

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

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

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

No safety data related to overdosing of atezolizumab or bevacizumab are available. The highest dose of sorafenib studied was 800 mg BID, at this dose, adverse events observed were primarily diarrhea and dermatologic. No information is available on adverse events associated with an overdose of sorafenib in nonclinical studies.

5.3.5.13 Patient-Reported Outcomes Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

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

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

5.4.1 Emergency Medical Contacts

Global Medical Monitor Contact Information

Medical Monitor: [redacted] M.D. (Primary)

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Back-up Medical Monitor: [redacted], *Ph.D. (Primary)*

Mobile Telephone No.: [redacted]

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

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

5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting 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 e-mailing the form using the fax number or e-mail address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting 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 e-mailing the form using the fax number or e-mail 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 $>$ 90 days after the last dose of study treatment 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 to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab or 6 months after the last dose of bevacizumab, or within 6 months after the last dose of sorafenib. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

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 last dose of bevacizumab or within 3 months after the last dose of sorafenib. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

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, new systemic anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it is determined that the study treatment or participation is not the cause of the adverse event. 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, e-mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 90 days after the last dose of study treatment or until

initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and e-mailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or e-mail 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 with use of the following reference documents:

- Atezolizumab Investigator's Brochure
- Bevacizumab Investigator's Brochure
- Summary of Product Characteristics for sorafenib

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

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The statistical considerations and analysis plan are summarized below. Further details on the statistical considerations and analysis plan will be provided in the Statistical Analysis Plan (SAP) as part of the Data Analysis Plan.

The global population will include all patients enrolled during the global enrollment phase (including patients enrolled in China during that phase), and the China subpopulation will include all patients enrolled in China (i.e., during both the global enrollment phase and the extended China enrollment phase). Separate analyses will be performed for the global population (see Sections 6.1–6.9) and the China subpopulation (see Section 6.11). Any deviations to this will be noted.

The analyses of PFS, time to progression (TTP), and OS will be performed on the basis of all randomized patients (the ITT population), with patients grouped according to the treatment assigned at randomization, regardless of whether they receive any assigned study drug. Objective response rate will be analyzed on the basis of all randomized patients who have measurable disease at baseline. Duration of response will be assessed only in patients who have an objective response. Time to deterioration (TTD) analyses will be conducted in the ITT population. Change from baseline analysis of PROs will be performed with use of patients who have both a baseline assessment and at least 1 post-baseline assessment, with patients grouped according to the treatment assigned at randomization.

Safety analyses will be performed on the basis of all randomized patients who received any amount of study drug (the safety population), with patients grouped according to the treatment the patient actually received.

6.1 DETERMINATION OF SAMPLE SIZE

A total of approximately 480 patients will be randomized in the global enrollment phase of this study, with use of a 2:1 randomization ratio to allocate patients to either the atezolizumab and bevacizumab arm (Arm A) or the sorafenib arm (Arm B). The final OS analysis will be conducted at approximately 33 months after the first patient is randomized (first patient in [FPI]). *The final OS analysis will be descriptive and considered as optional if statistical significance is achieved at one of the pre-planned interim analyses of OS.*

The co-primary efficacy endpoints for this study are as follows:

- Overall survival, defined as the time from randomization to death from any cause
- Independent Review Facility-assessed PFS, defined as the time from randomization to the occurrence of disease progression per RECIST v1.1 or death from any cause, whichever occurs first

The overall type I error rate for this study will be controlled at a 2-sided significance level of 0.05 by a graphical approach (i.e., α-splitting and recycling; Bretz et al. 2009; Burman et al. 2009). The overall 2-sided significance level of 0.05 will be split into a 2-sided significance level of 0.048 for the testing of OS and a 2-sided significance level of 0.002 for the testing of PFS as a first step. For further details, see Section 6.4.1.

The sample size of the study was determined based on the number of deaths required to demonstrate efficacy in terms of OS. To detect an improvement in OS using a log-rank test at a 2-sided significance level of 0.048, approximately 312 deaths will be required to achieve 80% overall power assuming a target HR of 0.71 (median OS improvement vs. control is 4.9 months). The minimum detectable difference (MDD) of OS is an HR of 0.783 (median OS improvement is 3.3 months). *Three-hundred and twelve deaths are* expected to occur approximately 33 months after FPI.

Overall Survival

The calculation of sample size and estimates of the OS analysis timelines are based on the following assumptions:

- Patients will be randomized to the atezolizumab and bevacizumab and sorafenib arms in a 2:1 ratio
- Overall survival follows a 1-piece exponential distribution
- The median OS in the control arm is 12 months
- The stopping boundaries of the interim and final analyses of OS use the O'Brien-Fleming boundaries approximated with use of the Lan-DeMets method (DeMets and Lan 1994)
- The dropout rate is 5% for the atezolizumab and bevacizumab arm and 10% for the sorafenib arm over 12 months for OS
- The recruitment of approximately 480 patients will take place over approximately 10 months

Independent Review Facility-Assessed Progression-Free Survival

To detect an improvement in IRF-assessed PFS using a log-rank test at a 2-sided significance level of 0.002, approximately 308 events will be accrued for the primary PFS analysis, which will provide approximately 97% power with a target HR of 0.55 (median PFS improvement of 3.3 months from 4–7.3 months). This is to ensure a minimal follow-up of approximately 6 months for all patients (i.e., to have a clinical cutoff date at approximately 6 months after the last patient is randomized to the study).
The MDD is a PFS HR of 0.688 (median PFS improvement of 1.8 months from 4–5.8 months). The clinical cutoff date for this primary PFS analysis is expected to occur approximately 16 months after the first patient was enrolled in the study.
The following assumptions were made for PFS based on the ITT population:

- Patients will be randomized to the atezolizumab and bevacizumab and sorafenib arms in a 2:1 ratio
- Progression-free survival follows a 1-piece exponential distribution
- The median duration of PFS in the control arm is 4 months
- The dropout rate is 5% for the atezolizumab and bevacizumab arm and 10% for the sorafenib arm over 12 months for PFS
- The recruitment of 480 patients will take place over 10 months

See Section 6.11 for sample size considerations for the China subpopulation.

6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment, study drug administration, reasons for discontinuation from the study drug, and reasons for study termination will be summarized by treatment arm for the ITT population. Major protocol deviations, including major deviations of inclusion/exclusion criteria, will be reported and summarized by treatment arm for the ITT population.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic characteristics such as age, sex, race/ethnicity, and baseline disease characteristics (e.g., ECOG Performance Status) will be summarized by treatment arm for the ITT population. Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

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

6.4 EFFICACY ANALYSES

Hypotheses will be formally tested on co-primary and key secondary endpoints (to be identified in the SAP) and details on the α-recycling method, including α-recycling sequence, will be specified in the SAP. Implementation of the statistical testing procedure will strongly control the overall type I error at 5% (2-sided). Additional details will be provided in the SAP.

6.4.1 Co-Primary Efficacy Endpoints

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab in combination with bevacizumab compared with sorafenib on the basis of the co-primary efficacy endpoints of OS and IRF-assessed PFS according to RECIST v1.1.

Overall survival and PFS will be tested initially in parallel with the overall type I error controlled at a 2-sided significance level of 0.05, where OS will be tested at a 2-sided significance level of 0.048 and PFS will be tested at a 2-sided significance level of 0.002.

6.4.1.1 Overall Survival

Overall survival is defined as the time from the date of randomization to the date of death from any cause. Patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Patients with no post-baseline information will be censored at the date of randomization.

The null and alternative hypotheses regarding OS can be phrased in terms of the survival functions $S_A(t)$ and $S_B(t)$ for Arm A (atezolizumab and bevacizumab) and Arm B (sorafenib), respectively:

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

The 2-sided log-rank test, stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL), will be used as the primary analysis to compare OS between the two treatment arms. The results from the unstratified log-rank test will also be provided as a sensitivity analysis to check the robustness of the results of the stratified log-rank test.

The Kaplan-Meier method will be used to estimate median OS for each treatment arm. Brookmeyer-Crowley methodology will be used to calculate the 95% CI for the median OS for each treatment arm. Stratified Cox proportional-hazards models will be used to estimate the HR and its 95% CIs. The stratification factors will be the same as those used for the primary stratified log-rank test. The unstratified HR will also be provided.

A group sequential design will be used for testing the co-primary efficacy endpoint OS to account for the conduct of 2 interim analyses. An α-spending with use of the Lan-De Mets method approximating O'Brien-Fleming boundaries (DeMets and Lan 1994) will be utilized to control the overall type I error rate of 0.048 for the OS co-primary efficacy endpoint. The first interim OS analysis will be conducted at time of the co-primary analysis of IRF-assessed PFS (see Section 6.4.1.2). The second interim OS analysis *is planned to* be conducted when approximately 243 OS events have been observed. *The final analysis of OS is expected to occur after approximately 312 deaths have occurred. If statistical significance is reached at one of the pre-planned interim analyses of OS, then that interim OS analysis will be regarded as the definitive analysis of OS and subsequent analyses of OS, including the final OS analysis, will be descriptive and considered as optional.*

In order to assess the homogeneity of the treatment effect with respect to the co-primary efficacy endpoint of OS across important subgroups, Forest plots (including the estimated HRs) will be provided. A full list of all pre-specified exploratory subgroup analyses for OS for this study will be provided in the SAP.

Further methodological details will be provided in the SAP.

6.4.1.2 Independent Review Facility-Assessed Progression-Free Survival

Independent Review Facility-assessed PFS is defined as the time from randomization to the occurrence of disease progression as determined by the IRF 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 on or prior to the clinical cutoff date. Patients with no post-baseline tumor assessment will be censored at the date of randomization.

Methods for PFS analyses are similar to those described for the OS endpoint.

6.4.2 Secondary Efficacy Endpoints

Investigator-Assessed Objective Response Rate

An objective response, defined as a CR or PR, will be determined by the investigator according to RECIST v1.1. Patients not meeting these criteria, including patients without any post-baseline tumor assessment, will be considered non-responders. A confirmed objective response is a response (CR or PR) seen at 2 consecutive tumor assessments at least 28 days apart.

Investigator-assessed ORR is defined as the percentage of patients who have an objective response per the investigator according to RECIST v1.1. The analysis population for ORR will be all randomized patients with measurable disease at baseline per the investigator according to RECIST v1.1.

The 2-sided Cochran-Mantel-Haenszel test, stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL), will be used to compare ORR between the two treatment arms.

Objective response rate will be estimated for each treatment arm. The respective 95% CIs will be calculated with use of the Clopper-Pearson method (Clopper and Pearson 1934). Finally, the difference in ORR between treatment arms will be computed with the associated 95% CI by normal approximation.

Investigator-Assessed Progression-Free Survival

Progression-free survival analyses will be performed separately based on investigator-assessed tumor response according to RECIST v1.1. The analysis methods are similar to those described for OS.

Investigator-Assessed Time to Progression

Time to progression is defined as the time from the date of randomization to the date of the first documented tumor progression. Patients without tumor progression, including death, will be censored at the last tumor assessment date. Patients who have no post-baseline tumor assessment will be censored at the date of randomization.

Investigator-assessed TTP analyses will be performed based on investigator-assessed tumor response according to RECIST v1.1. The analysis methods are similar to those described for OS.

Independent Review Facility-Assessed Objective Response

An objective response per IRF is defined as a CR or PR as determined by an IRF, according to RECIST v1.1 and separately according to HCC mRECIST. Patients not meeting these criteria, including patients without any post-baseline tumor assessment, will be considered non-responders. A confirmed objective response is a response (CR or PR) seen at 2 consecutive tumor assessments at least 28 days apart).

Objective response rate is defined as the proportion of patients who had an objective response. The analysis population for ORR per IRF will be all randomized patients with measurable disease at baseline per IRF according to RECIST v1.1 and HCC mRECIST. The analysis methods are similar to those described for the investigator-assessed ORR.

Duration of Response

Duration of response will be assessed in patients who had an objective response. Duration of response is defined as the time interval from the date of the first occurrence of a documented objective response (CR or PR, whichever status is recorded first) until the first date that disease progression or death is documented, whichever occurs first. Patients who have not progressed and who have not died at the time of the clinical cutoff date will be censored at the time of the last tumor assessment on or prior to the clinical cutoff date.

Duration of response analyses will be performed separately based on IRF- and investigator-assessed tumor response according to RECIST v1.1, and IRF-assessed tumor response according to HCC mRECIST. The analysis methods are similar to those described for OS.

Independent Review Facility-Assessed Time to Progression

Independent Review Facility-assessed TTP is defined the same as investigator-assessment TTP, except that analyses will be performed based on IRF-assessed tumor response according to RECIST v1.1. and HCC mRECIST. The analysis methods are similar to those described for OS.

Independent Review Facility-Assessed Progression-Free Survival

Progression-free survival analyses will be performed separately based on IRF-assessed tumor response according to HCC mRECIST. The analysis methods are similar to those described for OS.

Progression-Free Survival and Overall Survival by Baseline α-Fetoprotein

Investigator- and IRF-assessed PFS according to RECIST v1.1 and OS will be analyzed by subgroups of baseline serum AFP level ($<$400 ng/mL vs. $\geq$400 ng/mL). The analysis methods are similar to those described for the co-primary endpoints. Geographic region (Asia excluding Japan vs. rest of world) and macrovascular invasion and/or extrahepatic spread (presence vs. absence) will be used as stratification factors for stratified analyses.

Time to Deterioration

The primary analysis population for evaluation of TTD will be the ITT population.

Time to deterioration is defined as the time from randomization to first deterioration (decrease from baseline of ≥ 10 points) in the patient-reported GHS/QoL, physical function, or role function scales of the EORTC QLQ-C30, maintained for 2 consecutive assessments, or 1 assessment followed by death from any cause within 3 weeks. The Kaplan-Meier analysis methods for the analysis of TTD are similar to those described for PFS. Patients who do not have an observed deterioration at the time of discontinuation from study treatment or at the clinical cutoff date will be censored at the last available assessment date prior to or at the time of discontinuation from study treatment or clinical cutoff date, whichever is earlier. Patients without a post-baseline assessment will be censored at randomization date.

6.4.3 Exploratory Efficacy Endpoints

Objective response rate, PFS, TTP, and DOR will be determined by the investigator according to imRECIST, using the same definitions as for the primary/secondary endpoints determined by RECIST v1.1 and analyzed using the same analysis methods.

Independent Review Facility-assessed PFS according to RECIST v 1.1 and OS based on the following biomarkers in tumor tissue will be analyzed using similar statistical methods:

- Baseline expression of T effector gene signature in tumor tissue
- Baseline PD-L1 protein expression in tumor tissue
- CD8 protein expression level or CD8+ T-cell localization
- Immunohistochemistry or genes/gene signatures (by gene expression profiling) related to tumor microenvironments
- T-cell receptor sequence profile in tumor-associated T cells

Patient-Reported Outcomes Analyses

Completion rates and reasons for missing data will be summarized for each of the EORTC QLQ-C30 and EORTC QLQ-HCC18 measures at each cycle by treatment arm.

In addition, the following analyses will be conducted by treatment arm.

Exploratory TTD analyses will be conducted utilizing Kaplan-Meier methods, with TTD defined as the time from randomization to first deterioration (increase from baseline of ≥ 10 points), maintained for 2 consecutive timepoints, or 1 timepoint followed by death from any cause within 3 weeks for select subscales of the EORTC QLQ-C30 (appetite loss, diarrhea, fatigue, pain) and the EORTC QLQ-HCC18 (jaundice, fatigue, pain). Patients who do not have an observed deterioration at the time of discontinuation from study treatment or at the clinical data cutoff date will be censored at the last available assessment date prior to or at the time of discontinuation from study treatment

or clinical cutoff date, whichever is earlier. Patients without a post-baseline assessment will be censored at the randomization date.

Kaplan-Meier analysis methods similar to those described for OS will be used to assess long-term impact on GHS/HRQoL, physical function, and role function. For this exploratory analysis, TTD will be defined as the time from randomization to first deterioration (decrease from baseline of $\geq$10 points), maintained for 2 consecutive timepoints, or 1 timepoint followed by death from any cause within 3 weeks. Patients who do not have an observed deterioration at the time of the clinical data cutoff will be censored at the last available assessment date. Patients without a post-baseline assessment will be censored at randomization.

Visit mean summary and change from baseline analyses will be performed for all subscales of the EORTC QLQ-C30 and EORTC QLQ-HCC18. Summary statistics (number of patients, mean, standard deviation, median, minimum, maximum, 95% CI) of score(s) and score change(s) from baseline to each timepoint will be determined. Previously published minimally important differences (MID; e.g., 10-point MID) will be used to identify meaningful change from baseline within each treatment group on all scales of the EORTC QLQ-C30 and EORTC QLQ-HCC18 (Osoba et al. 1998).

Proportion of patients with a clinically meaningful change (improved, deteriorated, remained stable) in select scales of the QLQ-C30 (GHS/QoL, physical function, role function, appetite loss, diarrhea, fatigue, pain) and QLQ-HCC18 (jaundice, fatigue, pain) will be summarized by treatment arm.

Proportion of responses for the itching item of the QLQ-HCC18 jaundice subscale, the abdominal pain item of the QLQ-HCC18 pain subscale, and each timepoint while patients are on treatment will be summarized.

In the event of incomplete data for any questionnaire subscales, if more than 50% of the constituent items are completed, a prorated score will be computed, consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing (Fayers et al. 2001; Chie et al. 2012).

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least 1 full or partial dose of study treatment, with patients grouped according to treatment received.

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 v4.0.

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

The following events occurring during or after the first dose of study treatment will be summarized by treatment arm and NCI CTCAE grade:

- All adverse events
- All adverse leading to death
- All serious adverse events
- All severe adverse events (Grade ≥ 3)
- All adverse event of special interest
- All adverse events leading to study drug discontinuation or interruption

Multiple occurrences of the same event will be counted once at the maximum severity.

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

Descriptive statistics will be used to summarize changes in vital signs by treatment arm.

Deaths with causes of death reported during the study will be summarized by treatment arm.

Additional analyses may be performed as indicated.

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

The immunogenicity analysis population will consist of all patients with at least 1 ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized for ADA-evaluable patients. When determining post-baseline incidence, patients are considered to be ADA-positive if they are ADA-negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA-positive at baseline and the titer of 1 or more post-baseline samples is at least 0.60 titer units 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 post-baseline samples are negative, or if they are ADA-positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60 titer units 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 EXPLORATORY BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in an effort to understand the association of tissue or blood-based biomarkers (see Table 1) with response to atezolizumab in combination with bevacizumab versus sorafenib, or increase the understanding of HCC disease evolution under atezolizumab and bevacizumab treatment. Progression-free survival and OS will be analyzed using the methods outlined in Section 6.4. This may include appropriate multivariate analyses. Further details will be provided in the SAP.

6.9 EXPLORATORY HEALTH STATUS ANALYSIS

Health utility data from the EQ-5D-5L (see Appendix 7) will be evaluated in pharmacoeconomic models. The results from the health economic data analyses will be reported separately from the CSR.

6.10 INTERIM ANALYSIS

No interim analysis is planned for PFS in this study.

Two interim analyses of OS *are planned to* be performed. The first interim analysis will be performed at the time of the primary PFS analysis, estimated to occur at approximately 16 months after FPI. It is anticipated that at this time approximately 172 deaths will have been observed. The respective MDD OS HR is 0.633 (median OS improvement is 6.9 months). The second OS interim analysis is planned to be

conducted when approximately 243 deaths are accumulated, estimated to occur at approximately 24 months after FPI. The respective MDD OS HR is 0.728 (median OS improvement is 4.6 months).

To control the 2-sided significance level at 0.048 for the interim and final OS analyses, the Lan-DeMets method will be used to approximate the O'Brien-Fleming boundaries.

The planned interim analyses for OS will be conducted by the Sponsor.

Further details are given in Section 6.4.1.1.

Table 8 Analysis Timing and Stopping Boundaries for Overall Survival

Analysis Timing	Planned Information Fraction	Required Events/ Analysis Timing (estimated)	Stopping Boundary (2-Sided p-value)	
			α can be recycled to OS (i.e., OS α=0.05)	**α cannot be recycled to OS (i.e., OS α=0.048)**
1st OS interim analysis	55%	172/16 months	MDD.HR ≤ 0.636 (p-value ≤ 0.005)	MDD.HR ≤ 0.633 (p-value ≤ 0.005)
2nd OS interim analysis	78%	243/24 months	MDD.HR ≤ 0.73 (p-value ≤ 0.021)	MDD.HR ≤ 0.728 (p-value ≤ 0.02)
OS final analysis	100%	312/33 months	MDD.HR ≤ 0.784 (p-value ≤ 0.043)	MDD.HR ≤ 0.783 (p-value ≤ 0.041)

HR = hazard ratio; MDD = minimum detectable difference; OS = overall survival; PFS = progression-free survival.

Analysis timing shown in the table is projected based on protocol assumptions. Actual timing depends on the exact time that the required events have accrued.

The 1st OS interim analysis will be conducted when approximately 308 PFS events have happened. *If statistical significance is reached at one of the pre-planned interim analyses of OS, then that interim OS analysis will be regarded as the definitive analysis of OS and subsequent analyses of OS, including the final OS analysis, will be descriptive and considered as optional.*

6.11 CHINA SUBPOPULATION ANALYSES

The Sponsor is targeting a total enrollment of approximately 135 patients from mainland China. The sample size of the China subpopulation was determined by characterizing the efficacy and safety profile of atezolizumab in combination with bevacizumab. After approximately 480 patients have been randomized into the global portion of the study, in the event that fewer than 135 patients from mainland China are enrolled, additional patients in China may be subsequently randomized into the two treatment

arms in a 2:1 ratio in an extended China enrollment phase to ensure a total of approximately 135 patients from mainland China for inclusion in the China subpopulation.

The primary efficacy objective of the China subpopulation analysis is to assess efficacy, as measured by the co-primary endpoints of PFS by an IRF-assessment per RECIST v1.1 and OS, of atezolizumab and bevacizumab compared with sorafenib in the Chinese patients. The China subpopulation is not powered to demonstrate statistical significance in terms of efficacy, and no formal hypothesis testing will be performed.

The China subpopulation analyses will be conducted when sufficient PFS and/or OS events have occurred to demonstrate at least 80% probability of maintaining 50% of risk reduction compared with that estimated from the global population. The exact timing of analyses will be specified in the SAP.

The analysis methods for China subpopulation will be the same as for the global population unless elsewhere noted. The results of the China subpopulation analyses will be summarized in a separate report from the CSR for the global population.
The statistical details for such analyses in the China subpopulation will be documented in the SAP.

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.

Patient-reported outcomes data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

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 on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, paper PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, 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.

Roche 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 U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) 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 a Child's Informed 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.

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

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

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval,

and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

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

Approximately 120 sites globally will participate to randomize approximately 480 patients. Screening and enrollment will occur through an IxRS.

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

An IDMC will be employed to monitor and evaluate patient safety throughout the study. Tumor response and progression will be evaluated by the investigator as well as an IRF.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, 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 more details), and redacted CSRs and other summary reports will be made available upon request.
For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1 Schedule of Activities

Assessment Window (Days) [a]	Screening [b]		Treatment Phase (Q3W)	Treatment Discontinuation [c]	Survival Follow-Up
	–28 to –1	–7 to –1	Day 1 of Each Cycle [c]	≤ 30 Days after Last Dose	
Signed Informed Consent Form(s) [b]	x				
Review of eligibility criteria	x				
Medical, surgical, and cancer histories, including demographic information [d]	x				
Complete physical examination [e]	x				
Limited physical examination [f]			x [g]	x	
ECOG Performance Status		x	x [g]	x	
Patient-reported outcomes [h]			x [g]	x	x [h]
Tumor assessment [i]	x		See footnote [i]	x	x
Vital signs [j]	x		x	x	
Weight	x		x [k]	x	
Height	x				
12-lead ECG [l]	x		Perform as clinically indicated		
EGD [m]	x				
Hematology [n, z]		x	x [g]	x	
Serum chemistry [o, z]		x	x [g]	x	
HIV, HBV, HCV serology [p]	x				
Quantitative HBsAg, HBV DNA, HCV RNA [q]	x		x	x	
α-fetoprotein	x		x	x	
Coagulation panel (aPTT, INR) [z]		x	x [g]	x	
Urinalysis [r, z]		x	x [g]	x	

Appendix 1: Schedule of Activities (cont.)

Assessment Window (Days) [a]	Screening [b]		Treatment Phase (Q3W)	Treatment Discontinuation [c]	Survival Follow-Up
	–28 to –1	–7 to –1	Day 1 of Each Cycle [c]	≤ 30 Days after Last Dose	
TSH, free T3, free T4	x		Cycles 5, 9, 13, etc. (every 4 cycles)	x	
Pregnancy test		x [s]	x [t]	x	
Serum PK sample			See Appendix 2		
Serum ADA sample			See Appendix 2		
Pharmacodynamic samples for biomarkers			See Appendix 2	x	
Plasma sample for RBR (optional)			Any time (at investigator's discretion)		
Archival tumor tissue sample (or optional fresh biopsy if archival tissue is not available) for biomarkers	x				
Concomitant medications [u]		x	x	x	
Adverse events [v]	x		x	x	
Study treatment infusion [w]			x		
Sorafenib dispensing [x]			x		
Survival and anti-cancer therapy follow-up [y]					x

ADA = anti-drug antibody; CT = computed tomography; EGD = esophagogastroduodenscopy; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5-Dimension Questionnaire, 5-level version; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; imRECIST = immune-modified RECIST; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic; PRO = patient-reported outcome; Q3W = every 3 weeks; QLQ-C30 = quality-of-life questionnaire for cancer; QLQ-HCC18 = HCC disease-specific module; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted. Each cycle is 21 days in length.

[a] The first dosing date (Cycle 1, Day 1) should occur within 3 business days from randomization, with the exception of the emergence of an adverse event for which dosing may be postponed. All visits and infusions thereafter may be administered with a window of ± 3 days.

[b] Written informed consent can be obtained up to 30 days prior to study entry and is required before performing any study-specific tests or procedures. Results of standard of care tests or examinations performed prior to obtaining informed consent and per protocol relevant window may be used for screening assessments rather than repeating such tests. Screening local laboratory assessments obtained ≤ 96 hours prior to the initiation of study treatment do not have to be repeated for Cycle 1. Test results should be reviewed prior to administration of study treatment.

[c] Patients will be asked to return to the clinic 30 days after the last dose of study treatment for an end-of-treatment visit. After this visit, serious adverse events and protocol defined adverse events of special interest, regardless of attribution, will be recorded until 90 days after the last dose of study treatment or until initiation of another systemic anti-cancer therapy, whichever occurs first. Ongoing adverse events thought to be related to study treatment will be followed until the event has resolved to baseline grade or better, the event is assessed by the investigator as stable, new anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it is determined that the study treatment or participation is not the cause of the adverse event. Scans performed within 6 weeks prior to the treatment discontinuation visit do not need to be repeated.

[d] Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Demographic information includes age and self-reported race/ethnicity. Reproductive status and smoking history should also be captured.

[e] A complete physical examination at screening should include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Changes in abnormalities noted at baseline should be recorded at the end of the visit. New or worsened abnormalities should be recorded as adverse events if appropriate.

[f] A limited physical examination will be performed at other visits to assess changes from baseline abnormalities and any new abnormalities and to evaluate patient-reported symptoms. New or worsened abnormalities should be recorded as adverse events if appropriate.

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

[h] The EORTC QLQ-C30, EORTC QLQ-HCC18, and EQ-5D-5L questionnaires will be completed by all patients on paper starting on Day 1 of Cycle 1 and Day 1 of every cycle thereafter. All PRO questionnaires scheduled for administration during a clinic visit are required to be completed by the patient at the investigational site at the start of the clinic visit before discussion of the patient's health state, lab results or health record, before administration of study treatment, and/or prior to any other study assessment(s). This is to avoid any potential bias to patients' responses to ensure that the validity of the instrument is not compromised and that data quality meets regulatory requirements. Interview assessment by a member of the clinic staff will be allowed if the patient is not able to complete the measure on their own. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. During survival follow-up, all PRO questionnaires will be completed every 3 months (for 1 year), unless the patient withdraws consent or the Sponsor terminates the study. PRO questionnaires during the survival follow-up period may be completed at the investigational site should the patient come in for a clinic visit or be administered via interview in telephone calls.

[i] All measurable and evaluable lesions should be assessed and documented at the screening visit. Radiologic imaging performed during the screening period should consist of 1) CT and/or MRI of the chest/abdomen/pelvis and brain, 2) bone scan or PET scan as clinically indicated, and 3) any other imaging studies (CT scan of the neck, plain films, etc.) as clinically indicated by the treating physician. The same radiographic procedures and technique must be used throughout the study for each patient (e.g., if the patient had CT chest/abdomen/pelvis performed during screening, then she should subsequently undergo CT performed with use of the same radiologic protocol throughout the remainder of the study). Results must be reviewed by the investigator before dosing at the next cycle. Tumor assessments will be performed at baseline, every 6 weeks (± 1 week) for the first 54 weeks following the initiation of study treatment, and every 9 weeks (± 1 week) thereafter, with additional

scans as clinically indicated. All known sites of disease documented at screening should be re-assessed at each subsequent tumor evaluation. Tumor response will be evaluated by the investigator with use of RECIST version 1.1 and imRECIST. In the absence of disease progression, tumor assessments should continue regardless of whether patients discontinue study treatment or start new anti-cancer treatment, unless the patient dies, withdraws consent, or the study is terminated by the Sponsor, whichever occurs first.

[j] Vital signs include heart rate, respiratory rate, blood pressure, and temperature. For patients randomized to Arm A, on days of study treatment administration (atezolizumab and bevacizumab), the patient's vital signs should be determined up to 60 minutes before all infusions. Vital signs will be measured at the end of bevacizumab infusion and 2 (± 1) hours after end of the infusion and will also be collected during and after every infusion of atezolizumab if clinically indicated.

[k] The dose of bevacizumab 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. If re-baseline is needed the latest baseline weight should always be used to calculate percent change in weight for all subsequent doses.

[l] Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[m] All patients must undergo an EGD and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment.

[n] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated.

[o] Serum chemistry includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, and LDH.

[p] All patients will be tested for HIV locally prior to the inclusion into the study and if not in contradiction with local legislation; HIV-positive patients will be excluded from the clinical study. HBsAg, HBcAb, and HBsAb should be collected during screening and tested locally. HBV DNA must be collected prior to Cycle 1, Day 1 in patients who have negative serology for HBsAg and positive serology for anti-HBcAb.

[q] Only if patient tests positive for HBsAg, HBcAb, quantitative HBsAg and HBV DNA will be tested during screening; Cycle 5, Day 1; Cycle 9, Day 1; and at treatment discontinuation. Quantitative HBsAg will be tested by central laboratory. If a patient tests positive for HCV antibody at screening, quantitative HCV RNA must be tested locally at screening, Cycle 5 Day 1, Cycle 9 Day 1, and at treatment discontinuation.

[r] Urine dipstick includes specific gravity, pH, glucose, protein, ketones, and blood and should be repeated before every cycle during treatment. Urine dipstick for proteinuria must be < 2+ within 7 days prior to initiation of study treatment. Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate < 1 g of protein in 24 hours.

[s] Serum pregnancy test within 14 days before Cycle 1, Day 1.

[t] Urine pregnancy test; if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[u] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to initiation of study treatment should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

[v] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new anti-cancer therapy, whichever occurs first. After this period, investigators should report any serious adverse events and adverse events of special interest that are believed to be related to

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

[w] The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well-tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. The initial dose of bevacizumab will be delivered over 90 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 (± 10) minutes. If the 60-minute infusion is well-tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. For patients randomized to Arm A, atezolizumab will be administered first followed by bevacizumab, with a minimum of 5 minutes between dosing. In the absence of unacceptable toxicity, patients may continue study treatment until there is evidence of disease progression or lack of clinical benefit.

[x] Sorafenib is taken by mouth twice a day continuously.

[y] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 21 days) until death, loss to follow-up, or until study termination by the Sponsor. All patients will be followed for survival and new anti-cancer therapy (including targeted therapy and immunotherapy) information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

[z] Local laboratory assessments from each cycle must be reviewed prior to study treatment administration for each cycle.

Appendix 2 Schedule of Biomarker, Pharmacokinetic, and Immunogenicity Samples

Visit	Timepoint	Sample Type
Day 1 of Cycle 1	Prior to any drug administration	• Atezolizumab PK (serum) [a] • Atezolizumab ADA (serum) [a] • Biomarker (plasma, serum) [b]
	30 min after end of atezolizumab infusion	• Atezolizumab PK (serum) [a]
Day 1 of Cycle 2	Prior to any drug administration	• Atezolizumab PK (serum) [a] • Atezolizumab ADA (serum) [a] • Biomarker (plasma, serum) [b]
Day 1 of Cycle 3, Cycle 8, Cycle 12, Cycle 16	Prior to any drug administration	• Atezolizumab PK (serum) [a] • Atezolizumab ADA (serum) [a]
Day 1 of Cycle 4	Prior to any drug administration	• Atezolizumab PK (serum) [a] • Atezolizumab ADA (serum) [a] • Biomarker (plasma, serum) [b]
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) [a] • Atezolizumab ADA (serum) [a] • Biomarker (plasma, serum)

ADA = anti-drug antibody; PK = pharmacokinetic.

[a] For Arm A only.

[b] Biomarker samples must be collected for both arms before dosing. For Arm B: If the patient takes the morning dose before coming to the visit, samples should be taken before the evening dose.

Appendix 3 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 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

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

Malignant Lymph Nodes

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

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

DEFINITION OF NON-MEASURABLE LESIONS

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

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

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) 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 locoregional 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 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 1 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 2 dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and

qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

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

CALCULATION OF SUM OF DIAMETERS

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

Measuring Lymph Nodes

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

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

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.

- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

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

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

  All lymph nodes must be non-pathological in size ($<$10 mm short axis).
- Non-CR/Non-PD: Persistence of 1 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 a tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing 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.

REFERENCES

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 4 Immune-Modified Response Evaluation Criteria in Solid Tumors (imRECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immune-modified response criteria have been developed to incorporate new lesions into the assessment of total tumor burden and allow radiographic progression to be confirmed at a subsequent assessment. Immune-modified Response Evaluation Criteria in Solid Tumors (imRECIST), as described within this appendix, were adapted from RECIST, Version 1.1 (v1.1; Eisenhauer et al. 2009), in the same manner that immune-related response criteria were adapted from World Health Organization criteria (Wolchok et al. 2009) and RECIST v1.0 (Nishino et al. 2014). When not otherwise specified, RECIST v1.1 conventions will apply. Differences between imRECIST and RECIST v1.1 are summarized in Table 1.

Table 1 Comparison of RECIST v1.1 and imRECIST

	RECIST v1.1	imRECIST
Measurable new lesions	Always represent progression	Incorporated into the total tumor burden [a] and followed
Non-measurable new lesions	Always represent progression	Do not represent progression, but preclude CR
Non-target lesions	Contribute to defining CR, PR, SD, and PD	Contribute to defining CR only
CR	Disappearance of all lesions	Disappearance of all lesions
PR	≥ 30% decrease in sum of diameters of target lesions, in the absence of CR, new lesions, and unequivocal progression in non-target lesions	≥ 30% decrease in tumor burden, [a] in the absence of CR
PD	≥ 20% increase in sum of diameters of target lesions, unequivocal progression in non-target lesions, and/or appearance of new lesions	≥ 20% increase in tumor burden [a]
SD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CR = complete response; imRECIST = immune-modified RECIST; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Tumor burden is the sum of diameters of target lesions and measurable new lesions.

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 1 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," "New Lesions," and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

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

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) 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 locoregional 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 $\geq$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 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 prior studies, if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, 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.

<u>ASSESSMENT OF TUMOR BURDEN</u>

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 1 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 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 2 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").

NEW LESIONS

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST v1.1 (e.g., non–lymph node lesions must be $\geq$10 mm on the longest diameter; new lymph nodes must be $\geq$15 mm on the short axis [see note below]). All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of 5 measurable new lesions total (and a maximum of 2 lesions per organ) can be included in the calculation of tumor burden that is performed as part of the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST v1.1 cannot be included in the calculation of tumor burden and thus will not affect overall tumor response evaluation. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint can be included in the tumor response evaluation from that point on, if the maximum number of measurable new lesions has not been reached.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is $\geq$15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is $\geq$10 mm and $<$15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is $<$10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is $\geq$15 mm.

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 as a measure of tumor burden. At each subsequent tumor assessment, 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 plus measurable new lesions (up to 5 new lesions, with a maximum of 2 new lesions per organ) that have emerged after baseline. Hence, each net percentage change in tumor burden per assessment accounts for the size and growth kinetics of both old lesions and new lesions as they appear.

Measuring Lymph Nodes

If at first appearance the short axis of a new lymph node lesion is $\geq$15 mm, it will be considered a measurable new lesion and may be included in the sum of the diameters. If the new lymph node lesion is included in the sum of diameters, it will continue to be

measured and included in the sum of diameters at subsequent timepoints, even if the short axis decreases to < 15 mm (or even < 10 mm). However, if it subsequently decreases to < 10 mm and all other lesions are no longer detectable or have also decreased to a short axis of < 10 mm (if lymph nodes), a response assessment of complete response (CR) may be assigned.

Lymph nodes 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 in the sum of diameters, the sum 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 and up to 5 measurable new lesions (lymph node and non–lymph node) should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being “too small to measure.” When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes 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 AND NON-MEASURABLE NEW LESIONS

Measurements are not required for non-target lesions or non-measurable new lesions. Non-target lesions should be noted at baseline, and non-measurable new lesions should be noted at the time of identification. At subsequent evaluations, non-target lesions and non-measurable new lesions will be categorized as "present" or "absent."

After baseline, changes in non-target lesions or non-measurable new lesions (or measurable new lesions in excess of 5 total or 2 per organ) will contribute only in the assessment of CR (i.e., a CR is attained only with the complete disappearance of all tumor lesions, including non-target lesions and non-measurable new lesions) and will not be used to assess progressive disease.

RESPONSE CRITERIA

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

- Complete response (CR): Disappearance of all lesions

  Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of 5 total or 2 per organ), 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 all target lesions plus measurable new lesions (up to a maximum of 5 total or 2 per organ), taking as reference the smallest sum of diameters in the study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.

  New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is factored into the sum of the diameters, which is used to determine the overall imRECIST tumor response.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 2 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 2 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions and Measurable New Lesions [a]	Non-Target Lesions and Non-Measurable New Lesions [b]	Overall Response
CR	Absent	CR
CR	Present or not all evaluated	PR
PR	Any	PR
SD	Any	SD
Not all evaluated	Any	NE
PD	Any	PD

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

[a] Up to a maximum of 5 measurable new lesions total (and a maximum of 2 lesions per organ) can be included in the calculation of tumor burden, in addition to the target lesions identified at baseline.

[b] Also includes measurable new lesions in excess of 5 total or 2 per organ.

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 or measurable new 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 having "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy.

The objective response status of such patients is to be determined by evaluation of target and non-target lesions, as well as new lesions, as shown in Table 2.

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Appendix 5 European Organisation for 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):

	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

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your 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 6 EORTC QLQ-HCC18 Module

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ENGLISH

EORTC QLQ – HCC18

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. Did you feel thirsty?	1	2	3	4
32. Have you had problems with your sense of taste?	1	2	3	4
33. Have you lost muscle from your arms or legs?	1	2	3	4
34. Have you had abdominal swelling?	1	2	3	4
35. Have you been concerned by the appearance of your abdomen?	1	2	3	4
36. Have you been concerned by your skin or eyes being yellow (jaundiced)?	1	2	3	4
37. Have you had itching?	1	2	3	4
38. Have you had pain in your shoulder?	1	2	3	4
39. Have you had abdominal pain?	1	2	3	4
40. Have you had fevers?	1	2	3	4
41. Have you had chills?	1	2	3	4
42. Have you worried about getting enough nourishment?	1	2	3	4
43. Have you felt full up too quickly after beginning to eat?	1	2	3	4
44. Have you worried about your weight being too low?	1	2	3	4
45. Have you been less active than you would like to be?	1	2	3	4
46. Have you found it difficult to finish things?	1	2	3	4
47. Have you needed to sleep during the day?	1	2	3	4
During the past four weeks:				
48. Has the disease or treatment had any effect on your sex life?	1	2	3	4

Appendix 7 EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L)

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

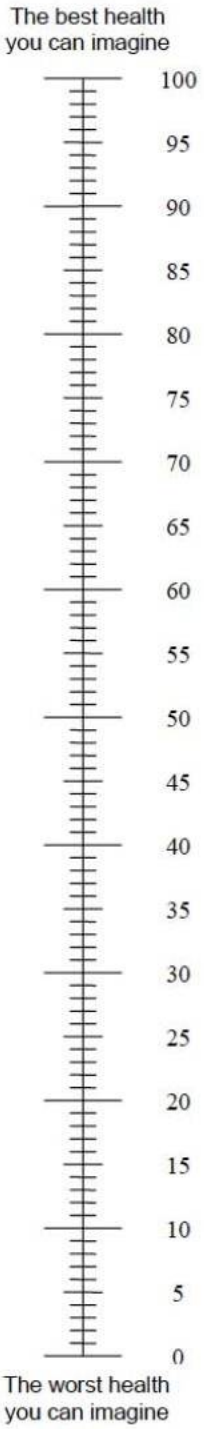
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

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

YOUR HEALTH TODAY = ☐



Appendix 8 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 while receiving another immunostimulatory anti-cancer agent.* Contact the Medical Monitor regarding 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 nephritis • 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 • 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 cirrhosis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix 9 Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

1. Stop the study treatment infusion.
2. Maintain an adequate airway.
3. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
4. Continue to observe the patient and document observations.

Appendix 10 Child-Pugh Classification

SCORING

Measure	Points Scored for Observed Finding		
	1 Point	2 Points	3 Points
Bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time, [a] seconds over control	1.0–3.0	4.0–6.0	>6.0
International normalized ratio	<1.7	1.7–2.3	>2.3
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Encephalopathy (grade)	None	Mild to moderate (Grade 1 or 2)	Severe (Grade 3 or 4)

[a] Prolonged time.

CLASSIFICATION

Points	Class
5–6	A
7–9	B
10–15	C

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Appendix 11 Overall Guidelines for Management of Patients who Experience Adverse Events

PATIENTS TREATED WITH ATEZOLIZUMAB AND BEVACIZUMAB (ARM A)

DOSE MODIFICATIONS: ARM A

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

TREATMENT INTERRUPTION: ARM A

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks 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 Medical Monitor agrees that the patient is likely to derive clinical benefit.

Bevacizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level. If bevacizumab 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. Bevacizumab can be resumed after being withheld for > 42 days if the Medical Monitor agrees that the patient is likely to derive clinical benefit.

Atezolizumab or bevacizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures), with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

If either study drug is withheld or discontinued, the other study drug can be continued as long as the patient is experiencing clinical benefit, as determined by the investigator per medical judgment.

See Section 4.3.2 for information on dose interruptions for reasons other than toxicity.

MANAGEMENT GUIDELINES: ARM A

Guidelines for the management of patients who experience specific adverse events are provided as outlined below. For cases in which management guidelines are not covered in the Atezolizumab or Bevacizumab Investigator's Brochures or this protocol, patients should be managed as deemed appropriate by the investigator according to best medical judgment.

Atezolizumab

Appendix 12 provides guidelines for the management of patients who experience atezolizumab-associated IRRs and immune-mediated adverse events (e.g., pulmonary, hepatic, gastrointestinal, endocrine, ocular, myocarditis, pancreatic, dermatologic, neurologic, meningoencephalitis, renal, myositis, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome events).

Bevacizumab

Table 1 provides guidelines for the management of patients who experience adverse events associated with bevacizumab.

Table 1 Management Guidelines for Adverse Events Associated with Bevacizumab

Event	Action to Be Taken
Infusion-Related Reaction	
IRR to bevacizumab, Grade 1	• 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, 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, Grade 3 or Grade 4	• Stop infusion • Discontinue bevacizumab.
Gastrointestinal events	
Gastrointestinal perforation, any grade	• Discontinue bevacizumab • Initiate treatment per institutional guidelines
Bowel obstruction, Grade 2	• Hold bevacizumab for partial obstruction requiring medical intervention • Bevacizumab may be restarted upon complete resolution of event

Table 1 Management Guidelines for Adverse Events Associated with Bevacizumab (cont.)

Event	Action to Be Taken
Bowel obstruction, Grade 3–4	• Hold bevacizumab for complete obstruction If surgery is necessary, patient may restart bevacizumab after full recovery from surgery and at investigator's discretion
Hypersensitivity/allergic reactions	• Permanently discontinue bevacizumab
Hypertension	
General Guidance	• Grade 2 or above, start antihypertensive therapy
Hypertension Grade 2	• Hold bevacizumab • Once blood pressure < 150/100 mmHg, patient may continue bevacizumab therapy
Hypertension Grade 3	• If blood pressure is not controlled to 150/100 mmHg with medication, discontinue bevacizumab
Hypertension Grade 4 (includes hypertensive encephalopathy)	• Discontinue bevacizumab
Hemorrhage	
Grade ≥ 2 hemoptysis (≥ 2.5 mL of bright red blood per episode)	• Discontinue bevacizumab
Grade 3, 4 bleeding	• Discontinue bevacizumab
Bleeding in patients on full-dose anticoagulant therapy	• Discontinue bevacizumab [a]
CNS bleeding, any grade	• Discontinue bevacizumab
Venous Thromboembolic Events	
Venous thromboembolic event Grade ≥ 3	• For Grade 3 thromboembolic events, hold bevacizumab for > 3 weeks. Bevacizumab treatment may be resumed during the period of therapeutic-dose anticoagulant therapy once the level of anticoagulation therapy is stabilized • Anticoagulant treatment should be administered per institutional guidelines • After administration of bevacizumab is restarted, if the patient experiences another Grade ≥ 3 venous thromboembolic event, bevacizumab should be discontinued • For Grade 4 thromboembolic events, discontinue bevacizumab

Table 1 Management Guidelines for Adverse Events Associated with Bevacizumab (cont.)

Event	Action to Be Taken
Arterial thromboembolic event, any Grade	• Discontinue bevacizumab
Arterial Thromboembolic Events	
Arterial thromboembolic event, any Grade	• Discontinue bevacizumab
Proteinuria	
Grade 1 (1+ proteinuria; urinary protein < 1.0 g/24 hour)	• Administer bevacizumab
Grade 2 (2+ proteinuria; urinary protein 1.0–3.4 g/24 hour)	• For 2+ dipstick: may administer bevacizumab and collect 24-hour urine prior to subsequent bevacizumab administration • For 3+ dipstick: must obtain 24-hour urine prior to administering bevacizumab • Withhold bevacizumab for urinary protein ≥ 2 g/24 hour. Resume bevacizumab when proteinuria is < 2 g/24 hour.
Grade 3 (urinary protein ≥ 3.5 g/24 hour)	• Withhold bevacizumab. Resume bevacizumab when proteinuria is < 2 g/24 hour.
Proteinuria with diagnosis of nephrotic syndrome	• Permanently discontinue bevacizumab
Fistula	
Tracheoesophageal fistula, any grade	• Discontinue bevacizumab
Fistula (non-racheoesophageal), Grade 4	• Discontinue bevacizumab
Wound Dehiscence	
Wound dehiscence, any grade requiring medical or surgical therapy	• Discontinue bevacizumab
Posterior Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome	
PRES/RPLS, any grade confirmed by MRI	• Discontinue bevacizumab

IRR = infusion-related reaction; MRI = magnetic resonance imaging.

[a] Follow guidelines of the treating institution.

PATIENTS TREATED WITH SORAFENIB (ARM B)

DOSE MODIFICATIONS AND TREATMENT INTERRUPTIONS: ARM B

Temporary interruption or dose modification may be required for management of toxicities. Any toxicity associated or possibly associated with sorafenib treatment should be managed according to standard medical practice. Suggested dose modifications for hand-foot skin reaction toxicities are provided in Table 2. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of sorafenib. When dose reduction is necessary, the sorafenib dose may be reduced to 400 mg once daily. If additional dose reduction is required, sorafenib may be reduced to a single 400 mg dose every other day. Once a dose reduction is made, the sorafenib dose may be re-escalated at the discretion of the investigator if the patient has been on a stable dose for 3 weeks or more without further toxicities requiring dose modification.

Table 2 Suggested Sorafenib Dose Modification for Hand–Foot Skin

Grade	Occurrence	Sorafenib Dose Modification
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema, or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any occurrence	• Continue treatment and consider topical therapy for symptomatic relief
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	• Continue treatment and consider topical therapy for symptomatic relief • Interrupt sorafenib treatment until toxicity resolves to Grade 0 or 1
	No improvement within 7 days or 2nd or 3rd occurrence	• Interrupt sorafenib treatment until toxicity resolves to Grade 0 or 1
		• When resuming treatment, decrease dose to 400 mg daily
	4th occurrence	• Discontinue sorafenib treatment
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform daily activities	1st or 2nd occurrence	• Interrupt sorafenib treatment until toxicity resolves to Grade 0 or 1
		• When resuming treatment, decrease dose to 400 mg daily
	3rd occurrence	• Discontinue sorafenib treatment

For adverse events associated with sorafenib that are not listed in Table 2, refer to guidelines in the applicable local prescribing information (if available).

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

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

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

PULMONARY EVENTS

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

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

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
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 • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent • If event resolves to Grade 1 or better, resume atezolizumab [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c] • For recurrent events, treat as a Grade 3 or 4 event
Pulmonary event, Grade 3 or Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Bronchoscopy or BAL is recommended • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

BAL = bronchoscopic alveolar lavage.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

HEPATIC EVENTS FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA

Immune-mediated hepatitis has been associated with the administration of atezolizumab. *Patients e*ligible *for study treatment* must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases; 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 for Patients with HCC

Event	Management
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 Medical Monitor* [c]
AST or ALT increases to >10 ×ULN or total bilirubin increases to >3 ×ULN	• *Permanently discontinue atezolizumab and contact 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*

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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 3.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with 3 to 5 specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

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 • Patient referral to GI specialist is recommended • For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent • If event resolves to Grade 1 or better, resume atezolizumab [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]
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 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • If event resolves to Grade 1 or better, resume atezolizumab [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]

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

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

GI = gastrointestinal.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, 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
Asymptomatic hypothyroidism	• Continue atezolizumab • Initiate treatment with thyroid replacement hormone • Monitor TSH weekly
Symptomatic hypothyroidism	• Withhold atezolizumab • Initiate treatment with thyroid replacement hormone • Monitor TSH weekly • Consider patient referral to endocrinologist • Resume atezolizumab when symptoms are controlled and thyroid function is improving
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab • Monitor TSH every 4 weeks **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism
Symptomatic hyperthyroidism	• Withhold atezolizumab • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed • Consider patient referral to endocrinologist • Resume atezolizumab when symptoms are controlled and thyroid function is improving • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism [c]
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer patient to endocrinologist • Perform appropriate imaging • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab • Initiate treatment with insulin if needed • Monitor for glucose control

Table 4 Management Guidelines for Endocrine Events (cont.)

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

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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 Medical Monitor [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Refer patient to ophthalmologist • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab. 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. 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.

Table 6 Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 1	• Refer patient to cardiologist • Initiate treatment as per institutional guidelines
Immune-mediated myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor • Refer patient to cardiologist • Initiate treatment as per institutional guidelines and consider anti-arrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate • Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement [a] • If event resolves to Grade 1 or better, resume atezolizumab [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]
Immune-mediated myocarditis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Refer patient to cardiologist • Initiate treatment as per institutional guidelines and consider anti-arrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement [a, b] • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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 atezozlizumab* may receive premedication with antihistamines or anti-pyretics/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.

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 medical management of IRRs and CRS are provided in Table 7.

Severe COVID-19 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 COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

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-pyretics, 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* [e] • *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 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-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS.*

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

Event	*Management*
	• *If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor*
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 Medical Monitor* [f] • *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* [e] • *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.*

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

Event	*Management*
Grade 4 [a] *Fever* [b] *with hypotension requiring multiple vasopressors (excluding vasopressin)* ***and/or*** *Hypoxia requiring oxygen by positive pressure (e.g., CPAP, Bi-PAP, intubation and mechanical ventilation)*	• *Permanently discontinue atezolizumab and contact 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.* [e] *For patients who are refractory to anti-cytokine therapy, experimental treatments* [g] *may be considered at the discretion of the investigator and in consultation with the Medical Monitor.* • *Hospitalize patient until complete resolution of symptoms*

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 NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] *Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.*

[b] *Fever is defined as temperature ≥ 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-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.*

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

[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] *There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.*

[f] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after consulting the Medical Monitor and considering the benefit–risk ratio.*

[g] *Refer to Riegler et al. (2019) for information on experimental treatments for CRS.*

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate 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	• Continue atezolizumab • Monitor amylase and lipase weekly • For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent
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 1–2 mg/kg/day oral prednisone or equivalent • If event resolves to Grade 1 or better, resume atezolizumab [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor [c]
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 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • If event resolves to Grade 1 or better, resume atezolizumab [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor [c]

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

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

GI = gastrointestinal.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. *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
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 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours • If event resolves to Grade 1 or better, resume atezolizumab [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab • Investigate etiology
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Investigate etiology • Initiate treatment as per institutional guidelines • If event resolves to Grade 1 or better, resume atezolizumab [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Initiate treatment as per institutional guidelines
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor [c] • Refer patient to neurologist • Initiate treatment as per institutional guidelines • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. 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 11

Table 11 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor [a] • Refer patient to neurologist • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

RENAL EVENTS

Immune-mediated nephritis has been associated with the administration of atezolizumab. 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 post-renal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically

indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab • Monitor kidney function, including creatinine, 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 Medical Monitor [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor • Refer patient to renal specialist and consider renal biopsy • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

[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 agreed upon by the investigator and the Medical Monitor.

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. 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 signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13 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 Medical Monitor • Refer patient to rheumatologist or neurologist • Initiate treatment as per institutional guidelines • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, resume atezolizumab [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact 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 Medical Monitor [c] • For recurrent events, treat as a Grade 4 event

Table 13 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact 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 agreed upon by the investigator and the Medical Monitor.

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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).

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 2 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 2 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 14.

Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor • Consider patient referral to hematologist • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines • Consider initiation of IV corticosteroids and/or an immunosuppressive agent • 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

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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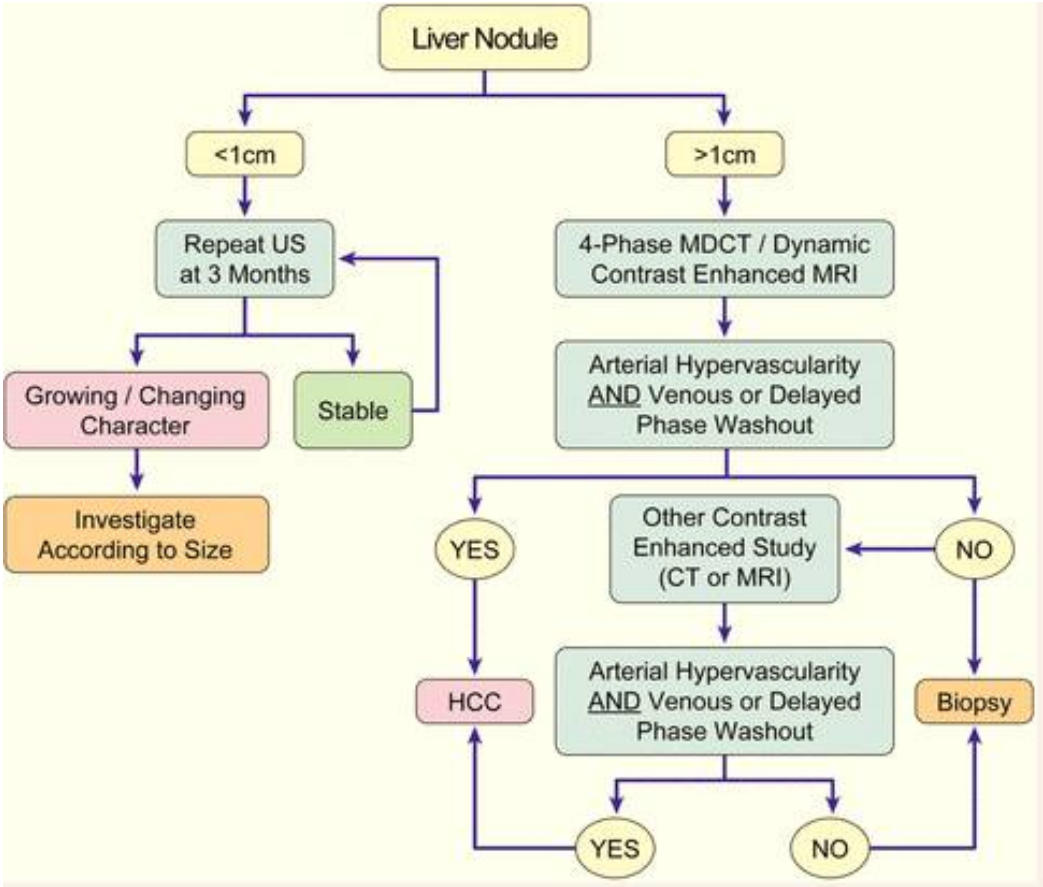
Appendix 13 American Association for the Study of Liver Diseases Criteria: Algorithm for Investigation of Small Nodules Found on Screening in Patients at Risk for HCC



AASLD = Association for the Study of Liver Diseases; CT = computed tomography; MDCT = multi-detector CT scan; MRI = magnetic resonance imaging; HCC = hepatocellular carcinoma.

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