Official Title: A Phase IIIB, Single-Arm, Multicenter Study of Atezolizumab (Tecentriq) in Combination With Bevacizumab to Investigate Safety and Efficacy in Patients With Unresectable Hepatocellular Carcinoma Not Previously Treated With Systemic Therapy - Amethista

NCT Number: NCT04487067

Document Date: Protocol Version 5: 11-Jan-2024

PROTOCOL

TITLE:	**A PHASE IIIB, SINGLE ARM, MULTICENTER STUDY OF ATEZOLIZUMAB (TECENTRIQ) IN COMBINATION WITH BEVACIZUMAB TO INVESTIGATE SAFETY AND EFFICACY IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA NOT PREVIOUSLY TREATED WITH SYSTEMIC THERAPY - AMETHISTA**
PROTOCOL NUMBER:	ML42243
VERSION NUMBER:	*5*
EUDRACT NUMBER:	2020-001973-66
IND NUMBER:	N/A
TEST PRODUCT:	Atezolizumab (RO5541267) Bevacizumab (RO4876646)
MEDICAL MONITOR:	[redacted]
SPONSOR:	Roche S.p.A.
DATE FINAL:	See electronic signature and date stamp on the final page of this document.

FINAL PROTOCOL APPROVAL

Version	Date Final
5	**See electronic signature and date stamp on the final page of this document.**
4	See electronic signature and date stamp on the final page of the document.
3	See electronic date stamp on title page
2	See electronic date stamp on title page
1	19 May 2020

PROTOCOL AMENDMENT, VERSION 5.0: RATIONALE

Protocol ML42243 has primarily been amended to update safety language following the release of the Atezolizumab Investigator's Brochure Version 20. Changes to the protocol, along with a rationale for each change, are summarized below:

- The Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab have been updated to align with the Atezolizumab Investigator's Brochure, Version 20 (Appendix 6).

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 IIIB, SINGLE ARM, MULTICENTER STUDY OF ATEZOLIZUMAB (TECENTRIQ) IN COMBINATION WITH BEVACIZUMAB TO INVESTIGATE SAFETY AND EFFICACY IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA NOT PREVIOUSLY TREATED WITH SYSTEMIC THERAPY – AMETHISTA**
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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 to your local study Monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IIIB, SINGLE ARM, MULTICENTER STUDY OF ATEZOLIZUMAB (TECENTRIQ) IN COMBINATION WITH BEVACIZUMAB TO INVESTIGATE SAFETY AND EFFICACY IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA NOT PREVIOUSLY TREATED WITH SYSTEMIC THERAPY – AMETHISTA**
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EUDRACT NUMBER:	2020-001973-66
IND NUMBER:	N/A
TEST PRODUCT:	Atezolizumab (RO5541267) Bevacizumab (RO4876646)
PHASE:	Phase IIIB
INDICATION:	Unresectable hepatocellular carcinoma (HCC)
SPONSOR:	Roche S.p.A.

Objectives and Endpoints

This study will evaluate the safety and efficacy of atezolizumab in combination with bevacizumab in patients with unresectable hepatocellular carcinoma (HCC) who have received no prior systemic treatment. In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., atezolizumab and bevacizumab).

Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective	**Corresponding Endpoint**
To evaluate the safety of atezolizumab + bevacizumab in terms of bleeding/haemorrhage	• Incidence of Grade 3-5 NCI CTCAE v.5 bleeding/haemorrhage
Main Secondary Objective	**Corresponding Endpoint**
To evaluate the efficacy of atezolizumab + bevacizumab	Overall survival (OS), defined as the time from initiation of study treatment to death from any cause

Other Secondary Objectives	Corresponding Endpoints
To further evaluate the safety of atezolizumab + bevacizumab	• Incidence and severity of adverse events (AEs), with severity determined according to NCI CTCAE v5.0 • Vital signs • Clinical laboratory test results
To further evaluate the efficacy of atezolizumab + bevacizumab	• Progression-free survival (PFS), defined as the time from initiation of study treatment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • Objective response rate (ORR), defined as a complete or partial response, as determined by the investigator according to RECIST v1.1 • Time to progression (TTP), defined as the time from initiation of study treatment to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1 • Duration of response (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 • Post-progression survival (PPS), defined as the time from the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 to death from any cause • Number/Rate of patients starting second or further lines of treatment
To evaluate Patient Reported Outcomes (PROs) and to describe the patient's experience while receiving atezolizumab + bevacizumab	• Patient self-reported symptomatic Adverse Events (AEs) using National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

Exploratory Efficacy Objectives	Corresponding Endpoints
• To evaluate whether the patterns of tumor progression (growth versus new lesion, intrahepatic versus extrahepatic) have a different impact on OS and PPS	• OS and PPS based on the following patterns of progression: - >20% increase in tumor size against a known baseline lesion (intrahepatic growth [IHG] or extrahepatic growth [EHG]) - new intrahepatic tumor lesion (NIH) - new extrahepatic lesion (NEH) and/or vascular invasion
• To evaluate if post-study treatment have impact on OS	• OS based on type and duration of each post-study treatments
• To evaluate if reason of treatment withdrawal has impact on OS	• OS based on the following reasons of treatment withdrawal: - Progressive disease (PD) vs AEs vs deteriorating liver function/clinical conditions

Exploratory Biomarker Objective	Corresponding Endpoint
• Gut Microbiome evaluation	• Relationship between the compositional and functional structure of the gut microbiome and antitumour responses following atezolizumab and bevacizumab
• **Exploratory Economic Objective**	**Corresponding Endpoint**
• To identify, quantify and valuate health care resources consumed for managing Grade 3 and 4 AEs related to the administration of atezolizumab + bevacizumab	• Relationship between AEs and health care resource consumption
• To assess the cost for managing adverse events related to the administration of atezolizumab + bevacizumab	• Cost description of health care resources consumed for managing Grade 3 and 4 AEs related to the administration of atezolizumab + bevacizumab

AE = Adverse Event; DOR = duration of response; EHG = extrahepatic growth; HCC = hepatocellular carcinoma; IHG = intrahepatic growth; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; NEH = new extrahepatic lesion; NIH = new intrahepatic lesion; ORR = Objective Response Rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PRO = Patient Reported Outcome; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PPS = Post-progression Survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; PPS=Post Progression Survival; TTP = Time to Progression

Study Design

Description of Study

This is a Phase IIIb, one arm, multicenter, open-label study designed to evaluate the safety and efficacy of atezolizumab + bevacizumab in patients with unresectable HCC who have received no prior systemic treatment.

This study will enroll approximately 150 patients in one arm of treatment:

- Atezolizumab 1200 mg intravenous (IV) infusions Q3W (dosed in 3-week cycles) + bevacizumab 15 mg/kg IV Q3W (dosed in 3-week cycles)

Patients treated with atezolizumab + bevacizumab arm who transiently discontinue or withdraw from 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 withdraw after discussion with the Medical Monitor (i.e., patients transiently discontinue or withdraw from bevacizumab for adverse effects may continue atezolizumab monotherapy and vice versa).

Patients will receive atezolizumab and/or bevacizumab 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 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) 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 or brain metastases) that cannot be managed by protocol-allowed medical interventions.

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, Version 5.0 (NCI CTCAE v5.0). Laboratory safety assessments will include the regular monitoring of haematology and blood chemistry.

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 according to RECIST V1.1, regardless of whether treatment has been discontinued (e.g., for toxicity) or until 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.

Patient samples of faeces will be collected for future exploratory biomarker assessments.

Number of Patients

This study will enroll approximately a sample of convenience (Lohr 2010) of 150 patients across 21 Italian sites.

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;
- Unresectable HCC with diagnosis confirmed by histology, with a biopsy within 6 months from recruitment;
- 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;
- At least one 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, SIRT 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 version 1.1;
- ECOG Performance Status of 0 or 1 within 7 days prior to recruitment;
- Child-Pugh class A within 7 days prior to recruitment;
- Patients must undergo an esophagogastroduodenoscopy (EGD), and all size of varices (small to large) must be assessed. In case of varices at high risk of bleeding (corresponding to medium (F2) or large (F3) varices, or F1 varices with cherry red spots or red wale marking) prophylatic treatment per local standard of care must be adopted 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 provided they had no varices at high risk of bleeding;
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 7 days prior to recruitment, 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 (PLT) count $\geq 75 \times 10^9$/L (75,000/μL) without transfusion;
  - Haemoglobin ≥ 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);
  - Total bilirubin $\leq 3 \times$ ULN;
  - Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault formula);
  - Serum albumin ≥ 28 g/L (2.8 g/dL) without transfusion;
  - For patients not receiving therapeutic anticoagulation: INR and aPTT *or PTT* ≤ 1.5 x 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 (or an alternative method such as protein: creatinine ratio, per local guidance) 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 with the following exception: patients with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count ≥200μL, and have an undetectable viral load;
- In patients with viral HCC, documented virology status of hepatitis, as confirmed by screening HBV and HCV serology test;
- For patients with active hepatitis B virus (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, and agreement to refrain from donating eggs, as defined below.

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year while they are receiving atezolizumab and bevacizumab and for 5 months after the final dose of atezolizumab and for 6 months after the final dose of bevacizumab. Women must refrain from donating eggs during the same period. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and *is not permanently infertile due to surgery* (removal of ovaries, *fallopian tubes* and/or uterus) *or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential.*

  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. 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 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.

Exclusion Criteria

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

- History of leptomeningeal disease or brain metastases;
- 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 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 severe infection that in the opinion of the investigator could impact patient's 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) or patients receiving rifaximin as prevention of encephalopathy are eligible for the study.

  Antibiotics administered within 30 days prior to initiation of study treatment will be collected.
- 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;
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within at least 5 months after the last dose of atezolizumab and 6 months after the last dose of bevacizumab;

  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;
- A prior bleeding event due to oesophageal and/or gastric varices within 6 months prior to initiation of study treatment;
- Clinically evident ascites;
- At least one clinically evident episode of encephalopathy in the past three months;
- Co-infection 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;
- Co-infection with HBV and hepatitis D viral infection;
- Symptomatic, untreated, or actively progressing central nervous system (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 haemorrhage or spinal cord haemorrhage;

- Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord);
- There is no evidence of interim progression between completion of CNS-directed therapy and initiation of study treatment;
- The patient has not undergone stereotactic radiotherapy, 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.
- If the patient is receiving anti-convulsivant therapy, the dose is considered stable

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 loco-regional 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.

- Clinically significant 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;
- 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.

  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) $\geq$ 150 mmHg and/or diastolic blood pressure $>$ 100 mmHg), based on an average of $\geq$ 3 BP readings on $\geq$ 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 haemoptysis (≥ 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 anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose;

  Prophylactic anticoagulation for the patency of venous access devices is allowed provided the activity of the agent results in an INR $< 1.5 \times$ ULN and aPTT *or PTT* is within normal limits within 14 days prior to initiation of study treatment.

  Prophylactic use of low-molecular-weight heparin (i.e., enoxaparin 40 mg/day) is allowed. However, the use of direct oral anticoagulant therapies such as dabigatran (Pradaxa®) and rivaroxaban (Xarelto®) is not recommended due to bleeding risk. Benefits and risks should be assessed and caution exercised for use of direct oral anticoagulants. The investigator should consider switching to other approved anticoagulants due to the risk of upper gastrointestinal (GI) bleeding in patients with HCC.
- 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 gastrointestinal (GI) fistula, 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 clinically significant intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including but not limited to complicated 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, SIRT 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 non-steroidal anti-inflammatory drug (NSAID), excluding acetyl acetic acid (aspirin) at doses <325 mg/day;

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

End of Study

The end of study will occur when all enrolled patients have either died, withdrawn consent, are lost to follow up, or have been followed for 36 months since the last study patient is enrolled, whichever occurs first.

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

Length of Study

The total length of the study, from screening of the first patient to the end of the study is approximately 4 years (12 months enrolment).

Investigational Medicinal Products

Test Product (Investigational Drug)

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).

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	Atezolizumab 1200 mg IV on Day 1
	Bevacizumab 15 mg/kg IV on Day 1

Comparator

Not applicable.

Non-Investigational Medicinal Products

Not applicable.

Statistical Methods

Determination of Sample Size

This study will enroll approximately a sample of convenience (Lohr 2010) of 150 patients across 21 Italian sites, possibly according to a competitive enrolment scheme (Kim et al. 2017).

According to the results of the YO40245 (IMbrave150) trial (Cheng et al. 2019), the expected incidence of Grade 3-5 bleeding events is 7.9% (that is, 6.4% incidence of Grade 3-4 bleeding events plus 1.5% incidence of Grade 5 bleeding events) during a 10.4 months timespan (that is, 7.4 months of median treatment duration plus 90 days or 3 months of follow-up).

Therefore, assuming a fixed rate with respect to time, the overall Grade 3-5 bleeding events rate (*r*) *per* month is (Miller and Homan 1984; Briggs et al. 2006):

$$r = -\frac{[\ln(1 - 0.079)]}{10.4}$$

or 0.007913, that, considering a convenience sample (Lohr 2010) of 150 patients and a 12-month lasting year (Wilkins 1990), can be converted into an annual probability (*one year p*) - or incidence - of Grade 3-5 bleeding events as follows (Miller and Homan 1984; Briggs et al. 2006):

$$one\ year\ p = [1 - \exp(-0.007913\text{x}12)]$$

or 0.090587.

According to this incidence point estimate and assuming no missing 1-year patient time and that each patient can experience only one Grade 3-5 bleeding event *per* year (that is, ruling out for sake of simplicity shared frailty issues, such as multiple occurrence of 3-5 bleeding events experienced by the same patient) (Therneau and Grambsch 2000), the expected number (#) of patients with Grade 3-5 bleeding event *per* year out of a convenience sample size (Lohr 2010) of 150 evaluable subjects can be calculated as follows:

$$\#\ of\ patients\ with\ bleeding\ events\ per\ year = (0.090587\text{x}150)$$

or about 14 patients with the event *per* year.

The achievable precision (width of 95% CI) for the incidence of Grade 3-5 bleeding events related to treatment is illustrated separately (**Table 9**). The sample variance of the binomial distribution is conditional on its sample mean (Agresti 2002) and both these statistics enter the formula for calculating the standard error of the sample distribution of the mean (Agresti 2002). Therefore, given the same sample size, a low incidence of Grade 3-5 bleeding events leads to a small width of the 95% CI, whereas a higher incidence of Grade 3-5 bleeding events results in a wider 95% CI.

In order to investigate the precision of the point estimate for the incidence of Grade 3-5 bleeding events under different scenarios, the Clopper-Pearson method (Clopper and Pearson 1934; Agresti 2002; Fleiss et al. 2003) for calculating incidence 95% CI and the width of 95% CI has been applied. Thus, assuming a sample size of 150 patients and the incidence of Grade 3-5 bleeding events which lies within the range of 0% - 9.33%, the precision (CI width) could vary from 2.43 to 9.96 percent points. In particular, considering the incidence of Grade 3-5 bleeding events around 8%, a

two-sided 95% confidence interval with a width equal to 9.36 percent points will be provided (see section 6.1 for details).

Safety Analysis

The safety analysis population (SAP) consists of all enrolled patients who had at least one full or partial administration of atezolizumab + bevacizumab.

Primary Analysis

The incidence of grade 3-5 NCI CTCAE bleeding/haemorrhage events will be calculated for the SAP, along with binomial exact (or Clopper-Pearson) (Clopper and Pearson 1934; Agresti 2002; Fleiss et al. 2003) 95% (CI).

Primary analysis

The overall incidence of Grade 3-5 NCI CTCAE bleeding events will be calculated for the SAP, along with Clopper-Pearson (Clopper and Pearson 1934; Agresti 2002; Fleiss et al. 2003) 95% CI.

No hypothesis testing is intended, as the focus of the statistical analyses is on the precision of the obtained estimate of the incidence of this key safety parameter.

For the primary safety endpoint, that is overall Grade 3-5 bleeding events, in addition to the annual probability of experiencing such AEs, the annual and overall bleeding rate (BR) will be calculated as follows:

$$BR = \#events/PY$$

where #events is the total number of Grade 3-5 bleeding events (including multiple occurrences *per* patient), and PY is the total number of patient-years under observation. The BR point estimate will be provided along with 95% CI, assuming a Poisson distribution (Poisson 1837; Agresti 2001; Hilbe 2014) for the underlying number of related events.

Secondary analysis

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

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

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

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

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events

of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths with causes of death reported during the study will be summarized.

The following events occurring during or after the first dose of study treatment will be summarized by NCI CTCAE grade v5.0:

- All Adverse Events (AEs)
    - All severe AEs (Grade 3-4)
- All treatment related AEs;
    - All severe treatment-related AEs (Grade 3 -4)
- All serious AEs
    - All treatment-related serious AEs
- All immune-mediated AEs
    - All severe immune-mediated AEs (Grade 3-4)
- All adverse events leading to withdrawal from any component
- All adverse events leading to withdrawal from atezolizumab
- All adverse events leading to withdrawal from bevacizumab
- All Grade 5 AEs
    - All treatment related Grade 5 AE
- All adverse event of special interest (AESIs) of atezolizumab
    - All severe AESIs of atezolizumab (Grade 3-4)
- All adverse event of special interest (AESIs) of bevacizumab
    - All severe AESIs of atezolizumab (Grade 3-4)
- All adverse events leading to dose temporary interruption of any component
- All adverse events leading to dose temporary interruption of atezolizumab
- All adverse events leading to dose temporary interruption of bevacizumab

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

The following descriptive statistics on the selected items will be reported (Pagano and Gavreau 2000):

- Continuous and count variables:
  - ✓ location measures: mean and median;
  - ✓ dispersion measures: standard deviation and range;
- Categorical variables: absolute and relative frequencies.

Summary statistical tables including number of and patients with adverse events along with 95% CI assuming an underlying Poisson distribution (Poisson 1837; Agresti 2001; Hilbe 2014) as well as number absolute and relative frequencies of adverse events along with Clopper-Pearson 95% CI (Clopper and Pearson 1934; Agresti 2002; Fleiss et al. 2003) will be produced.

Additional analyses may be performed as indicated.

Missing values will be classified and managed using the methods outlined in Section 6.7.

According to its relevance to possible AEs experienced by patients on atezolizumab + bevacizumab, a subset of the about 80 items included in the Italian translation of the Item Library Version 1.0 of the NCI-PRO-CTCAE™ questionnaire (Appendix 7) (Smith et al. 2016; National Cancer Institute, 2017) will be selected by a working group composed of study investigators and patient advocates.

The following descriptive statistics on the selected items (possibly grouping in domains items that share common features) (Brazier et al.2017) of the Italian translation of the Item Library Version 1.0 of the NCI-PRO-CTCAE™ questionnaire version 1.0 of the NCI-PRO-CTCAE™ questionnaire will be reported (Pagano and Gavreau 2000):

- Ordinal count variables:
  - ✓ location measures: mean and median;
  - ✓ dispersion measures: standard deviation and range;
- Categorical variables: absolute and relative frequencies.

Missing data for items and patients will be summarized to improve results interpretation (National Cancer Institute, 2020).

Missing values will be classified and managed using the methods outlined in Health economic analysis paragraph.

Secondary Analysis

Efficacy

Efficacy analysis includes both main and other secondary objectives,

All baseline summaries and efficacy analyses will be based on the intent-to-treat (ITT) analysis set defined as all recruited patients.

Time-dependent variables OS, PFS, TTP, DOR and PPS will be analyzed using Kaplan-Meier (K-M) methods and Greenwood's formula. Medians and the quartiles with 95% confidence interval (CI) will be derived from the K-M curves. Kaplan-Meier plots with a 95% CI for OS, PFS, DOR and PPS will be prepared.

ORR will simply be summarised. The ORR will be calculated as the percentage of patients who have a CR or PR before any evidence of progression. A 95% CI will be derived for the ORR using Wilson score intervals (CIs for a single proportion).

Following disease progression, patients will be followed-up to evaluate whether the patterns of tumor progression (growth versus new lesion, intrahepatic versus extrahepatic) have a different impact on OS and PPS. OS and PPS will be described based on the following patterns of progression:

- >20% increase in tumor size against a known baseline lesion (intrahepatic growth [IHG] or extrahepatic growth [EHG])
- new intrahepatic lesion (NIH)
- new extrahepatic lesion (NEH) and/or vascular invasion

To evaluate if post-study treatments have impact on OS following disease progression, patients will be followed for anti-cancer therapies and survival with a descriptive analysis. In details, number and rate of patients starting second or further lines of treatment will be described indicating time and duration of each post-study treatment. OS based on type and duration of each post-study treatment will be described.

To evaluate if reason of treatment withdrawal has impact on OS, OS based on the following reasons of treatment withdrawal will be described:

- Progressive disease (PD) vs adverse event (AE) vs deteriorating liver function/clinical conditions.

Missing values will be classified and managed using the methods outlined described above.

For the primary safety endpoint of grade 3-5 bleeding events, the overall bleeding rate (BR) will be calculated in Health economic analysis paragraph.

- Continuous and count variables:
  - ✓ location measures: mean and median;
  - ✓ dispersion measures: standard deviation and range;
- Categorical variables: absolute and relative frequencies.

Health economic analysis

The health care resources consumed for managing Grade 3 and 4 AE related to the administration of atezolizumab + bevacizumab by the sample of convenience (Lohr 2010) of approximately 150 patients enrolled in 20 Italian clinical sites will be prospectively identified and quantified, using the ITT analysis population.

Following the Italian National Health Service (INHS) viewpoint (Drummond et al. 2015), the abovementioned health care resources will be valued and detailed via a partial technique of economic evaluation of health care programmes (Drummond et al. 2015), named cost description (Drummond et al. 2015). Cost description describes the health care resources cost but neither takes their effects on patient's health state into account, nor informes any choice among different health care programmes (Drummond et al. 2015).

The cost description will focus on the following INHS-funded health care resources (Lazzaro et al. 2013; Lazzaro et al. 2018; Lazzaro et al. 2019):

- Laboratory tests;
- Diagnostic imaging;
- Instrumental tests;
- Drugs (posology; number of administrations *per diem*; length of treatment);
- Other medications (eg, oxygen therapy);
- Transfusions (RBC and/or PLTs);

- Specialist follow-up visits;
- Hospitalizations:
  - ✓ day-hospital setting (type of ward; number of accesses);
  - ✓ inward setting (type of ward; number of episodes; number of days per episode);
- Emergency room (number of admittances).

The cost description will be carried out via a three-step approach that encompasses (i) INHS-funded health care resources identification and (ii) quantification, followed by (iii) their valuation. INHS-funded health care resources consumed by patients for managing Grade 3 and Grade 4 AEs related to the administration of atezolizumab + bevacizumab will be identified and quantified via the Adverse Event eCRF.

INHS-funded health care resources valuation will be performed via multiplying by an item-specific unitary cost the volume of INHS-funded health care resources consumed by patients for managing Grade 3 and Grade 4 AEs related to the administration of atezolizumab + bevacizumab.

Since the cost description will follow the INHS standpoint:

- Drugs will be valued at consumer price (Lazzaro et al. 2019).
- For health care services that differ from drugs, INHS tariffs will be used to value health care resources consumed for managing Grade 3 and Grade 4 AEs related to the administration of atezolizumab + bevacizumab (Ministero della Salute, 2012; Conferenza Permanente per i Rapporti tra lo Stato le Regioni e le Province Autonome di Trento e Bolzano, 2019).

The monetary standards will be consistent with the delivery setting of each health care procedure (outpatient; day-hospital; inward).

It is expected that INHS-funded health care resources consumed by patients for managing Grade 3 and Grade 4 AEs related to the administration of atezolizumab + bevacizumab (visits, diagnostic imaging and tests) will be mostly valued as outpatient procedures via the Italian Ministry of Health tariffs in force for outpatient setting (Ministero della Salute, 2012).

Had any of the abovementioned health care procedures been performed in day-hospital or inpatient setting, only the hotel cost for hospital stay (Conferenza Permanente per i Rapporti tra lo Stato le Regioni e le Province Autonome di Trento e Bolzano, 2019) will be added to the cost of the health care procedure itself calculated according to the Italian Ministry of Health tariffs in force for outpatient setting (Ministero della Salute, 2012).

Emergency room admittance will be valued according to a dedicated INHS tariff (Ministero della Salute, 2007).

As the reference literature on the economic evaluation of health care programmes (Drummond et al 2015) requires that the resource costing procedure refers to the same and, preferably, the most recent year (imposing a proper inflation rate, when necessary), all costs will be reported in € at 2020 values.

The following descriptive statistics concerning INHS-funded health care resources consumption (type and volume) and valuation (cost) due to Grade 3 and 4 AEs related to the administration of atezolizumab + bevacizumab management will be reported (Pagano and Gavreau 2000):

- Continuous and count variables:
  - ✓ location measures: mean and median;
  - ✓ dispersion measures: standard deviation and range;
- Categorical variables: absolute and relative frequencies.

Both base case statistical analyses and cost description (Drummond et al. 2015) will be performed on all the evaluable patients included in the study database (Complete Case Analysis - CCA) (Little and Rubin 2002). If the CCA sample will prove to be too limited, an available case analysis (ACA) (Little and Rubin 2002) will replace CCA.

The frequency of missing data will be reported for all analyzed variables and patients.

Missing data will be diagnosed and classified according to their underlying missing mechanism (Missing Completely At Random - MCAR; Missing At Random - MAR; Missing Not At Random - MNAR) and pattern (monotonic; generalized; univariate) (Van Buuren et al. 1999; Little and Rubin 2002; Van Buuren 2018).

Missing data will be dealt with via one or more multiple imputation regression models and/or other statistical methods consistent with their underlying missing mechanism (Van Buuren et al., 1999; Little & Rubin 2002; Van Buuren 2018).

Therefore CCA (or ACA) and fully imputed descriptive statistics for quantitative non-monetary and quantitative monetary variables (Anthony and Young 2002) will be presented.

Non-parametric bootstrap method will be applied to INHS-funded health care sector-related costs data for calculating 95% CIs in CCA (or ACA) (Efron and Tibshirani 1993; Desgagné et al. 1998; Barber and Thompson 2000).

Statistical analyses will be supported by Stata/SE software v 16.0 (StataCorp LP, College Station, TX, USA).

In order to carry out the cost description and statistical analyses concerning the abovementioned INHS-funded health care resources consumed by patients for managing Grade 3 and Grade 4 AEs related to the administration of atezolizumab + bevacizumab, a dedicated excerpt of the original database will be provided by the Sponsor of the study.

According to the YO40245 (IMbrave150), the expected incidence of grade 3-5 bleeding events is 7.9% (6.4% of Grade 3-4 and 1.5% of Grade 5).

Interim Analyses

An interim analysis of safety will be performed at the time of 50 recruited patients, estimated to occur at approximately 6 months after first patient in (FPI).

A second interim analysis will be performed when patients have completed a period of follow-up of approximately 10 months. This follow-up period corresponds to that reported in the published YO40245 (IMbrave150) trial (Cheng et al. 2019; Finn et al. NEJM 2021), which has been taken into consideration in the sample size calculation for this study with regard to the expected incidence of Grade 3-5 bleeding events. This second interim analysis will take into account all the efficacy and safety endpoints with descriptive purposes.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-FU	5-fluorouracyl
ACA	Available Case Analysis
ADA	Anti-drug Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
ATE	Arterial Thromboembolic Event
BID	Bis In Die (twice daily)
BP	Blood Pressure
BR	Bleeding Rate
CCA	Complete Case Analysis
CHF	Congestive Heart Failure
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	*Coronavirus Disease 2019*
CR	Complete Response
CRC	Colorectal Carcinoma
CRO	Contract Research Organization
CRS	Cytokine-release Syndrome
CT	Computerized Tomography
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration Of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGD	Esophagogastroduodenoscopy
EHG	Extrahepatic Growth
EMA	European Medicine Agency
EOC	Epithelial Ovarian Cancer
FDA	Food and Drug Administration
FPI	First Patient In
FTC	Fallopian Tube Cancer
GBM	Glioblastoma Multiforme
GHS	Global Health Status
GI	Gastrointestinal
HBV	Hepatitis B Virus
HBcAb	Hepatitis B virus core antibody
HBsAg	Hepatitis B virus surface antigen
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLH	Hemophagocytic Lymphohistiocytosis
HR	Hazard Ratio
HRQoL	Health-related Quality of Life
ICH	International Council for Harmonisation
IFN	Interferon
IgG	Immunoglobulin G
IHG	Intrahepatic Growth
IL	Interleukin
IMP	Investigational Medicinal Product
INHS	Italian National Health Service
INR	International Normalized Ratio
IRB	Institutional Review Board
IRF	Independent Review Facility
IRR	Infusion-related Reaction
ITT	Intention-to-treat
IV	Intravenous
IVIG	IntraVenous ImmunoGlobulin
IxRS	Interactive Voice/Web Response System
K-M	Kaplan Meier

LDH	Lactate Dehydrogenase
LL	Lower Limit
LMWH	Low Molecular Weight Heparin
MAR	Missing At Random
MAS	Macrophage Activation Syndrome
MCAR	Missing Completely At Random
MNAR	Missing Not At Random
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
N/A	Not Applicable
NAFLD	Non-alcoholic Fatty Liver Disease
NCI	National Cancer Institute
NCNN	National Comprehensive Cancer Network
NCI CTCAE v 5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NE	Not Evaluable
NEH	New Extrahepatic Lesion
NIH	New Intrahepatic Lesion
NSAID	Non-steroidal Antinflammatory Drug
NSCLC	Non-small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PD-L1	Programmed Death-ligand 1
PET	Positron Emission Tomography
PF	Physical Functioning
PFS	Progression-free Survival
PK	Pharmacokinetic
PLT	Platelets
PPC	Primary Peritoneal Cancer
PPS	Post-progression Survival
PR	Partial Response
PRO	Patient-reported Outcome
PTT	Partial Thromboplastin Time
Q2W	Every 2 weeks

Q3W	Every 3 weeks
QLQ-C30	Quality-of-life Questionnaire for Cancer
QLQ-HCC18	HCC disease-specific module
QoL	Quality of Life
RBC	Red Blood Cell
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RF	Role Functioning
SAP	Statistical Analysis Plan also Safety Analysis Population
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Stable Disease
SIRT	Selective Internal Radiation Therapy
SITC	Society for Immunotherapy of Cancer
T3	Free Triiodothyronine
T4	Free Tyroxine
TNF-α	Tumor Necrosis Factor-alpha
TSH	Thyroid Stimulating Hormone
TTD	Time To Deterioration
TTE	TransThoracic Echocardiogram
TTP	Time To Progression
UC	Urothelial Carcinoma
UL	Upper Limit
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
VTE	Venous Thromboembolism
WBC	White Blood Cell

1. BACKGROUND

1.1 BACKGROUND ON HEPATOCELLULAR CARCINOMA

Liver cancer is the fifth most common cancer, accounting for 7% of all cancers, and the second most frequent cause of cancer-related death globally, with 854,000 new cases and 810,000 deaths per year. Hepatocellular carcinoma (HCC) represents approximately 90% of primary liver cancers and thus represents a significant global public health issue. On the basis of annual projections, the World Health Organization estimates that in excess of 1 million people will die from liver cancer in 2030 (Villanueva 2019).

The majority of HCCs occur in patients with underlying liver disease, mostly as a result of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or alcohol abuse. HBV infection accounts for the majority of HCC cases worldwide; however, in Western countries and Japan, HCV is the main cause of HCC (Villanueva 2019). Universal HBV vaccination and wide implementation of direct-acting antiviral agents against HCV are likely to change the etiologic landscape of HCC. However, the incidence of non-alcoholic fatty liver disease (NAFLD), which is a risk factor for HCC, is increasing worldwide and NAFLD will soon become a leading cause of liver cancer in Western countries (Villanueva 2019).

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% to 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 multikinase inhibitor, was first approved in 2007 by the U.S. 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 two 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 overall survival (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 (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 aetiology and supportive care (Llovet et al. 2008; Cheng et al. 2009).

Despite the survival benefit reported from these two 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, diarrhoea, hypertension, weight loss, fatigue, anorexia, alopecia, nausea, and rash/desquamation. Drug-related adverse events reported were predominantly Grade 1 or 2 in severity. 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 two 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, frontline 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) (Kudo et al. 2018) in phase III non-inferiority REFLECT trial. In addition, lenvatinib showed statistically significant superiority compared to sorafenib in terms of PFS, TTP, and ORR, as determined by the local investigator tumor assessments per mRECIST. Of note, patients with ≥50% liver involvement, clear invasion of the bile duct, or main portal vein invasion were excluded from the trial. Lenvatinib had a generally manageable tolerability profile, with the most common treatment-emergent adverse events being hypertension, diarrhoea, decreased appetite and decreased weight. The REFLECT led to approval of lenvatinib in Japan, the US (July 2018) and EU (October 2018) However, 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 programmed death-ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

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

In EMA countries, 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. In May 2020 and in November 2020, atezolizumab in combination with bevacizumab was approved by the U.S. Food and Drug Administration (FDA) and by European Medicine Agency (EMA) respectively for the treatment of unresectable or metastatic HCC in patients who have not received prior systemic therapy.

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 a 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 monotherapy.

To date, atezolizumab as single agent has shown minimal activity in the treatment of HCC patients 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, oesophageal 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 cut-off 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 cut-off 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 investigator per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1). Four patients (33.3%) had stable disease (SD) < 24 weeks. No patients had SD ≥ 24 weeks. Median progression-

free survival (PFS) per investigator assessment per RECIST v1.1 was 2.3 (95% CI: 1.3, 3.4) months and median OS was 5.3 (95% CI: 2.4, NE) months.

Study YO29233

Study YO29233 is a Phase I, open-label, multicenter study evaluating the pharmacokinetics, safety, and preliminary anti-tumor activity of atezolizumab as monotherapy in Chinese patients with locally advanced or metastatic gastric cancer, nasopharyngeal carcinoma, oesophageal 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 cut-off date of 1 April 2018, 21 patients with HCC had received atezolizumab monotherapy. At the time of the clinical cut-off date, 7 patients remained on treatment (3 first-line HCC patients), 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 a best response of SD. Median PFS was 2.8 months (95% CI: 1.4, 7.8 months) 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 monotherapy.

Overall, bevacizumab as a single agent demonstrated minimal activity in HCC, and is unlikely to demonstrate a meaningful clinical benefit over 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 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 centre, 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, 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, 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 favourable 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 patents 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-centre, single-arm trial designed to evaluate the efficacy, safety, and potential biomarkers of 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 one dose of bevacizumab.

Among the 38 response-evaluable patients, six patients achieved a PR (ITT) objective response rate [ORR], 14%; 95% CI: 4%, 24%), 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 vascularised tumor, and that several proangiogenic 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 frequency of myeloid-derived suppressor cells, decrease production of suppressive cytokines, and lower expression of inhibitory checkpoints on CD8+ T cells in tumors (Roland et al. 2009; Voron et al. 2015).

Therefore, the immunomodulatory effect of bevacizumab is expected to increase CD8-positive T-cell recruitment and relieve intratumoral immunosuppression, thereby boosting the effects of atezolizumab.

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

The efficacy and safety of atezolizumab + bevacizumab combination therapy as first-line treatment of non-resectable or metastatic HCC is currently being assessed in two studies: GO30140 and YO40245 (IMbrave150).

Study GO30140

Study GO30140 is a Phase Ib, multicenter, open-label study of atezolizumab in combination with bevacizumab and/or chemotherapy as first-line therapy in patients with various metastatic cancers (Lee et al. 2020). Arms A and F of GO30140 were specific to unresectable or advanced HCC. Arm A was designed to evaluate the combination of atezolizumab + bevacizumab in 104 patients with locally advanced or metastatic HCC who have not received prior systemic therapy. Arm F was later added to the study to compare combination treatment with atezolizumab + bevacizumab to atezolizumab alone, in which 119 patients with locally advanced or metastatic HCC were randomized 1:1 to atezolizumab + bevacizumab or atezolizumab monotherapy. Results for Arm A and Arm F have been recently presented (Lee et al 2019).

Arm A

As of the clinical cut-off date of 14 June 2019, the efficacy data for Arm A showed clinically meaningful and durable objective responses. The confirmed objective response rate (ORR) based on Independent-Review Facility (IRF) assessment per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) was 35.6% (37 of 104 patients; Table 1). Among the 37 responders, 12 patients (11.5%) achieved a CR and the remaining 25 patients (24.0%) achieved a PR. Median DOR was not reached at the time of this analysis.

Arm F

At the same clinical cut-off date of 14 June 2019, Arm F met its primary efficacy endpoint by demonstrating a statistically significant and clinically meaningful improvement in progression-free survival (PFS) with the combination compared to atezolizumab monotherapy.

Median PFS for the combination was 5.6 months compared to 3.4 months for the monotherapy resulting in a HR of 0.55 and a stratified p-value of 0.0108 (Table 1).

These results demonstrate the need for combination therapy rather than checkpoint inhibition alone to effectively increase progression free survival in patients with HCC.

Table 1 Study GO30140: Overall Efficacy Summary

Arm	Median Duration of Follow-Up	Key Efficacy Endpoint
Arm A	12.4 m	ORR (95% CI): 35.6% (26.4-45.6%) Median DOR: Not reached with 76% ongoing responders
Arm F	6.6 m	Median PFS: 5.6 m (Atezo - Bev) vs. 3.4 m (Atezo) Stratified HR (80% CI): 0.55 (0.40-0.74) Stratified p-value: 0.0108

Abbreviations: Atezo = atezolizumab; Bev = bevacizumab; DOR = duration of response; HR = hazard ratio; m = month; ORR = objective response rate; PFS = progression-free survival.

The combination of atezolizumab + bevacizumab was generally 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. The most common adverse events were proteinuria, decreased appetite, fatigue, pyrexia, and rash.

Study YO40245 (IMbrave150)

Study YO40245 (IMbrave150) is a Phase III, multicenter, randomized, open-label study designed to evaluate the efficacy and safety of atezolizumab + bevacizumab versus sorafenib in patients with advanced or metastatic HCC who have received no prior systemic treatment (Cheng et al. 2019; Finn et al. 2020). The study enrolled 501 patients randomized in a 2:1 ratio to one of the following treatment arms:

- Arm A (experimental arm): atezolizumab 1200 mg IV every 3 weeks (Q3W) + bevacizumab 15 mg/kg IV Q3W (336 patients)

- Arm B (control arm): sorafenib 400 mg by mouth, twice per day, continuously (165 patients)

The co-primary efficacy endpoints were OS and IRF-assessed PFS by RECIST v1.1.

The last patient was enrolled in April 2019. Based on a clinical cut-off date of 29 August 2019, the primary analysis of Study YO40245 demonstrated statistically significant and clinically meaningful improvements with atezolizumab + bevacizumab compared with sorafenib in the co-primary endpoints of OS and IRF-assessed PFS per RECIST v1.1 in the ITT population (Table 2) (Cheng et al. 2019).

- The co-primary endpoint of OS demonstrated a statistically significant and clinically meaningful improvement for atezolizumab + bevacizumab over sorafenib. The observed OS translated into a reduction in the risk of death by 42% in the atezolizumab

+ bevacizumab arm compared with sorafenib (HR = 0.58 [95% CI: 0.42, 0.79], p = 0.0006, median OS: NE vs. 13.24 months).

OS benefits were generally consistent across predefined subgroups.

- The co-primary endpoint of IRF-assessed PFS per RECIST v1.1 demonstrated a statistically significant and clinically meaningful improvement for atezolizumab + bevacizumab over sorafenib (HR = 0.59 [95% CI: 0.47, 0.76]; p = 0.0001; median PFS: 6.83 vs. 4.27 months).

  These PFS benefits were generally consistent across predefined subgroups.

Similar to Study GO30140, the safety of the combination was consistent with the known safety profile of each agent and no new safety signals were identified.

Table 2 Study YO40245: Overall Efficacy Summary

Co-primary Efficacy Endpoints	Median Duration of Follow-up		Sorafenib (n = 165)	Atezo + Bev (n = 336)
OS	8.6 months	Median (months) (95% CI)	13.2 (10.4, NE)	NE
		Stratified HR (95% CI)	0.58 (0.42, 0.79)	
		Stratified log-rank p-value	0.0006	
IRF-PFS	8.6 months	Median (months) (95% CI)	4.3 (4.0-5.6)	6.8 (5.7-8.3)
		Stratified HR (95% CI)	0.59 (0.47-0.76)	
		Stratified log-rank p-value	<0.0001	

Abbreviations: Atezo = atezolizumab; Bev = bevacizumab; HR = hazard ratio; IRF = Independent Review Facility; NE = Not Estimable; OS = Overall Survival; PFS = progression-free survival.

At a clinical cutoff on 31 August 2020, after 12 months of additional follow up from the primary analysis (median follow up 15.6 months), an updated OS analysis was reported. This descriptive analysis shows a median OS of 19.2 months in atezo+bev arm vs 13.4 months in sorafenib arm; HR = 0.66 (95% CI: 0.52, 0.85), confirming the significant and consistent clinical benefit of atezo+bev observed in the primary analysis. (*Cheng J of Hepatology 2022*).

1.6.3 Benefit-risk Assessment

Atezolizumab has been combined with bevacizumab in patients with a range of different tumor types in Phase I-III studies. Overall, the adverse events observed with atezolizumab in combination with bevacizumab are consistent with the known risks of each individual study treatment across tumor types including HCC (Socinski et al. 2018; Rini et al. 2019).

This trial will enroll patients with locally advanced or metastatic HCC who have received no prior systemic treatment. Given the poor prognosis and limited treatment options for these patients, this population is considered amenable for treatment with combined PD-L1 and VEGF antagonists.

The benefit-risk profile for atezolizumab in combination with bevacizumab in this patient population is expected to be favourable.

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

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

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

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

Given the mechanism of action for atezolizumab and bevacizumab, immune-mediated adverse events are potential overlapping toxicities associated with combination use of these two agents.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may

positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy of Cancer [SITC] 2020).

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

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

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

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety and efficacy of atezolizumab in combination with bevacizumab in patients with unresectable HCC who have received no prior systemic treatment.

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

Specific objectives and corresponding endpoints for the study are outlined below.

2.1 PRIMARY OBJECTIVE

The primary objective of the study is to evaluate the safety of atezolizumab + bevacizumab in terms of bleeding/haemorrhage on the basis of the following endpoint:

- Incidence of Grade 3-5 NCI CTCAE v.5 bleeding/haemorrhage

2.2 SECONDARY OBJECTIVES

2.2.1 Main Secondary Objective

The main secondary objective of the study is to evaluate the efficacy of atezolizumab + bevacizumab on the basis of the following endpoint:

- Overall survival (OS), defined as the time from initiation of study treatment to death from any cause

2.2.2 Other Secondary Objectives

The other secondary objectives of the study are:

1) To further evaluate the safety of atezolizumab + bevacizumab on the basis of the following endpoints:

   - Incidence and severity of adverse events (AEs), with severity determined according to NCI CTCAE v5.0
   - Vital signs
   - Clinical laboratory test results

2) To further evaluate the efficacy of atezolizumab + bevacizumab on the basis of the following endpoints:

   - Progression-free survival (PFS), defined as the time from initiation of study treatment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
   - Objective response rate (ORR), defined as a complete or partial response, as determined by the investigator according to RECIST v1.1
   - Time to progression (TTP), defined as the time from initiation of study treatment to the first occurrence of disease progression, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
   - Duration of response (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

- Post-progression survival (PPS), defined as the time from the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 to death from any cause

3) To evaluate Patient Reported Outcomes (PROs) and to describe the patient's experience while receiving atezolizumab + bevacizumab on the basis of the following endpoint:

- Patient self-reported symptomatic AEs using National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

2.3 EXPLORATORY OBJECTIVES

2.3.1 Exploratory Efficacy Objectives

The exploratory efficacy objectives of the study are:

1) To evaluate whether the patterns of tumor progression (growth versus new lesion, intrahepatic versus extrahepatic) have a different impact on overall survival (OS) and PPS on the basis of the following endpoints:

- OS and PPS based on the following patterns of progression:
  - >20% increase in tumor size against a known baseline lesion (intrahepatic growth [IHG] or extrahepatic growth [EHG])
  - new intrahepatic lesion (NIH)
  - new extrahepatic lesion (NEH) and/or vascular invasion

2) To evaluate if post-study treatments have impact on OS on the basis of the following endpoints:

- Number/Rate of patients starting second or further lines of treatment
- OS based on type and duration of each post-study treatments

3) To evaluate if reason of treatment withdrawal has impact on OS on the basis of the following endpoint:

- OS based on the following reasons of treatment withdrawal:
  - Progressive disease (PD) vs adverse event (AE) vs deteriorating liver function/clinical conditions

2.3.2 Exploratory Biomarker Objective

The exploratory biomarker objective of the study is:

- Gut Microbiome evaluation on the basis of the following endpoint:
  - Relationship between the compositional and functional structure of the gut microbiome and antitumour responses following atezolizumab and bevacizumab

2.3.3 Exploratory Economic Objectives

The exploratory economic objectives of the study are:

1) To identify, quantify and valuate health care resources consumed for managing Grade 3 and 4 AEs related to the administration of atezolizumab + bevacizumab on the basis of the following endpoint:
   - Relationship between AEs and health care resource consumption
2) To assess the cost for managing adverse events related to the administration of atezolizumab + bevacizumab on the basis of the following endpoint:
   - Cost description of health care resources consumed for managing Grade 3 and 4 AEs related to the administration of atezolizumab + bevacizumab

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase IIIb, one arm, multicenter, open - label study designed to evaluate the safety and efficacy of atezolizumab + bevacizumab in patients with unresectable HCC who have not received prior systemic treatment.

This study will enroll a sample of convenience (Lohr 2010) of approximately 150 patients in one arm of treatment:

- Atezolizumab 1200 mg IV infusions Q3W (dosed in 3-week cycles) + bevacizumab 15 mg/kg Q3W (dosed in 3-week cycles)

Patients treated with atezolizumab + bevacizumab arm who transiently discontinue or withdraw from 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 discontinue or withdraw from bevacizumab for adverse effects may continue atezolizumab monotherapy and vice versa).

Patients will receive atezolizumab and/or bevacizumab 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 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) 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 or brain metastases) that cannot be managed by protocol-allowed medical interventions.

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, Version 5.0 (NCI CTCAE v5.0). Laboratory safety assessments will include the regular monitoring of haematology and blood chemistry.

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) or until 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.

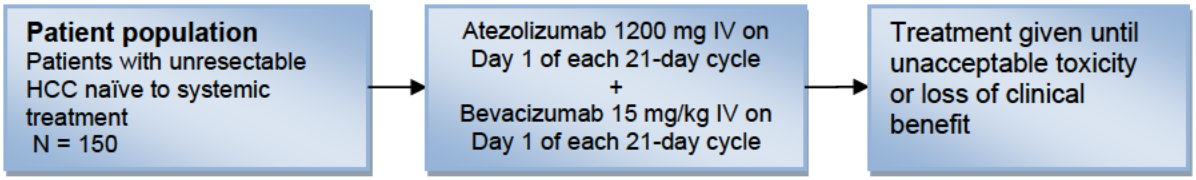
Following disease progression, patients will be followed for survival and subsequent anti-cancer therapies until death, loss to follow-up, withdrawal of consent, or study termination by Sponsor, whichever occurs first.

Patients' samples of faeces, will be collected for exploratory biomarker assessments.

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

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

Figure 1 Study Schema



3.1.2 Independent Data Monitoring Committee

Not applicable. An independent Data Monitoring Committee (iDMC) has been considered as not necessary for this study.

3.2 END OF STUDY AND LENGTH OF STUDY

End of Study

The end of study will occur when all enrolled patients have either died, withdrawn consent, are lost to follow up, or have been followed for 36 months since the last study patient is enrolled, whichever occurs first.

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

Length of Study

The total length of the study, from screening of the first patient to the end of the study is approximately 4 years (12 months enrolment).

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 an approved dosage for atezolizumab, as outlined in the prescribing information. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no DLTs were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

More over both the above-mentioned dose and schedule of atezolizumab in combination with bevacizumab were indicated as generally safe and well tolerated by the results of GO30140 (Lee et al. 2020) and YO40245 (IMbrave150) (Cheng et al. 2019 *Finn et al.*

2021) trials. In addition, no new safety signals related to the combination therapy were identified beyond the established safety profile for each individual agent

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 (Avastin® local labels).

This dose schedule aligns with the atezolizumab dose schedule highlighted above as the dose used in combination with atezolizumab in Study GO30140 and YO40245 (IMbrave150).

3.3.3 Rationale for Patient Population

This study will enroll patients with unresectable HCC who have not received prior systemic treatment. Given the poor prognosis and limited treatment options for these patients, this population is considered amenable for treatment with combined PD-L1 and VEGF antagonists.

The broad patient population selected is similar to that enrolled in Study GO30140, the initial study testing this combination in first-line HCC patients.

Although sorafenib and lenvatinib are approved for the first-line treatment of patients with advanced HCC, the prognosis of these patients remains poor with a median OS reported of 10.7 – 14.7 months for sorafenib (Llovet et al. 2008; Yau et al. 2019) and 13.6 months for lenvatinib (Kudo et al. 2018) .

Therefore, there is a continuing need for more efficacious, better tolerated treatments for the first line treatment of patients with unresectable HCC.

3.3.4 Rationale for Control Group

Not applicable.

3.3.5 Rationale for Open-Label Study

The primary objective of this study is to assess the safety profile of atezolizumab + bevacizumab in a non-comparative fashion. Thus, as all patients are pre-specified to receive active treatment, the study will have an open-label and non-randomized design.

3.3.6 Rationale for Primary Safety Endpoint

In this study, the primary safety end-point is incidence of Grade 3-5 NCI CTCAE v.5 bleeding/haemorrhage.

Bevacizumab use has been associated with an increase in the risk of bleeding. Although bleeding events involved typically minor epistaxis and other self-limited mucosal bleeding, severe (Grade ≥3) bleeding events have also been reported in clinical trials across all

indications (*Leighl et al. 2011*). In patients treated with bevacizumab, the overall incidence of Grade 3–5 bleeding reactions ranged from 0.4–6.9% (European Medicines Agency 2017 *SmPC Avastin* *https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf*. There were initial concerns regarding the bleeding toxicity in evaluating the treatment of bevacizumab in advanced HCC, due to the concomitant presence in these patients of cirrhosis, and consecutively portal hypertension, oesophageal varices, thrombocytopenia, and coagulopathy. Of note upper gastrointestinal bleeding is a common and severe complication in patients with HCC. In this setting the drug has been studied both as monotherapy, as well as in combination with the epidermal growth factor receptor inhibitor erlotinib and with cytotoxic chemotherapy (Siegel et al. 2008, Boige et al. 2012, Zhu et al. 2006, Thomas et al. 2009, Hsu et al. 2010, Sun et al. 2011, Kaseb et al. 2012, Yau et al. 2012). Most trials have been small, Phase II trials; bevacizumab was given at dose of 5 mg/kg or 10 mg/kg every 2 weeks, or 7.5 mg/kg every 3 weeks. The treatment seemed to be fairly well tolerated. Notably, bleeding/haemorrhage Grade 3-5 incidence was reported up to 11% of patients and instances of gastro-intestinal (GI) bleeding were seen in 5-9% of patients (Frenette et al. 2012). The cause of GI bleeding was typically esophageal varices and/or portal hypertension. One important learning from these studies is that esophageal varices must be assessed by upper GI endoscopy and treated as primary prophylaxis with either propranolol or banding in all patients with significant varices before starting treatment with bevacizumab. This was a requirement in the studies included in clinical development of atezolizumab + bevacizumab.

In the YO40245 (IMbrave150) phase III trial (Cheng et al. 2019), bleeding/haemorrhage ≥Grade 3 were considered as Adverse Events of Special Interest (AESI) for bevacizumab and collected up to 90 days after the end of treatment. In the study with a median treatment duration of bevacizumab 6.9 months (range 0-16 months), atezolizumab 7.4 months (range 0-16 months) and sorafenib 2.8 months (range 0-16) the bleeding/haemorrhage results were as follows (*Roche on file data; Finn et al, 2020*):

- a numerically lower proportion of patients experienced bleeding/hemorrhage in the sorafenib arm (17.3%) compared to the Atezo+Bev arm (25.2%)

- the AE of hemoptysis was reported with a higher incidence (≥ 2% difference) in the sorafenib arm, whereas the AEs of epistaxis, hematuria, gingival bleeding, and esophageal varices hemorrhage were reported with a higher incidence (≥ 2% difference) in the Atezo+Bev arm)

- the majority of bleeding/hemorrhage were of Grade 1-2 intensity

- the proportion of patients experiencing Grade 3-4 bleeding (5.7% [sorafenib] vs 6.4% [Atezo+Bev] was comparable between the two treatments arms (mainly gastrointestinal and upper gastrointestinal/varices esophageal bleeding events

were reported). One Grade 3-4 bleeding event (gastrointestinal haemorrhage) was assessed as related to Bev and 3 events (1 gastrointestinal haemorrhage and 2 upper gastrointestinal haemorrhage events) were assessed as related to Atezo and Bev

- a similar proportion of patients in the sorafenib (7.7%) and Atezo+Bev arm (9.1%) had AESIs of bleeding/hemorrhage that were reported as serious (most frequent were gastrointestinal haemorrhage 1.9% vs. 2.4% [Atezo+Bev] and esophageal varices hemorrhage (0.6% vs 2.4 % [Atezo+Bev])

- one patient (0.6) in the sorafenib arm and 16 patients (4.9%) in the Atezo+Bev arm were withdrawn from study treatment due to AESI of bleeding/hemorrhage

- similar proportion of patients in sorafenib (3.8%) and Atezo arm (4.3%) had study treatment interruption/study modification due to AESIs of bleeding/haemorrhage

- a lower proportion of patients experienced Grade 5 AESIs of bleeding/hemorrhage in the sorafenib arm (1 patient, 0.6%) compared to the Atezo+Bev arm (5 patients, 1.5%). In the sorafenib arm one Grade 5 event of peritoneal haemorrhage was reported. In the Atezo+Bev arm, Grade 5 events of gastrointestinal hemorrhage, (3 patients with gastrointestinal bleeding, 0.9%), esophageal varices hemorrhage and subarachnoid hemorrhage (1 patient each, 0.3%) were reported. Of the 4 above reported events of upper gastrointestinal haemorrhage (3 gastrointestinal hemorrhage and one esophageal varices haemorrhage), three events were assessed as unrelated to atezolizumab and bevacizumab, but as related to the disease under study, and one event was assessed by the investigator as related to both atezolizumab and bevacizumab and also as related to the disease under study. The subarachnoid haemorrhage event was assessed as related to both bevacizumab and arterial hypertension.

As above reported, in YO40245 (IMbrave150), incidence of bleeding/haemorrhage Grade 3-5 was 7.9% (6.4% of Grade 3-4 and 1.5% of Grade 5) with collection up to 90 days after end of treatment as AESIs. Even if the results of the trial have shown that the incidence of bleeding/haemorrhage Grade 3-5 was consistent with the known safety profile of bevacizumab and no new safety signals were identified, additional information collected using this endpoint in the same patient population as the above study have the potential to reinforce the safety data already available, given the particular attention paid to bleeding/haemorrhage toxicity in this setting of patients.

At data cut off of august 31, 2020 , after a median follow up of 15.6 months , overall there were 6 grade 5 bleeding events in the atezolizumab plus bevacizumab arm (5 upper gastrointestinal bleeding events [3 gastrointestinal hemorrhage, 2 esophageal varices hemorrhage] and 1 subarachnoid hemorrhage) and 1 in the sorafenib arm (peritoneal

hemorrhage). Only 1 of the 5 upper gastrointestinal bleeding events in the combination arm, which occurred within 3 months of the first dose, was considered to be related to the study treatment by the investigator. All patients who had grade 5 upper gastrointestinal bleeding in the combination arm had macrovascular invasion; 3 had varices at baseline and 1 had hypertensive gastropathy. (Cheng J of Hepatology 2022).

3.3.7 Rationale for Atezolizumab + Bevacizumab Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response, partial response, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response has been termed pseudoprogression (Hales et al. 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed immune cells and no viable cancer cells. Therefore, this study will allow all patients to continue their treatment after apparent radiographic progression per RECIST v1.1, provided the benefit-risk ratio is judged to be favourable 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 3.1.1 for details).

3.3.8 Rationale for Gut Microbiome Evaluation

The microbiome is defined as the collective genomes of microbes within a community, whereas the term microbiota refers to the microbes themselves in aggregate.

The impact of the gut microbiota on response to immune checkpoint blockade was first studied in mouse models, with landmark publications in Science in 2015 demonstrating that the composition of the gut microbiota could influence the response to immune checkpoint inhibitors targeting the cytotoxic T lymphocyte antigen-4 (CTLA-4) and the programmed death receptor-1 (PD-1) (Vetizou et al. 2015, Sivan et al. 2015).

These studies were further supplemented by multiple studies demonstrating a role for the gut microbiota in patients on immune checkpoint blockade (Chaput et al., 2017, Frankel et al., 2017, Gopalakrishnan et al., 2018, Matson et al., 2018, Routy et al., 2018). In patients with non-small-cell lung cancer, renal cell carcinoma, or urothelial cancer, antibiotic use actually had a negative impact on response to immune checkpoint blockade. A different profile of the gut microbiota was associated with improved response to immune checkpoint therapy. Similarly, a so-called “favorable” profile of the gut microbiota has been suggested to play a role in the reduction of adverse side effects and the incidence of recurrence. The feasibility of manipulating the intestinal microbiota in order to influence

the response to therapy has recently been demonstrated in a mouse model (Routy et al., 2018). However, the studies available to date show some discrepancies in defining such a “favorable” profile, mainly related to differences in techniques and bioinformatics pipelines used to analyse samples, as well as to a series of host confounders, especially diet, lifestyle and other geographical influences.

In this study, the gut microbiome will be evaluated to detect a possible relashionship with the response to treatment. Specifically, we aim to reconstruct the temporal dynamics of the gut microbiota and identify possible microbial predictors, at a taxonomic and functional level, of long-term response vs. recurrence, as well as of the onset and severity of side effects.

3.3.9 Rationale for Non-standard Clinical Outcome Assessments

Cancer treatments, particularly combination therapies, can produce significant symptomatic adverse events. Recent research has shown that clinicians may underreport the incidence and severity of symptoms experienced by patients receiving treatment for cancer (Fromme et al. 2004; Trotti et al. 2007; Pakhomov et al. 2008; Basch 2010; Quinten et al. 2011; Atkinson et al. 2012; Basch et al. 2014). Collecting adverse event information directly from patients can provide a better understanding of treatment characteristics and their effects. In order to evaluate the tolerability of atezolizumab in combination with bevacizumab in HCC, patients will be asked to report on their experience related to atezolizumab in combination with bevacizumab treatment-related symptoms selected from the validated PRO-CTCAE item bank (see Appendix 7). These symptoms were identified as being salient to patients' experience with current treatment on the basis of preliminary safety data, drug class, mode of administration, mechanism of action.

4. MATERIALS AND METHODS

4.1 PATIENTS

A sample of convenience (Lohr 2010) of approximately 150 patients with unresectable HCC who have not received prior systemic treatment will be enrolled in *21* Italian sites.

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 Informed Consent Form;
- Ability to comply with the study protocol, in the investigator's judgment;
- Unresectable HCC with diagnosis confirmed by histology , with a biopsy within 6 months from recruitment;

- 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;
- At least one 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, SIRT 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 version 1.1;
- ECOG Performance Status of 0 or 1 within 7 days prior to recruitment;
- Child-Pugh class A within 7 days prior to recruitment;
- 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 provided they had no active varices or varices at risk of bleeding;
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 7 days prior to recruitment, 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);
  - PLT count $\geq 75 \times 10^9$/L (75,000/μL) without transfusion;
  - Haemoglobin $\geq$ 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);
  - Total 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 and aPTT *or PTT* ≤ 1.5 x ULN;

- Urine dipstick for proteinuria < 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 (or an alternative method such as protein:creatinine ratio, per local guidance) 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 with the following exception: patients with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count ≥ 200 µL, and have an undetectable viral load;

- In patients with viral HCC, documented virology status of hepatitis, as confirmed by screening HBV and HCV serology test;

- For patients with active hepatitis B virus (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, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year while they are receiving atezolizumab and bevacizumab and for 5 months after the final dose of atezolizumab and for 6 months after the final dose of bevacizumab. Women must refrain from donating eggs during the same period. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and *is not permanently infertile due to surgery* (removal of ovaries, *fallopian tubes* and/or uterus) *or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential.*

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. 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 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.

4.1.2 Exclusion Criteria

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

- History of leptomeningeal disease or brain metastases;

- 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 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 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) or patients receiving Rifaximin as prevention of encephalopathy are eligible for the study.

  Antibiotics administered within 30 days prior to initiation of study treatment have to be recorded in eCRF.

- 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;

- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within at least 5 months after the last dose of atezolizumab and 6 months after the last dose of bevacizumab;

  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 oesophageal and/or gastric varices with bleeding or high-risk for bleeding;

- A prior bleeding event due to oesophageal and/or gastric varices within 6 months prior to initiation of study treatment;

- Clinically evident moderate or severe ascites;

- At least one clinically evident episode of encephalopathy in the past three months;
- Co-infection 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;
- Co-infection with HBV and hepatitis D viral infection;
- Symptomatic, untreated, or actively progressing central nervous system (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 haemorrhage or spinal cord haemorrhage;
  - Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord);
  - There is no evidence of interim progression between completion of CNS-directed therapy and initiation of study treatment;
  - The patient has not undergone stereotactic radiotherapy, 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.
  - If the patient is receiving anti-convulsivant therapy, the dose is considered stable;

  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 loco-regional therapy if appropriate prior to enrollment.

- Clinically significant 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;

- 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.

  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 haemoptysis (≥ 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 anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose;

  Prophylactic anticoagulation for the patency of venous access devices is allowed provided the activity of the agent results in an INR < 1.5 × ULN and aPTT *or PTT* is within normal limits within 14 days prior to initiation of study treatment.

  Prophylactic use of low-molecular-weight heparin (i.e., enoxaparin 40 mg/day) is allowed. However, the use of direct oral anticoagulant therapies such as dabigatran (Pradaxa®) and rivaroxaban (Xarelto®) is not recommended due to bleeding risk. Benefits and risks should be assessed and caution exercised for use of direct oral anticoagulants. The investigator should consider switching to other approved anticoagulants due to the risk of upper gastrointestinal (GI) bleeding in patients with HCC.

- 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 GI fistula, 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 clinically significant intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including but not limited to complicated 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, SIRT 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 non-steroidal 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 AND BLINDING

4.2.1 Treatment Assignment

This is an open-label study. After written informed consent has been obtained, the study site will obtain the patient's identification number from the eCRF.

4.2.2 Blinding

Not applicable.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMP) for this study are atezolizumab + bevacizumab.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Atezolizumab

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

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

4.3.1.2 Bevacizumab

Bevacizumab 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 bevacizumab (25 mg/mL). The vial contains approximately 4 mL or 16 mL of bevacizumab solution.

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

4.3.2 Study Treatment Dosage, Administration, and Compliance

Patients will receive treatment as outlined in Table 3 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).

Table 3 Study Treatment regimens

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	Atezolizumab 1200 mg IV on Day 1
	Bevacizumab 15 mg/kg IV on Day 1

Atezolizumab will be administered first followed by bevacizumab, with a minimum of 5 minutes between dosing.

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 is postponed for fewer than 3 days, the patient can resume the original schedule.

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

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

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

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 6 (Atezolizumab) and Appendix 5 (Bevacizumab).

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, local biopsy results (if available), and clinical status (see Section 3.1.1 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 4. Atezolizumab infusions will be administered per the instructions outlined in Table 4.

Table 4 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion.[a] • 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 *IRR* with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an *IRR*, or 60 (±15) minutes if the patient experienced an *IRR* with the previous infusion. • If the patient experienced an *IRR* with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion.

IRR = infusion-related reaction

[a]For patients with borderline blood pressure, repeated measurements can be used to obtain an average blood pressure

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 6.

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 3).

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 4.

Bevacizumab infusions will be administered per the instructions outlined in Table 5.

Table 5 Administration of First and Subsequent Bevacizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the bevacizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Bevacizumab should be infused over 90 (± 15) minutes. • Vital signs should be measured at the end of infusion and 2 (± 1) hour 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 *IRR* with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Bevacizumab should be infused over 60 (± 10) minutes if the previous infusion was tolerated without an *IRR*, or 90 (± 15) minutes if the patient experienced an *IRR* 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 measured at the end of infusion and 2 (± 1) hour after the infusion.

IRR = infusion-related reaction

Guidelines for dosage modification and treatment interruption or discontinuation because of toxicities are provided in Appendix 5.

4.3.3 Investigational Medicinal Product Handling and Accountability

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

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

accordance with the labelled storage conditions, with access limited to the investigator and authorized staff.

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

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

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

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 unresectable HCC;
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for unresectable 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:

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

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL 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 drug to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

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

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 4.1.1);
- Hormone-replacement therapy;
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section 4.4.3).
- Megestrol acetate administered as an appetite stimulant;
- Mineralocorticoids (e.g., fludrocortisone);
- Inhaled or low-dose 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;
- 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. Treatment with bevacizumab should be suspended during palliative radiotherapy.

- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

  - The patient has no evidence of progression or haemorrhage 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 three or fewer non-target lesions may still be eligible to continue study treatment after Medical Monitor approval has been obtained.

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

In general, investigators should manage a patient's care (including pre-existing conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnoea, 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). Refer to Appendix 4 for Guidelies on Anaphylaxis Precautions.

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.2.1 Corticosteroids, *Immunosuppressive Medications*, and TNF-α Inhibitors

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

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 6 for details).

4.4.2.2 Herbal Therapies

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

4.4.3 Prohibited Therapy

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

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy, radiotherapy to the brain 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 final dose of atezolizumab;

- Systemic immunostimulatory agents (including, but not limited to, IFNs and IL-2) are prohibited within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab;

- Current use of full dose anticoagulants, thrombolytic therapy at therapeutic doses, or anti-platelet therapy are prohibited.

  Local label recommended doses for prophylactic use of anticoagulants or thrombolytic therapies are allowed. Benefits and risks should be assessed and caution exercised for use of direct oral anticoagulants. Other approved anticoagulants should be considered due the risk of upper GI bleeding in patients with HCC.

  Low-dose aspirin (< 325 mg/day) is permitted. Co-administration 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 with atezolizumab only (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. All activities should 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 is postponed for fewer than 3 days, the patient can resume the original schedule.

After six complete cycles, one of three cycles may be delayed by 1 week (28 days instead of 21 days for one cycle) to allow for vacations/holidays. Following the delay, the next cycle visit must be 21 days from the previous Day 1 visit: two 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 detailed record of all patients screened to document eligibility or record reasons for screening failure, as applicable.

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

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition any previous therapies or procedures linked to esophageal varices (if applicable) such as non-cardioselective beta-blockers, banding, sclerosing injections etc. will be recorded at baseline. Finally, infectious disease and pharmacological history (episodes of diarrhea, gastroenteritis, pneumonia, urinary tract infections, antibiotic treatments received and with which drugs) starting from three months before enrolment will be recorded. Moreover 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, or patient contact by means of telephone, 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 *or* ethnicity.

4.5.3 Physical Examinations

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

cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified 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 blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Vital signs are to be measured before, during, and after infusions as outlined in Table 6, and at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

Table 6 Timing for Vital Sign Measurements for First and Subsequent Infusions

Drug	Timing for Vital Sign Measurements	
	First Infusion	Subsequent Infusions
Atezolizumab	• Within 60 minutes prior to the atezolizumab infusion • Record patient's vital signs during or after the infusion if clinically indicated.	• Within 60 minutes prior to the atezolizumab infusion • Record patient's vital signs during or after the infusion if clinically indicated
Bevacizumab	• 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, 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 3.1.1 for details). Thus, tumor

assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

All measurable and*/or* evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening, *so long as they meet criteria outlined below*.

4.5.5.1 Radiographic Assessments

Screening assessments must include CT scans with IV contrast (and oral contrast per site standard of care) or MRI scans of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen and pelvis should be performed. A CT scan with contrast or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

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

All post-baseline imaging assessments will include CT scans with IV contrast (and oral contrast per site standard of care) or MRI scans of the chest, abdomen, and pelvis; scans of the head will be included per local practice or as clinically indicated.

All measurable and*/or* evaluable lesions identified at baseline should be re-assessed at each subsequent tumor evaluation according to the schedule described above. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). *To facilitate evaluation of post-progression tumor changes while treatment is ongoing tumor assessments must be continued after disease progression per RECIST v1.1 for patients who receive treatment beyond progression.* This includes continued measurement of target lesions, evaluation of non-target lesions (including monitoring for further worsening of any non-target lesions that have shown unequivocal progression), and evaluation of any newly identified lesions (including measurements, if lesions are measurable) at all subsequent assessments.

The use of radiopharmaceutical products (e.g., 18F-FDG, Tc-99m, MIBG) and contrast agents (e.g., gadolinium-based or iodinated contrast media) in study imaging assessments will be consistent with standard/local practice, and will not involve a route of administration, dose, patient population, or any other factor that significantly increases the risk (or decreases the acceptability of the risk) to patients. The products employed in these procedures will be at the discretion of participating investigators, and shall be locally authorized or otherwise used in compliance with local regulations. The results of this study will not be used to support any new indication or change in labeling for these products.

4.5.5.2 *Response Evaluation*

Objective response will be determined by the Investigator *at specified timepoints* according to RECIST v1.1 (see Appendix 2). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

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

- Haematology: WBC count, RBC count, haemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells);
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), *serum troponin (at baseline, if considered standard of care/required per local clinical practice, and as clinically indicated during the study),* sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, and LDH;
- α-fetoprotein (AFP)
- Coagulation: INR, and aPTT *or PTT*;
- Thyroid function testing: thyroid-stimulating hormone (TSH), free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4);
- HIV serology: HIV-1 antibody;
- HBV serology: HBsAg, HBsAb, and total HBcAb, for all patients; HBV DNA for patients with negative HBsAg and HBsAb tests and a positive total HBcAb test;
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA;

- 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 post-menarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

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

The following samples will be stored locally, until shipment to a central laboratory (the Unit of Holobiont microbiome and microbiome engineering, Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy) identified by the Sponsor, for microbiome analysis:

- Faeces samples for exploratory research on potential biomarkers;

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

Faeces samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

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

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

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

4.5.7 Electrocardiograms

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

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

4.5.8 Clinical Outcome Assessments

Patient-reported outcome (PRO) instruments will be completed to more fully characterize the clinical profile of atezolizumab and bevacizumab. In addition, PRO instruments will enable the capture of each patient's direct experience with atezolizumab and bevacizumab.

PRO data will be collected through use of the following instruments: PRO-CTCAE.

4.5.9 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered at home on Day 15 of each Cycle (see schedule of activities in Appendix 1). *At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment.*

PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor in pre-printed booklets to enable the instrument to be administered in the correct order at each specified timepoint. The booklets will be labeled with the timepoint of administration.

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

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

Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

4.5.10 Description of Clinical Outcome Assessments Instruments

PRO-CTCAE

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

A subset of 14 symptoms deemed most applicable to the current treatments has been selected for this study (see Appendix 7). Symptoms have been selected on the basis of toxicities associated with the drug's class, mechanism of action, or mode of administration and toxicities reported with the drug in another indication.

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

Not apllicable.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (atezolizumab + bevacizumab) if any of the following criteria are met:

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

- Use of another non-protocol anti-cancer therapy;
- Pregnancy;
- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details).

If one component of study treatment (atezolizumab or bevacizumab) 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 ≤30 days after the final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments and PRO assessments as outlined in the schedule of activities (see Appendix 1).

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study).

Refer to the schedule of activities (see Appendix 1) for details on follow-up assessments to be performed for patients who permanently discontinue study treatment. If a patient requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

4.6.2 Patient Discontinuation from the Study

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

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

- Patient withdrawal of consent;

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

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. 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 Section 5.1.1 and Section 5.1.2).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab and bevacizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing patients who experience anticipated adverse events, including criteria for treatment interruption or discontinuation, are provided in Appendix 5 (bevacizumab) and Appendix 6 (atezolizumab). Refer to 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., American Society of Clinical Oncology or European Society for Medical Oncology).

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

5.1.1 Risks Associated with Atezolizumab

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

5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: gastrointestinal (GI) perforations, gall bladder perforation, bleeding/haemorrhage, pulmonary haemorrhage, arterial thromboembolic events (ATE), fistulae other than GI, wound-healing complications, hypertension, congestive heart failure (CHF), cardiac disorders (excluding CHF and ATE), neutropenia, infections, necrotizing fasciitis, thrombocytopenia, venous thromboembolic events, posterior reversible encephalopathy syndrome, pulmonary hypertension, ovarian failure, embryo fetal development disturbance, hypersensitivity reactions/infusion reactions, peripheral sensory neuropathy, osteonecrosis of the jaw, non mandibular osteonecrosis, thrombotic microangiopathy, and proteinuria.

Refer to Appendix 5 of the protocol and Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for Bevacizumab.

5.1.3 Risks Associated with Combination Use of Atezolizumab and Bevacizumab

The risk of overlapping toxicities between atezolizumab and bevacizumab is anticipated to be minimal. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., haemorrhage, 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 5 (bevacizumab) and Appendix 6 (atezolizumab) 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, refer to adverse event management guidelines in Appendix 5 (bevacizumab) and Appendix 6 (atezolizumab) 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 Section 5.3.5.9 and Section 5.3.5.10 for more information);
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline;
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment;
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

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

see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Systemic lupus erythematosus;
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH and MAS;
- Nephritis;
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis);
- Grade $\geq$2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis);
- Vasculitis
- Autoimmune haemolytic anaemia;
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- *Myelitis*
- *Facial paresis*

- Grade ≥3 hypertension
- Grade ≥3 proteinuria
- Any grade GI perforation, abscess, or fistula
- Grade ≥2 non-GI fistula or abscess
- Grade ≥3 wound-healing complication
- Hemorrhage
    - Any grade CNS bleeding
    - Grade ≥ 2 hemoptysis
    - Other Grade ≥ 3 hemorrhagic event
- Any ATE
- Grade ≥3 venous thromboembolic event
- Any grade posterior reversible encephalopathy syndrome
- Grade ≥3 CHF

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

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

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

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

Table 8 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

The health care resources consumed for managing all Grade 3 and Grade 4 AEs will be identified and quantified in a dedicated section of the Adverse Event eCRF.

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

5.3.5.1 Infusion-Related Reactions and Cytokine-Release Syndrome

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

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

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

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

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms;

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

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

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

5.3.5.8 Deaths

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

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 pre-existing 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 pre-existing 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 pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of unresectable Hepatocellular Carcinoma

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of HCC on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated 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 criteria. 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 pre-existing condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event.

- Hospitalization due solely to progression of the underlying cancer.

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

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

5.3.5.12 Cases of Accidental Overdose or Medication Error

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

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

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

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

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

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one

entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

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

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

Special situations and non serious AEs associated with special situations need to be reported on the Adverse Event eCRF within 30 calendar days after learning of the event

5.3.5.13 Patient-Reported Outcome Data

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

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

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

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

5.4.1 Medical Monitors and Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor:	[redacted]
Mobile Telephone No.:	[redacted]
Roche Medical Responsible:	[redacted]
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]

To ensure the safety of study patients, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

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

5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

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

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab or 6 months after the final dose of bevacizumab.

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

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should

be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the final dose of bevacizumab.

The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

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

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

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

During the adverse event reporting period (defined in Section 5.3.1), 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, with follow-up information on the infant collected according to procedures outlined in Section 5.4.3.

5.5.2 *Sponsor Follow-Up*

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the

investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

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

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

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

Drug	Document
Atezolizumab	Atezolizumab Investigator's Brochure
Bevacizumab	Bevacizumab Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

No hypothesis testing is intended, as the focus of the statistical analyses is on the precision of the obtained estimate of the incidence of this key safety parameter.

6.1 DETERMINATION OF SAMPLE SIZE

This study will enroll approximately a sample of convenience (Lohr 2010) of 150 patients across 21 Italian sites, possibly according to a competitive enrolment scheme (Kim et al. 2017).

According to the results of the YO40245 (IMbrave150) trial (Cheng et al. 2019), the incidence of Grade 3-5 bleeding events is 7.9% (that is, 6.4% incidence of Grade 3-4 bleeding events plus 1.5% incidence of Grade 5 bleeding events) during a 10.4 months timespan (that is, 7.4 months of median treatment duration plus 90 days or 3 months of follow-up).

Therefore, assuming a fixed rate with respect to time, the overall Grade 3-5 bleeding events rate (*r*) *per* month is (Miller and Homan 1984; Briggs et al. 2006):

$$r = -\frac{[\ln(1 - 0.079)]}{10.4}$$

or 0.007913, that, considering a convenience sample (Lohr 2010) of 150 patients and a 12-month lasting year (Wilkins 1990), can be converted into an annual probability (*one year p*) - or incidence - of Grade 3-5 bleeding events as follows (Miller and Homan 1984; Briggs et al. 2006):

$$one\ year\ p = [1 - \exp(-0.007913\text{x}12)]$$

or 0.090587.

According to this incidence point estimate and assuming no missing 1-year patient time and that each patient can experience only one Grade 3-5 bleeding event *per* year (that is, ruling out for sake of simplicity shared frailty issues, such as multiple occurrence of 3-5 bleeding events experienced by the same patient) (Therneau and Grambsch 2000), the expected number (#) of patients with Grade 3-5 bleeding event *per* year out of a convenience sample size (Lohr 2010) of 150 evaluable subjects can be calculated as follows:

$$\#\ of\ patients\ with\ bleeding\ events\ per\ year = (0.090587\text{x}150)$$

or about 14 patients with the event *per* year.

The achievable precision (width of 95% CI) for the incidence of Grade 3-5 bleeding events is illustrated separately (**Table 9**). The sample variance of the binomial distribution is conditional on its sample mean (Agresti 2002) and both these statistics enter the formula for calculating the standard error of the sample distribution of the mean (Agresti 2002). Therefore, given the same sample size, a low incidence of Grade 3-5 bleeding events leads to a small width of the 95% CI, whereas a higher incidence of Grade 3-5 bleeding events results in a wider 95% CI.

In order to investigate the precision of the point estimate for the incidence of Grade 3-5 bleeding events under different scenarios, the Clopper-Pearson method (Clopper and Pearson 1934; Agresti 2002; Fleiss et al. 2003) for calculating incidence binomial exact 95% CI has been applied (**Table 9**).

Table 9 Clopper-Pearson 95% CI for the Incidence of Grade 3-5 Bleeding Events, Based on 150 Evaluable Subjects

# Patients with events	Incidence (%)	Precision - CI Width (%)	LL 95% CI (%)	UL 95% CI (%)
0	0	2.43	0	2.43
1	0.67	3.65	0.02	3.67
2	1.33	4.57	0.16	4.73
3	2.00	5.32	0.41	5.73
4	2.67	5.96	0.73	6.69
5	3.33	6.52	1.09	7.61
6	4.00	7.02	1.48	8.50
7	4.67	7.48	1.90	9.38
8	5.33	7.90	2.33	10.23
9	6.00	8.30	2.78	11.08
10	6.67	8.67	3.24	11.91
11	7.33	9.03	3.71	12.74
12	8.00	9.36	4.20	13.56
13	8.67	9.66	4.70	14.36
14	9.33	9.96	5.20	15.16

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrolment, study drug administration, and discontinuation from the study will be summarized for the ITT population, defined as all recruited patients. The reasons for study drug discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized for the ITT population.

All safety analyses will be conducted in the SAP, defined as all enrolled patients who had at least one administration of atezolizumab +bevacizumab.

All efficacy analyses will be conducted on the ITT population.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity, and baseline disease characteristics, e.g., ECOG performance status) will be summarized using means,

standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate.

Missing values will be classified and managed using the methods outlined in Section 6.7.

6.4 SAFETY ANALYSES

The safety SAP consists of all enrolled patients who had at least one full or partial administration of atezolizumab + bevacizumab.

Primary analysis

The overall incidence of Grade 3-5 NCI CTCAE *v5.0* bleeding events will be calculated for the SAP, along with Clopper-Pearson (Clopper and Pearson 1934; Agresti 2002; Fleiss et al. 2003) 95% CI.

No hypothesis testing is intended, as the focus of the statistical analyses is on the precision of the obtained estimate of the incidence of this key safety parameter.

For the primary safety endpoint, that is overall Grade 3-5 bleeding events, in addition to the incidence of Grade 3-5 bleeding events, the annual and overall bleeding rate (BR) will be calculated as follows:

$$BR = \#events/PY$$

where #events is the total number of Grade 3-5 bleeding events (including multiple occurrences *per* patient), and PY is the total number of patient-years under observation. The BR point estimate will be provided along with 95% CI, assuming a Poisson distribution (Poisson 1837; Agresti 2001; Hilbe 2014) for the underlying number of related events.

Secondary analysis

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

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

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

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

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading

to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths with causes of death reported during the study will be summarized.

The following events occurring during or after the first dose of study treatment will be summarized by NCI CTCAE grade v5.0:

- All Adverse Events (AEs)
    - All severe AEs (Grade 3-4)
- All treatment related AEs;
    - All severe treatment-related AEs (Grade 3 -4)
- All serious AEs
    - All treatment-related serious AEs
- All immune-mediated AEs
    - All severe immune-mediated AEs (Grade 3-4)
- All adverse events leading to withdrawal from any component
- All adverse events leading to withdrawal from atezolizumab
- All adverse events leading to withdrawal from bevacizumab
- All Grade 5 AEs
    - All treatment related Grade 5 AE
- All adverse event of special interest (AESIs) of atezolizumab
    - All severe AESIs of atezolizumab (Grade 3-4)
- All adverse event of special interest (AESIs) of bevacizumab
    - All severe AESIs of atezolizumab (Grade 3-4)
- All adverse events leading to dose temporary interruption of any component
- All adverse events leading to dose temporary interruption of atezolizumab
- All adverse events leading to dose temporary interruption of bevacizumab

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

The following descriptive statistics on the selected items will be reported (Pagano and Gavreau 2000):

- Continuous and count variables:
  - ✓ location measures: mean and median;
  - ✓ dispersion measures: standard deviation and range;
- Categorical variables: absolute and relative frequencies.

Summary statistical tables including number of and patients with adverse events along with 95% CI assuming an underlying Poisson distribution (Poisson 1837; Agresti 2001; Hilbe 2014) as well as number absolute and relative frequencies of adverse events along with Clopper-Pearson 95% CI (Clopper and Pearson 1934; Agresti 2002; Fleiss et al. 2003) will be produced.

Additional analyses may be performed as indicated.

Missing values will be classified and managed using the methods outlined in Section 6.7.

According to its relevance to possible AEs experienced by patients on atezolizumab + bevacizumab, a subset of the about 80 items included in the Italian translation of the Item Library Version 1.0 of the NCI-PRO-CTCAE™ questionnaire (Appendix 7) (Smith et al. 2016; National Cancer Institute, 2017) will be selected by a working group composed of study investigators and patient advocates.

The following descriptive statistics on the selected items (possibly grouping in domains items that share common features) (Brazier et al.2017) of the Italian translation of the Item Library Version 1.0 of the NCI-PRO-CTCAE™ questionnaire version 1.0 of the NCI-PRO-CTCAE™ questionnaire will be reported (Pagano and Gavreau 2000):

- Ordinal count variables:
  - ✓ location measures: mean and median;
  - ✓ dispersion measures: standard deviation and range;
- Categorical variables: absolute and relative frequencies.

Missing data for items and patients will be summarized to improve results interpretation (National Cancer Institute, 2020).

6.5 EFFICACY ANALYSES

Efficacy analysis includes both secondary and exploratory objectives.

Analysis of main and other secondary endpoints

All baseline summaries and efficacy analyses will be based on the ITT analysis set defined as all recruited patients.

Time-dependent variables OS, PFS, TTP, Duration of Response (DOR) and PPS will be analyzed using Kaplan-Meier (K-M) methods (Kaplan and Meier 1958) and Greenwood's

formula (Greenwood 1926). Medians and the quartiles with 95% confidence interval (CI) will be derived from the K-M curves. K-M plots with a 95% CI for OS, PFS, DOR and PPS will be prepared.

ORR will simply be summarised. The ORR will be calculated as the percentage of patients who have a CR or PR before any evidence of progression. A 95% CI will be derived for the ORR using Wilson score intervals (CIs for a single proportion) (Wilson 1927).

Analysis of exploratory endpoints Following disease progression, patients will be followed to evaluate whether the patterns of tumor progression (growth versus new lesion, intrahepatic versus extrahepatic) have a different impact on OS and PPS. OS and PPS will be described based on the following patterns of progression:

- >20% increase in tumor size against a known baseline lesion (intrahepatic growth [IHG] or extrahepatic growth [EHG])

- new intrahepatic lesion (NIH)

- new extrahepatic lesion (NEH) and/or vascular invasion

To evaluate if post-study treatments have impact on OS following disease progression, patients will be followed-up for anti-cancer therapies and survival with a descriptive analysis. In details, number and rate of patients starting second or further lines of treatment will be described indicating time and duration of each post-study treatment. OS based on type and duration of each post-study treatments will be described.

To evaluate if reason of treatment withdrawal has impact on OS, OS based on the following reasons of treatment withdrawal will be described:

- Progressive disease (PD) vs adverse event (AE) vs deteriorating liver function/clinical conditions.

Missing values will be classified and managed using the methods outlined in Section 6.7.

6.6 BIOMARKER ANALYSES

For all fecal samples, the gut microbiota composition will be profiled by 16S rRNA gene-based next-generation sequencing, as previously described (Ayeni et al., 2018). Briefly, microbial DNA will be extracted from faeces and the 16S rRNA V3-V4 region will be sequenced on Illumina MiSeq platform. Bioinformatics analysis for alpha/beta diversity and taxonomic assignment will be carried out using the QIIME pipeline (Bolyen et al., 2019). To get species-level and functional insights, a subset of samples, selected based on 16S rDNA data, will be subjected to shotgun metagenomics on Illumina NextSeq. Sequenced metagenomes will be analysed by de novo assembling using available

software (e.g. Meta-Velvet) and ORF annotation using web servers (e.g. MG-RAST) against GenBank or KEGG database, and/or by direct read mapping on NCBI database, using bowtie2 or bwa algorithms (Rampelli et al., 2020). Viral and fungal components of the gut microbiome (i.e., the gut virome and mycobiome, respectively) will be searched as well, by using dedicated pipelines, such as ViromeScan (Rampelli et al., 2016) and HumanMycobiomeScan (Soverini et al., 2019). Publicly available microbiome sequencing data from healthy age/gender-matched subjects possibly from the same geographical location will be downloaded (e.g. from MG-RAST or NCBI SRA) and used for comparative purposes.

The effect of host variables (e.g. gender, age, BMI, dietary pattern, drugs use, etc.) on the gut microbiota will be modelled using regression analysis. Clusters of microbiota structures will be identified by hierarchical clustering and their co-occurrence/co-inhibition networks and temporal dynamics will be reconstructed. Correlations between microbial taxa/genes and host metadata will be sought by uni/multivariate methods, including simple correlation tests, dimension-reduction techniques and multivariate correlation methods. Machine-learning methods, including Random Forests, will be used to identify discriminating taxa/genes. All statistical analysis will be performed in R. P-values will be corrected for multiple comparisons using the Benjamini–Hochberg method when appropriate. A p-value ≤ 0.05 will be considered statistically significant.

Exploratory biomarker analyses will be performed in an effort to increase the understanding of HCC disease evolution under atezolizumab + bevacizumab treatment. PFS and OS will be analyzed using the methods outlined in Section 6.5. This may include appropriate multivariate analyses. Further details will be provided in the statistical analysis plan (SAP).

6.7 HEALTHECONOMIC ANALYSIS

The health care resources consumed for managing Grade 3 and 4 AE related to the administration of atezolizumab + bevacizumab by the sample of convenience (Lohr 2010) of approximately 150 patients enrolled in *21* Italian clinical sites will be prospectively identified and quantified, using the ITT analysis population.

Following the Italian National Health Service (INHS) viewpoint (Drummond et al. 2015), the abovementioned health care resources will be valued and detailed via a partial technique of economic evaluation of health care programmes (Drummond et al. 2015), named cost description (Drummond et al. 2015). Cost description describes the health care resources cost but neither takes their effects on patient's health state into account, nor informes any choice among different health care programmes (Drummond et al. 2015).

The cost description will focus on the following INHS-funded health care resources (Lazzaro et al. 2013; Lazzaro et al. 2018; Lazzaro et al. 2019):

- Laboratory tests;
- Diagnostic imaging;
- Instrumental tests;
- Drugs (posology; number of administrations *per diem*; length of treatment);
- Other medications (eg, oxygen therapy);
- Transfusions (RBC and/or PLTs);
- Specialist follow-up visits;
- Hospitalizations:
    - ✓ day-hospital setting (type of ward; number of accesses);
    - ✓ inward setting (type of ward; number of episodes; number of days per episode);
- Emergency room (number of admittances).

The cost description will be carried out via a three-step approach that encompasses (i) INHS-funded health care resources identification and (ii) quantification, followed by (iii) their valuation. INHS-funded health care resources consumed by patients for managing Grade 3 and Grade 4 AEs related to the administration of atezolizumab + bevacizumab will be identified and quantified via the Adverse Event eCRF.

INHS-funded health care resources valuation will be performed via multiplying by an item-specific unitary cost the volume of INHS-funded health care resources consumed by patients for managing Grade 3 and Grade 4 AEs related to the administration of atezolizumab + bevacizumab.

Since the cost description will follow the INHS standpoint:

- Drugs will be valued at consumer price (Lazzaro et al. 2019).
- For health care services that differ from drugs, INHS tariffs will be used to value health care resources consumed for managing Grade 3 and Grade 4 AEs related to the administration of atezolizumab + bevacizumab (Ministero della Salute, 2012; Conferenza Permanente per i Rapporti tra lo Stato le Regioni e le Province Autonome di Trento e Bolzano, 2019).

The monetary standards will be consistent with the delivery setting of each health care procedure (outpatient; day-hospital; inward).

It is expected that INHS-funded health care resources consumed by patients for managing Grade 3 and Grade 4 AEs related to the administration of atezolizumab + bevacizumab (visits, diagnostic imaging and tests) will be mostly valued as outpatient procedures via the Italian Ministry of Health tariffs in force for outpatient setting (Ministero della Salute 2012).

Had any of the abovementioned health care procedures been performed in day-hospital or inpatient setting, only the hotel cost for hospital stay (Conferenza Permanente per i Rapporti tra lo Stato le Regioni e le Province Autonome di Trento e Bolzano, 2019) will be added to the cost of the health care procedure itself calculated according to the Italian Ministry of Health tariffs in force for outpatient setting (Ministero della Salute 2012).

Emergency room admittance will be valued according to a dedicated INHS tariff (Ministero della Salute 2007).

As the reference literature on the economic evaluation of health care programmes (Drummond et al 2015) requires that the resource costing procedure refers to the same and, preferably, the most recent year (imposing a proper inflation rate, when necessary), all costs will be reported in € at 2020 values.The following descriptive statistics concerning INHS-funded health care resources consumption (type and volume) and valuation (cost) due to Grade 3 and 4 AEs related to the administration of atezolizumab + bevacizumab management will be reported (Pagano and Gavreau 2000):

- Continuous and count variables:
  - ✓ location measures: mean and median;
  - ✓ dispersion measures: standard deviation and range;
- Categorical variables: absolute and relative frequencies.

Both base case statistical analyses and cost description (Drummond et al. 2015) will be performed on all the evaluable patients included in the study database (Complete Case Analysis - CCA) (Little and Rubin 2002). If the CCA sample will prove to be too limited, an available case analysis (ACA) (Little and Rubin 2002) will replace CCA.

The frequency of missing data will be reported for all analyzed variables and patients.

Missing data will be diagnosed and classified according to their underlying missing mechanism (Missing Completely At Random - MCAR; Missing At Random - MAR; Missing Not At Random - MNAR) and pattern (monotonic; generalized; univariate) (Van Buuren et al. 1999; Little and Rubin 2002; Van Buuren 2018).

Missing data will be dealt with via one or more multiple imputation regression models and/or other statistical methods consistent with their underlying missing mechanism (Van Buuren et al. 1999; Little and Rubin 2002; Van Buuren 2018).

Therefore CCA (or ACA) and fully imputed descriptive statistics for quantitative non-monetary and quantitative monetary variables (Anthony and Young 2002) will be presented.

Non-parametric bootstrap method will be applied to INHS-funded health care sector-related costs data for calculating 95% CIs in CCA (or ACA) (Efron and Tibshirani 1993; Desgagné et al. 1998; Barber and Thompson 2000).

Statistical analyses will be supported by Stata/SE software v 16.0 (StataCorp LP, College Station, TX, USA).

In order to carry out the cost description and statistical analyses concerning the abovementioned INHS-funded health care resources consumed by patients for managing Grade 3 and Grade 4 AEs related to the administration of atezolizumab + bevacizumab, a dedicated excerpt of the original database will be provided by the Sponsor of the study.

6.8 EXPLORATORY ANALYSES OF PRO-CTCAE DATA

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

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

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

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

6.9 INTERIM ANALYSES

6.9.1 Planned Interim Analyses

An interim analysis of safety will be performed at the time of 50 recruited patients, estimated to occur at approximately 6 months after FPI. A second interim analysis will be performed when patients have completed a period of follow-up of approximately 10

months. This follow-up period corresponds to that reported in the published YO40245 (IMbrave150) trial (Cheng et al. 2019; Finn et al. NEJM 2021), which has been taken into consideration in the sample size calculation for this study with regard to the expected incidence of Grade 3-5 bleeding events. This second interim analysis will take into account all the efficacy and safety endpoints with descriptive purposes.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) 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 CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7~~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 Sponsor policy on study data publication (see Section 9.~~6~~5).

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

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9. ~~6~~5).

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor has implemented a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor identified potential risks associated with critical trial processes and data and implemented plans for evaluating and controlling these risks.

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Roche S.p.A, 20900 Monza, Italy.

The Sponsor will provide clinical operations management, data management, and medical monitoring.

Twenty-one sites in Italy will participate in the study to enroll approximately 150 patients. Screening and enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., biomarker analyses). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

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

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 Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

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

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

10. REFERENCES

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Appendix 1
Schedule of Activities

	Screening [b]		Treatment Phase (Q3W)	Treatment Discontinuation [c]	Survival Follow-Up
Assessment Window (Days) [a]	–28 to –1	–7 to –1	Day 1 of Each Cycle [a] *(± 3 days)*	≤ 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				
Infectious disease and pharmacological history (episodes of diarrhea, gastroenteritis, pneumonia, urinary tract infections, antibiotic treatments received and with which drugs) starting from three months before enrolment	x				
Complete physical examination [e]	x				
Limited physical examination [f]			x [g]	x	
Child-Pugh *score*	x				
ECOG Performance Status		x	x [g]	x	
Tumor assessment [h]	x		See footnote [h]	x	x
Vital signs [i]	x		x	x	
Weight	x		x [j]	x	
Height	x				
12-lead ECG [k]	x		Perform as clinically indicated		
EGD [l]	x				
Previous therapies or procedures linked to esophageal varices (if applicable) such	x				

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 [a] *(± 3 days)*	≤ 30 Days after Last Dose	
as non-cardioselective beta-blockers, banding, sclerosing injections etc.					
Haematology [m, y]		x	x [g]	x	
Serum chemistry [n, y]		x	x [g]	x	
HIV, HBV, HCV serology [o]	x				
Quantitative HBsAg, HBV DNA, HCV RNA [p]	x		x	x	
α-fetoprotein (AFP)	x		x	x	
Coagulation panel (aPTT or PTT, INR) [y]		x	x [g]	x	
Urinalysis [q, y]		x	x [g]	x	
TSH, free T3, free T4	x		Cycles 5, 9, 13, etc. (every 4 cycles)	x	
Pregnancy test		x [r]	x [s]	x	
Faeces for microbiome evaluation [z]	x		x [z]		
Concomitant medications [t]		x	x	x	
Adverse events [u]	x		x	x	*x*
Identification and quantification of health care resources consumed for managing Grade 3 and 4 AEs			x	x	
Study treatment infusion [v]			x		
PRO [w]			x		
Survival and anti-cancer therapy follow-up [x]					x

CT = computed tomography; EGD = esophagogastroduodenscopy; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PET = positron emission

tomography; PRO = patient-reported outcome; Q3W = every 3 weeks; 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] All visits and infusions 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 alcohol 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 and local laboratory assessments may be obtained ≤ 96 hours before Day 1 of each cycle.

[h] 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 performer during screening, then she should subsequently undergo CT performed using 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 using RECIST Version 1.1. 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. 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.

[j] 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.

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

[l] 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.

[m] Haematology consists of CBC, including RBC count, haemoglobin, 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.

[n] Serum chemistry includes bicarbonate or total carbon dioxide (if considered standard of care for the region), serum troponin (at baseline, if considered standard of care/required per local clinical practice, and as clinically indicated during the study), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, and LDH .

[o] All patients will be tested for HIV locally prior to the inclusion into the study and if not in contradiction with local legislation; patients with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count ≥200µL, and have an undetectable viral load. HBsAg, HBsAb, and total HBcAb 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 HBsAb tests and a total HBcAb.

[p] 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 locally. 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. If local quantitative HBsAg test is not available, a qualitative HBsAg followed by quantitative HBV DNA can be performed as an alternative.

[q] 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 (or protein creatinine ratio as an alternative per local guidance) and must demonstrate < 1 g of protein in 24 hours. 24 hour urine collection (or protein:creatinine ratio as an alternative per local guidance) should be done prior to bevacizumab administration according to the guidelines in Appendix 5.

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

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

[t] 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.

[u] 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 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 anti-cancer therapy, whichever occurs first.

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

. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, 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.

[v] 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 tollerate 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. 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.

[w] The NCI-CTCAE questionnaire (Appendix 7) will be completed by all patients on paper starting on Day 15 of each Cycle. All PRO questionnaires are scheduled for self-administration at home and are required to be completed by the patient, to avoid any potential bias to patients' responses to ensure that the validity of the instrument is not compromised. Interview assessment by a family member 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 and record responses in eCRF.

[x] 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.

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

[z] Faeces samples from 150 subjects will be collected in sterile containers (1-5 grams are sufficient), stored locally (preferably at -80°C), and then shipped to a central laboratory (the Unit of Holobiont microbiome and microbiome engineering, Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy) for analysis, where they will be stored at -80°C until processing. For each patient, faecal samples will be collected at screening, and at weeks 3, 6, 12, and 51 during treatment (within 3 days).

Appendix 2
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 *and* lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

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

Malignant Lymph Nodes

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

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

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with short axis ≥ 10 mm but <15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lungs, 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, positron emission tomography *(PET)* scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

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

Lesions with Prior Local Treatment:

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

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and not usually more than 4 weeks prior to the beginning of the treatment.

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

CLINICAL LESIONS

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

CHEST X-RAY

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

CT AND MRI SCANS

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

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without MRI 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 (with or without MRI IV contrast) 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, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new

lesions on a different modality, *because* the same lesion may appear to have a different size using a new modality.

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

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

ASSESSMENT OF TUMOR BURDEN

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

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

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

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

should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

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

CALCULATION OF SUM OF DIAMETERS

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

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, given that 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 *is* 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 *during* 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 *the* 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 *the* 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 "*unequivocal* 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 following criteria used to determine objective tumor response for target lesions are provided below:

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

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

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

CRITERIA FOR NON-TARGET LESIONS

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

- CR: Disappearance of all non-target lesions

  All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

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

NEW LESIONS

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

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

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it truly represents truly new disease. If repeat scans

confirm there is definitely a new lesion, progression should be declared *as of* 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

Target Lesions	*Non-Target Lesions*	*New Lesions*	*Timepoint Response*
CR	*CR*	*No*	*CR*
CR	*Non-CR/non-PD or NE*	*No*	*PR*
PR	*CR, non-CR/Non-PD, or NE*	*No*	*PR*
SD	*CR, non-CR/Non-PD, or NE*	*No*	*SD*
NE	*Non-PD*	*No*	*NE*
PD	*Any*	*Yes or no*	*PD*
Any	*PD*	*Yes or no*	*PD*
Any	*Any*	*Yes*	*PD*
CR	*NED* [b]	*No*	*CR*
PR	*NED* [b]	*No*	*PR*
SD	*NED* [b]	*No*	*SD*
NED [a]	*Non-CR/non-PD*	*No*	*Non-CR/non-PD*
NED [a]	*CR*	*No*	*CR*
NED [a]	*NE*	*No*	*NE*
NED [a]	*NED* [b]	*No*	*NED*

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

[a] *No target lesions identified at baseline*

[b] *No non-target lesions identified at baseline.*

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging *or* measurement is performed at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing

lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "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 treatment. 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.

Fluorodeoxyglucose (FDG)-PET is **not yet validated** for use in clinical trials to determine response but may complement CT/MRI in the assessment of progression.

FDG-PET imaging to identify new lesions is described in the following table.

Baseline FDG-PET	Post-Baseline FDG-PET	Determination
Negative FDG-PET	Positive FDG-PET	New lesion (PD)
None	Positive FDG-PET corresponds to a new site of disease confirmed by CT/MRI	New lesion (PD)
None	Positive FDG-PET not confirmed as a new site of disease on CT/MRI	Additional follow-up CT/MRI scans are needed to determine if there is truly progression occurring at that site. If so, new lesion (PD) with the date of PD being the date of the initial abnormal FDG-PET scan date If not, it is not a new lesion.
None	Positive FDG-PET that corresponds to a preexisting site of disease on CT/MRI that is not progressing on the basis of the anatomic images	Not a new lesion

CT = computed tomography; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography.

Note: A positive FDG-PET scan lesion indicates one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

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.

Schwartz LH., Litiére S, de Vries SE, et al. RECIST 1.1–update and clarification: from RECIST Committee. Eur J Cancer 2016; 62:132–7.

Appendix 3
Preexisting Autoimmune Diseases and Immune Deficiencies

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

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • *Autoimmune myelitis* • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome	• 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 *cholangitis* • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

• Crohn disease		

Appendix 4
Anaphylaxis Precautions

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

REQUIRED EQUIPMENT AND MEDICATION

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

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

PROCEDURES

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

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

Appendix 5
Guidelines for Management of Adverse Events Associated with Atezolizumab + Bevacizumab

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab.

However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit.

The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

MANAGEMENT GUIDELINES

Guidelines for management of patients who experience adverse events associated with atezolizumab and bevacizumab are provided in Appendix 6 (Tables 1-14) and Appendix 5 (Table 1), respectively.

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 6 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, *pericardial disorders,* pancreatic, dermatologic, neurologic, meningoencephalitis, renal, myositis, hemophagocytic lymphohistiocytosis).

Bevacizumab

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

Appendix 5: Guidelines for Management of Adverse Events Associated with Atezolizumab + Bevacizumab

Table 1 Guidelines for Management of Patients Who Experience Adverse Events Associated with Bevacizumab

Event	Action to Be Taken
General guidance for treatment delays and discontinuation	• When a treatment cycle is delayed because of a toxicity resulting from any component of the regimen, all study treatment should generally be withheld and resumed together to remain synchronized. • If one drug is discontinued, treatment with the other drug may be continued for patients experiencing clinical benefit as determined by the investigator after discussion with the Medical Monitor. • Permanently discontinue study treatment if an adverse event requires treatment to be withheld for >21 days.
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 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 intervention. • Bevacizumab may be restarted upon complete resolution of the event.

Appendix 5: Guidelines for Management of Adverse Events Associated with Atezolizumab + Bevacizumab

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 hypertensive 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 < 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 pre 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.
Arterial thromboembolic events	
Arterial thromboembolic event, any grade	• Discontinue bevacizumab.

Appendix 5: Guidelines for Management of Adverse Events Associated with Atezolizumab + Bevacizumab

Proteinuria	
Grade 1 (1 + proteinuria, urinary protein < 1.0 g/24 hr)	• Administer bevacizumab
Grade 2 (2 + proteinuria, urinary protein 1.0-3.4 g/24 hr)	• 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 hr. Resume bevacizumab when proteinuria is < 2 g/24 hr.
Grade 3 (urinary protein > 3.5 g/24 hr)	• Withhold bevacizumab. Resume bevacizumab when proteinuria is < 2 g/24 hr.
Proteinuria with diagnosis of nephritic syndrome	• Permanently discontinue bevacizumab.
Fistula	
Tracheoesophageal fistula, any grade	• Discontinue bevacizumab.
Fistula (non tracheoesophageal), 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/LPRS, any grade confirmed by MRI	• Discontinue bevacizumab.

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

[a] Follow guidelines of the treating institution.

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

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

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

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

- *The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections. In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.*

- *Consider withholding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5−1 mg/kg/day of prednisone or equivalent) may be administered.*

- *For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.*

- *Withhold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1−2 mg/kg/day oral prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.*

- *In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by*

*hormonereplacement therapy.*The investigator should consider the benefit–risk balance for a given patient prior to further administration of atezolizumab. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Guidelines for managing patients who experience selected adverse events are provided in the following sections. Management guidelines are presented by adverse event severity based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

PULMONARY EVENTS

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

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

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

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

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

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

Event	Management

BAL = bronchoscopic alveolar lavage. NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

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

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

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

HEPATIC EVENTS

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

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

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

Table 2 Management Guidelines for Hepatic Events

Event	Management
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. Events of > 5 days' duration: ● Consider initiating treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. ● If event resolves to baseline or to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to baseline or to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
AST or ALT increases to > 10 x ULN or total bilirubin increases to > 3 x ULN	● Permanently discontinue atezolizumab and contact the Medical Monitor. [c] ● Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. ● Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. ● If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to baseline, taper corticosteroids over ≥ 1 month.

LFT = liver function test; ULN = upper limit of normal.

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

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

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

GASTROINTESTINAL EVENTS

Management guidelines for diarrhoea or colitis are provided in Table 3.

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

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

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

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • If strong clinical suspicion for immune-mediated colitis, initiate empiric IV corticosteroids while waiting for definitive diagnosis. • Patient referral to GI specialist is recommended.For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent 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, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to GI specialist for evaluation and *confirmatory* biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal. NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

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

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

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table 4.

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

Table 4 Management Guidelines for Endocrine Events

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

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

Hyperthyroidism Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Refer patient to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hyperthyroidism.[c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone. NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

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

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

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grades 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone. NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

[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 assessment by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

Table 4 Management Guidelines for Endocrine Events (cont.)

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

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone. NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

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

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

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

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

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

NCI CTCAE v5.0 : National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

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

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

IMMUNE-MEDIATED CARDIAC EVENTS

In high-risk patients (including those with abnormal baseline cardiac troponin levels, when available), transthoracic echocardiogram (TTE) monitoring should be considered, as clinically indicated, and based on local clinical practice. Management guidelines for cardiac events are provided in Table 6.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., *troponin,* B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on immune-mediated pericardial disorders below) and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of pre-existing cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, *a TTE for evaluation of left ventricular injection fraction and global longitudinal strain,* and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate aetiology, should be treated according to the guidelines in Table 6.

IMMUNE-MEDIATED PERICARDIAL DISORDERS

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on *immune-mediated* myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer (e.g. metastatic disease), *cancer treatment (e.g.,* chest

radiotherapy), cardiac injury *(e.g. injury due to* myocardial infarction or iatrogenesis), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, *TTE*, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

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

Event	Management
Immune-mediated myocarditis, Grades 2-4 or Immune-mediated pericardial disorders, Grades 2–4	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider anti-arrhythmic drugs, temporary pacemaker, ECMO, VAD or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1g/kg/day IV methylprednisolone for 3-5 days and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 24 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device. NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, anti-pyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 7.

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

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

Event	Management
Grade 1[a] Fever[b] with or without constitutional symptoms	• Immediately interrupt infusion • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment,[c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2[a] Fever[b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen[d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment.[c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact the Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretic medications, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Medical Monitor.

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

Event	Management
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab and contact the Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact the Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

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

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: The management guidelines have been adapted from the NCCN guidelines for the management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v 5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

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

[c] Symptomatic treatment may include oral or IV antihistamines, anti-pyretic medications, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at $\leq$ 6 L/min, and high flow is defined as oxygen delivered at $>$ 6 L/min.

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator . The Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after *assessing* the benefit–risk ratio.

[f] Refer to Riegler et al. (2019).

PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate 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

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

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. [c]

GI = gastrointestinal. NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

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

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

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

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

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal. NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

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

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

DERMATOLOGIC EVENTS

The majority of cases of rash *reported with the use of atezolizumab* were mild in severity and self limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

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

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact 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

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

NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

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

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

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative aetiologies. *Myasthenia may be associated with myositis (see section on immune-mediated myositis) and patients should be managed accordingly.* Management guidelines for neurologic disorders are provided in Table 10, with specific guidelines for myelitis provided in Table 111.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab.Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • For general immune-mediated neuropathy: – If event resolves to Grade 1 or better, resume atezolizumab. [b] – If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] • For facial paresis: – *Initial observation OR initiate prednisone 1–2 mg/kg/day (if progressing from mild). Initiate treatment with gabapentin, pregabalin, or duloxetine, for pain.* – If event resolves fully, resume atezolizumab [b] – If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines *and proceed as per Guillain-Barré syndrome management..*
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day

	oral or IV prednisone. • *Consider IVIG or plasmapheresis in patients with rapid progression with development of bulbar and/or respiratory symptoms.* • *In life-threatening cases, consider IV methylprednisone 1 g/day for 3–5 days and consider other immunosuppressive agent.*

NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

IVIG = intravenous immunoglobulin.

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

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

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

Table 11 Management Guidelines for Immune-Mediated Myelitis

Event	Management
Immune-mediated myelitis, Grade 1	• Continue atezolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Investigate etiology and refer patient to neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated	• Permanently discontinue atezolizumab and contact the Medical Monitor.

myelitis, Grade 3 or 4	• Initiate *non-opioid* treatment *(e.g., pregabalin, gabapentin, duloxetine) for pain.* • *Hospitalize patient.* – *Initiate treatment with corticosteroids equivalent to 1 g/day IV methylprednisolone.* – *If event does not improve or there is worsening of symptoms within 3 days, consider IVIG or plasmapheresis and manage* as per institutional guidelines. • *Refer patient to neurologist.*

IVIG = intravenous immunoglobulin.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

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

Table 12 Management Guidelines for Immune-Mediated Meningoencephalitis

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

NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

RENAL EVENTS

Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including

prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in *Table 113*.

Table 113 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function *closely*, including creatinine and urine protein, until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

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

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

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

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase*/creatine phosphokinase* increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. *Patients may initially present with low grade nondescript symptoms including mild pain and weakness; thus, there should be a low threshold for suspicion of myositis.* Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis *(see section on immune-mediated myocarditis) and myasthenia gravis (bulbar symptoms such as dysphagia, dysphonia, and dyspnea; see section on neurologic disorders).*

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

Table 14 Management Guidelines for Immune-Mediated Myositis

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

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

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. • *Consider IVIG or plasmapheresis.* • If event does not improve within 24-48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. • For recurrent events, treat as a Grade 4 event. Permanently discontinue atezolizumab and contact the Medical Monitor.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • *Consider IVIG or plasmapheresis.* • If event does not improve within 24-48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE v5.0.

IVIG = intravenous immunoglobulin.

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

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

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

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever $\geq 38.5°C$
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected HLH should be treated according to the guidelines in *Table* .

Table 15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis

Event	Management
Suspected HLH	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact the Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH = hemophagocytic lymphohistiocytosis;.

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Appendix 7
NCI-PRO CTCAE ITEMS (Item Library Version 1.0)

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an in the one box that best describes your experiences over the past 7 days.

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

2.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost con-stantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost con-stantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

4.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost con-stantly

5.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost con-stantly
	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

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

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

8.	In the last 7 days, how OFTEN did you feel a POUNDING OR RACING HEARTBEAT (PALPITATIONS)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your POUNDING OR RACING HEARTBEAT (PALPITATIONS)? at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

9.	In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

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

11.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

12.	In the last 7 days, did you have any URINE COLOR CHANGE?	
	○ Yes	○ No

13.	In the last 7 days, how OFTEN did you have UNEXPECTED OR EXCESSIVE SWEATING DURING THE DAY OR NIGHTTIME (NOT RELATED TO HOT FLASHES/FLUSHES)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your UNEXPECTED OR EXCESSIVE SWEATING DURING THE DAY OR NIGHTTIME (NOT RELATED TO HOT FLASHES/FLUSHES) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

14.	In the last 7 days, how OFTEN did you have HOT FLASHES/FLUSHES?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HOT FLASHES/FLUSHES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

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