Official Title: A Phase IIIB, Single Arm, Multicenter Study of Atezolizumab in Combination with Bevacizumab to Investigate Safety and Efficacy in Spanish Patients with Unresectable or Unsuitable for Locoregional Treatments Hepatocellular Carcinoma Not Previously Treated with Systemic Therapy

NCT Number: NCT04732286

Document Date: Protocol Version 2: 16-March-2023

PROTOCOL

TITLE:	**A PHASE IIIB, SINGLE ARM, MULTICENTER STUDY OF ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB TO INVESTIGATE SAFETY AND EFFICACY IN SPANISH PATIENTS WITH UNRESECTABLE OR UNSUITABLE FOR LOCOREGIONAL TREATMENTS HEPATOCELLULAR CARCINOMA NOT PREVIOUSLY TREATED WITH SYSTEMIC THERAPY**
ACRONYM:	ATHECA study
PROTOCOL NUMBER:	ML42600
VERSION NUMBER:	2
EUDRACT NUMBER:	2020-005268-71
IND NUMBER:	Not applicable
NCT NUMBER:	NCT04732286
TEST PRODUCT:	Atezolizumab (RO5541267) Bevacizumab (RO4876646)
MEDICAL MONITOR:	[redacted]
SPONSOR:	Roche Farma S.A.
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL AMENDMENT APPROVAL

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PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol ML42600, Version 2, changes to the protocol Version 1, along with a rationale for each change, are summarized below:

- Language regarding Exploratory Efficacy, Exploratory Biomarker Analysis for Tissue and Blood biomarker Plan and Exploratory Radiomic Analysis Plan have been updated (Sections 2.2, 2.4, 3.1.1, 4.1.1 and Appendixes 1, 2 and 3).
- Language of exclusion criteria has been added to indicate that - Patients with vascular invasion of the portal or hepatic veins may be enrolled (4.1.2).
- Immunosuppressive medications have been removed from the prohibited therapy section (4.4.3) and added to the cautionary therapy section (4.2.2.1) to align with atezolizumab management guidelines in Appendix 10 that permit use of immunosuppressive medications for the treatment of corticosteroid-refractory immune-mediated adverse events.
- The list of identified risks for atezolizumab has been revised to include pericardial disorders, myelitis, and facial paresis (Section 5.1.2).
- Hemophagocytic lymphohistiocytosis has been updated from a potential risk to an identified risk associated with atezolizumab and language has been revised accordingly (Section 5.1.2).
- The list of adverse events of special interest has been revised to include myelitis and facial paresis (Section 5.2.3).
- Emergency Medical Contacts section have been updated (Section 5.4.1).
- Management of study quality has been modified. Establishment of quality tolerance limits has been deleted. (Section 9.3).
- Administrative structure from the Sponsor (Roche Farma S.A.) has been modified. (Section 9.5).
- Appendix 7 has been revised to indicate that 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 anticancer agent.
- Appendix 7 has been revised to include autoimmune myelitis and the term “primary biliary cirrhosis” has been replaced with “primary biliary cholangitis” as the term “primary biliary cirrhosis” is outdated in clinical practice.
- Management guidelines for Bevacizumab have been updated (Appendix 9).
- Risks and management guidelines for atezolizumab have been updated to align with the Atezolizumab Investigator’s Brochure Version 19 and addenda (Appendix 10).
- Amylase, lipase and α-fetoprotein have been added to section 4.5.6 and Appendix 1 (subtitle n)

Additional minor changes have been made to improve clarity and consistency.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IIIB, SINGLE ARM, MULTICENTER STUDY OF ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB TO INVESTIGATE SAFETY AND EFFICACY IN SPANISH PATIENTS WITH UNRESECTABLE OR UNSUITABLE FOR LOCOREGIONAL TREATMENTS HEPATOCELLULAR CARCINOMA NOT PREVIOUSLY TREATED WITH SYSTEMIC THERAPY**
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TEST PRODUCT:	Atezolizumab (RO5541267) Bevacizumab (RO4876646)
PHASE:	IIIb
INDICATION:	Hepatocellular carcinoma
SPONSOR:	Roche Farma S.A.

Objectives and Endpoints

This study will evaluate primarily the safety of Atezolizumab in combination with Bevacizumab in patients with unresectable hepatocellular carcinoma who have received no prior systemic treatment and are considered unsuitable for locoregional therapy, by assessing the incidence and severity of adverse events that lead to discontinuation of any study agent. In this protocol, "study treatment" refers to the combination of agents assigned to patients as part of this study (i.e., Atezolizumab and Bevacizumab). Efficacy of Atezolizumab in combination with Bevacizumab in this study, in contrast with IMbrave150 study, is considered within secondary and exploratory objectives.

Primary Objective	**Corresponding Endpoint**
To evaluate the safety of Atezolizumab + Bevacizumab	- Incidence and severity of adverse events of grade ≥ 3. that lead to discontinuation of Atezolizumab and/ or Bevacizumab.
Main Secondary Objective	**Corresponding Endpoint**
To evaluate the efficacy of Atezolizumab + Bevacizumab	**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	- Adverse Event severity will be determined according to NCI CTCAE v5.0 during patient's treatment. - Change from baseline in targeted Vital signs. - Change from baseline in targeted Clinical laboratory test results.
To further evaluate the efficacy of Atezolizumab + Bevacizumab	- **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, on two consecutive occasions ≥ 4 weeks apart, 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 criteria. - **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. - **Number/Rate of patients** starting second line treatment
To evaluate deterioration of Liver function during the treatment	- **Hepatic function assessed** according to the following parameter: o International normalized ratio (INR). o Presence or absence of Ascites and /or Hepatic Encephalopathy. o Albumin-Bilirubin (ALBI) assessment grades of 1 to 3.*

***** ALBI assessment grades 1 to 3 (Johnson et al. 2015) are based on calculated ALBI score (log10 bilirubin [µmol/L] × 0.66) + (albumin [g/L] × −0.0852) values as follows: ALBI score ≤ −2.60 = ALBI grade 1; > −2.60 to ≤ −1.39 =ALBI grade 2); and > −1.39 = ALBI grade 3.
NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; OS = overall survival; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours, Version 1.1.

Exploratory Response Objectives	Corresponding Endpoint
To further, evaluate whether the Tumour Responses patters to Atezolizumab + Bevacizumab treatment using different criteria have a different impact on OS and PFS	- **Tumour Response** will be primarily assessed by RECIST 1.1. And the results in efficacy on terms of OS and PFS reported accordingly. - Additionally, a secondary analysis will include HCC mRECIST, EASL and iRECIST criteria, based on the following patterns of progression: o **HCC mRECIST,** by measuring for any increase (confirmed in follow up visit) in the sum of longest diameter of viable tumour (unidimensional measurement). o **EASL**, by measuring for any increase (confirmed in follow up visit) in the area of viable tumour (bidimensional measurement). o **iRECIST**, by taking into consideration tumour pseudoprogression.
To further evaluate whether the patterns of tumour progression (growth versus new lesion, intrahepatic versus extrahepatic) have a different impact on OS and PFS	- **Tumour Progression** (and the results in efficacy on terms of OS and PFS) will be primarily assessed by RECIST v1.1 criteria based on the following patterns of progression: o > 20% increase in tumour size against a known baseline lesion (intrahepatic growth [IHG] or extrahepatic growth [EHG]) o new intrahepatic lesion (NIH) o new extrahepatic lesion and/or vascular invasion (NEH). - Additionally, a secondary analysis for the registration of tumour progression will include HCC mRECIST, taking into consideration the RECIST modifications described for SHARP (Reig 2015). - Exploratory assessment on OS and PFS will be performed based on the following patterns of progression: o New intrahepatic nodules are considered progression if: - They exceed 10 mm in diameter and present arterial enhancement at dynamic imaging. - Non-specific non-hypervascular nodules ≥ 10 mm (absence of the above definitions) present a doubling tumour size reaching a diameter > 20 mm since its initial detection or showing hyperenhancement during the follow-up. - Ascites and pleural effusion reflect progression only if malignant cells are pathology (cytology) proven. - Vascular invasion may be classified as progression if expansive and/or displaying arterial enhancement at dynamic imaging. - Hilar lymph nodes will be considered malignant if the smaller diameter exceeds 20 mm. Growth of existing nodes uses the same cut-offs as other lesions. - Lobar or segmental portal invasion with growth of the tumour thrombus reaching the main trunk of the portal vein.
To explore if post-study treatments have an impact on OS	- OS will be analysed according to type and duration of each post-study treatment.
To evaluate if reasons for treatment withdrawal have an impact on OS	- OS based on the following reasons of treatment withdrawal: o PD vs AE vs deteriorating liver function based on: - INR assessments; - presence or increase in ascites and/or hepatic encephalopathy; - increase in ALBI assessment scores grading.*

To analyse the organ-specific response rate (OS-RR) using RECIST 1.1 and the cumulative incidence probability of organ-specific progression	- We hypothesized that treatment efficacy varies across different metastatic sites. Comparison of OS-RR including target lesions from the liver, lungs, lymph nodes and non-target lesions in bones.
To determine the applicability of depth of response as surrogate for OS	- Depth of response (decrease in tumour burden) compared to baseline measurement according to: ○ RECIST 1.1 ○ EASL ○ mRECIST ○ iRECIST
Exploratory Biomarker Objective	**Corresponding Endpoint**
To identify Tissue & Blood based Biomarkers that might be associated with response patterns to Atezolizumab + Bevacizumab and patient outcomes under Atezolizumab+ Bevacizumab treatment	**Tumour biopsy sample** if available to characterize: (1) Tumour immune-cell infiltrate (2) The specificities of T lymphocyte receptors against tumour-specific antigens. (3) Specific expression patterns that may constitute gene signatures with prognostic and/or predictive power of response to Atezolizumab + Bevacizumab. (4) Specific set of mutations associated with response to Atezolizumab + Bevacizumab **Biomarker (blood, plasma, and serum) samples** to evaluate one or more of the following: (1) Cytokines. (2) cfDNA exome sequencing to capture mutations present in circulating DNA. (3) Sequencing the TCRs of circulating T cells to detect specific antigenicity of tumour antigens. (4) Characterization of circulating immune populations which changes could predict response to Atezolizumab + Bevacizumab

***** ALBI assessment grades 1 to 3 (Johnson et al. 2015) are based on calculated ALBI score (log10 bilirubin [µmol/L] × 0.66) + (albumin [g/L] × −0.0852) values as follows: ALBI score ≤ −2.60 = ALBI grade 1; > −2.60 to ≤ −1.39 =ALBI grade 2); and > −1.39 = ALBI grade 3.

ALBI = Albumin-Bilirubin; EASL = European Association for the Study of the Liver; HCC = hepatocellular carcinoma; iRECIST = modified Response Evaluation Criteria in Solid Tumours for immune therapeutics; mRECIST = modified Response Evaluation Criteria in Solid Tumours; ORR = Objective Response Rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours, Version 1.1.

Exploratory Radiomic Objective	Corresponding Endpoint
CT-radiomics analysis towards a more precise evaluation of response to Atezolizumab and Bevacizumab in patients with unresectable hepatocellular carcinoma included.	- To explore correlation of CT-radiomics signatures (including shape, first-order and higher-order texture features) at baseline with response to treatment. - To explore correlation in early changes in CT-radiomics signatures with response to treatment. - To explore inter- and intra- tumour CT-radiomics changes in relation to differences in responder/non-responder lesions and with the patient clinical outcome. - To explore correlation of radiomics features with tumour mutational status to develop radiogenomics phenotypes. - To explore correlation of CT-radiomics features with the tumour microenvironment including tumour immunophenotype by RNA seq and multiparametric immunofluorescence and vascularisation from tumour samples.

Efficacy Objectives

Secondary Efficacy Objective

Efficacy analysis includes both main and other secondary objectives.

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

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

ORR will simply be summarized. 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 for survival to evaluate whether the patterns of tumour 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 tumour 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 an 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 the 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 vs radical treatment.

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

Continuous and count variables:

- location measures: mean and median;
- dispersion measures: standard deviation and range;
- categorical variables: absolute and relative frequency.

Study Design

a) Description of the Study

This is a Phase IIIb, one arm, multicentre, open - label study designed to primarily evaluate the safety and efficacy of Atezolizumab + Bevacizumab in patients with locally advanced or metastatic HCC who have received no prior systemic treatment.

The treatment schemed for all patients included in the study will be:

- 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, who transiently withhold or permanently discontinue either Atezolizumab or Bevacizumab, may continue on single-agent therapy as long as the patients are experiencing clinical benefit in the opinion of the investigator and after discussion with the Medical Monitor (i.e., patients transiently withhold or permanently discontinue 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).

The patients who are clinically stable will be allowed to continue on treatment beyond initial RECIST v1.1 defined progression, until next assessment (between 4 to 8 weeks later) to ensure patient's suitability for treatment, as recommended by iRECIST criteria.

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 tumour 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.

Tumour assessments will be performed at baseline and at regular intervals during study treatment. Additional scans will be performed as clinically indicated. Tumour assessments will continue until disease progression according to RECIST v1.1 criteria and confirmed in the patient's next follow-up (providing there is a further increase of at least 5 mm of target tumour burden or new target lesion or any increase in non-target disease), regardless of whether treatment has been discontinued (e.g., for toxicity). Patients who meet RECIST v1.1 criteria for progression will undergo tumour assessments until loss of clinical benefit. In the absence of disease progression, tumour assessments should continue 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 my withdraw their consent for study participation but can continue to participate in the study survival follow up program should they wish to do so.

Patient samples, including serum and plasma, will be collected for the exploratory Tissue and Blood Biomarker Plan assessments.

b) Assessment of response and progression

Registration of Response: Tumour Response will be primarily assessed by RECIST 1.1 as a main assessment. Since activity may be detected by appearance of necrosis, a secondary **exploratory** analysis will include HCC mRECIST and EASL criteria. HCC mRECIST measures the sum of longest diameter of viable tumour and EASL the area of viable tumour.

Registration of response will be also assessed by applying iRECIST rules and compared with other response criteria in terms of OS and PFS.

Bevacizumab induces vasoconstriction and this reduces splanchnic blood flow and thus, hepatic artery blood flow. This may reduce the intensity of contrast uptake that should not be registered as necrosis. In any case, registration of response or of stable disease will not affect in treatment maintenance.

Registration of progression: Tumour Progression will be primarily assessed by RECIST 1.1 and the efficacy results in in terms of OS and PFS will be registered based on the following patterns of progression:

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

Secondary exploratory analysis will include HCC mRECIST, taking into consideration the RECIST modifications described for SHARP (Reig 2015) for the capture of tumour progression to prevent over registration of progression and improper treatment interruption. Exploratory assessment on OS and PFS will be performed based on the following patterns of progression:

- New intrahepatic nodules will be considered progression if:
  - They exceed 10 mm in diameter and present arterial enhancement at dynamic imaging.
  - Non-specific non-hypervascular nodules ≥ 10 mm (absence of the above definitions) present a doubling tumour size reaching a diameter > 20 mm since its initial detection or showing hyperenhancement during the follow-up.
  - Ascites and pleural effusion reflect progression only if malignant cells are pathology (cytology) proven.
  - Vascular invasion may be classified as progression if expansive and/or displaying arterial enhancement at dynamic imaging.

- Hilar lymph nodes are considered malignant if the smaller diameter exceeds 20mm and/or are hypervascular with these characteristics confirmed on the next follow up. Growth of existing nodes uses the same cut-offs as other target lesions.

- Registration of progression will be also assessed by applying iRECIST rules and compared with other response criteria in terms of OS and PFS.

- Additional exploratory assessment of the depth of response by means of changes in TL tumour burden and its association with OS and PFS will be analysed.

- Finally, based on the hypothesis that treatment efficacy varies across different metastatic sites, will carry out a comparison of organ-specific – response rate including target lesions from the liver, lungs, lymph nodes and non-target lesions in bones.

c) Criteria for treatment discontinuation

Safety events related to treatment discontinuation is the primary endpoint of the study; this may be reached through several events.

- **Development of SAEs** ≥ grade 3 clinically significant considered related to any study treatment and irrespective of tumour evolution.

- **Tumour progression outside the liver:** this includes confirmed growth in sequential imaging, and metastasis spread in any location, new lymph nodes, new vascular invasion – note that vascular invasion should never be considered a target lesion.) assessed by RECIST v1.1 and confirmed by iRECIST

- **Tumour progression within the liver:** assessed by RECIST v1.1as confirmed by iRECIST for target lesions. However, in case of new intrahepatic (NIH) tumour sites, treatment should not be interrupted upon detection of new nodules at first time. Further growth during follow-up should be registered to decide treatment interruption.

- **Liver function deterioration:**

    - Associated to progression will also represent a criterion for treatment interruption as it will also fit into SAEs ≥ 3.

    - Associated to appearance of ascites in need of treatment, jaundice or encephalopathy will be considered also a criterion for treatment discontinuation.

According to these definitions, treatment may be maintained beyond progression in very specific circumstances following the iRECIST and the refinements related to HCC as per registration of progression.

Number of patients

This study will enrol approximately 100 patients in one arm of treatment.

a) Target Population Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form.
- Age ≥ 18 years at time of signing Informed Consent Form.
- Ability to comply with the study protocol, in the investigator's judgment.
- Locally advanced or metastatic and/or unresectable HCC with diagnosis confirmed by histology or radiologically, following the AASLD criteria.
- 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 detected by CT scan.
- Patients who received prior local therapy such as radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, transarterial embolization (excluding transarterial radioembolization.) 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: Those patients.
- For those patients who received external beam radiotherapy as prior locoregional therapy should be necessary to wait at least 3 months before they could be included in this study.
- ECOG Performance Status of 0 or 1 within 7 days prior to recruitment.
- Child-Pugh class A with compensated ascites, within 7 days prior to recruitment.
- Patients should submit a pre-treatment tumour tissue sample. If tumour tissue is not available (e.g., depleted for prior diagnostic testing), it is **recommendable** to take a new biopsy if it´s clinically possible. If tumour tissue is available: A formalin-fixed, paraffin-embedded (FFPE) tumour specimen in a paraffin block (preferred) or a total of 28 slides (12 slides for histologic studies and 2x8 slides for genomic studies) containing unstained, freshly cut, serial sections should be submitted as detailed in the sample manual.

- Adequate haematologic and end-organ function, defined by the following laboratory test results, obtained within 7 days prior to recruitment, unless otherwise specified:
  - ANC ≥ 1.5 × 10^9/L (1500/μL) without granulocyte colony-stimulating factor support.
  - Lymphocyte count ≥ 0.5 × 10^9/L (500/μL).
  - Platelet count ≥ 75 × 10^9/L (75,000/μL) without transfusion.
    - Haemoglobin ≥ 90 g/L (9 g/dL).
    - AST, ALT, and alkaline phosphatase (ALP) ≤ 5 × upper limit of normal (ULN)
  - Serum bilirubin ≤ 3 × ULN.
  - Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault formula).
  - Serum albumin ≥ 28 g/L (2.8 g/dL) without albumin infusion.
  - INR ≤ 1.5.
  - 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 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.
- Negative HIV test at screening.
- 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 with a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of Atezolizumab and 6 months after the last dose of Bevacizumab. Women must refrain from donating eggs during this same period.

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

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

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

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive 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.

b) Exclusion Criteria

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

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

    - Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone treatment 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 within the previous 12 months.

- 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, Stage I uterine cancer or bladder carcinoma in situ.

- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteraemia, or severe pneumonia.

- 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**.

- 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.

  - 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 enrolment. 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 high risk of 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 that might require any treatment.

- 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.

- Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases.

- Uncontrolled tumour-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 enrolment. 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 enrolment.

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

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

- Treatment with investigational therapy within 28 days prior to initiation of study treatment.

- Treatment with strong CYP3A4 inducers within 14 days prior to initiation of study treatment, including rifampin (and its analogues) or St. John's wort.

- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies.

- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment.

- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

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

    - Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids (e.g., prednisone 10mg or equivalent) 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 ($\geq$ 2.5 mL of bright red blood per episode) within 1 month prior to initiation of study treatment.

- Evidence of bleeding diathesis or significant coagulopathy.

- 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 is within normal limits within 14 days prior to initiation of study treatment.

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

- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to the first dose of Bevacizumab.

- History of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months prior to initiation of study treatment.

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

    - Patients with signs/symptoms of sub-/occlusive syndrome/intestinal obstruction at time of initial diagnosis **may be enrolled** if they had received definitive (surgical) treatment for symptom resolution.

- Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure.

- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture.

- Metastatic disease that involves major airways or blood vessels like vena cava, or centrally located mediastinal tumour masses (< 30 mm from the carina) of large volume.

    - Patients with vascular invasion of the portal or hepatic veins may be enrolled.

- History of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including but not limited to 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, transarterial radioembolization 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**.

End of Study and Length of Study

a) 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 24 months since the last study patient is enrolled, whichever occurs first.

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

b) Length of Study

The total length of the study, from screening of the first patient to the end of the study is approximately 3 years (12 months enrolment).

Investigational Medicinal Products

Patients will receive treatment as outlined below until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). For those patients clinically stable to continue on treatment beyond initial RECIST v1.1 defined progression, will be allowed to continue on treatment until next assessment (between 4 to 8 weeks later) to ensure patient's suitability for treatment, as is it recommended by iRECIST criteria.

Treatment Arm	Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
A	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

This is not a hypothesis testing study but an exploratory study with predefined precision of estimates for key safety parameters for sample size determination; there are no formal statistical hypotheses tests to be tested, and there will be no adjustments for multiplicity of endpoints or within-subgroups comparisons.

The safety analysis population will consist of all enrolled patients who received at least one full or partial dose of study treatment.

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.

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

The following events occurring during or after the first dose of study treatment will be summarized by NCI CTCAE 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.
- Immune-related 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 events leading to temporary interruption of any component.
- All adverse events leading to temporary interruption of Atezolizumab.
- All adverse events leading to temporary interruption of Bevacizumab.

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

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

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

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

Additional analyses may be performed as indicated.

Determination of Sample Size

This is a Phase IIIb, one arm, prospective multicentre, open - label study designed to evaluate the safety and efficacy of Atezolizumab + Bevacizumab in patients with untreated or unsuitable for locoregional treatments hepatocellular carcinoma who have received no prior systemic treatment.

Approximately 100 patients will be recruited in 12 months, and we estimate 25 sites will participate in the study.

There is no formal statistical hypothesis, hence all safety (primary) endpoints results will be presented by 95% confidence intervals and descriptively explained.

For proportions exceeding 10-20%, estimates of the observed frequencies will have an acceptable precision (e.g., 95% confidence limit ± 5-6%) while for rare AE's, rather imprecise estimates will be obtained. For example, with an expected frequency of 1-2% (2-3 events in the 100 patients) the 95% CI of the observed proportion will cover a range of values compatible with the expected results with a 12-fold or greater of variation.

For the same reason, a 2-3-fold increase over the expected frequencies might easily be observed by chance. As a consequence, for rare AEs the results of this study will have to be interpreted with caution.

Exploratory Biomarker Analysis for Tissue and Blood biomarker Plan

Exploratory biomarker analyses will be performed in an effort to understand the association of tissue or blood-based biomarkers with response to Atezolizumab + Bevacizumab and increase the understanding of HCC disease evolution under Atezolizumab + Bevacizumab

treatment. This may include appropriate multivariate analyses. Blood based samples will be obtained at several timepoints of the study: Screening, Cycle 2 (Week 3) and Cycle 3 (Week 6).

The exploratory biomarker analyses of the Tissue and Blood Biomarker Plan include the following assessments:

- Multiplex Immunofluorescence T/B series & PDL1 (6-Plex+DAPI): S5 Oncomine™ TCR Beta-SR Assay Sequencing, NGS-based somatic mutation panel, and RNA sequencing, will be performed on tumour biopsy samples to characterize:
  - the tumour immune cell infiltrate
  - the specificities of T lymphocyte receptors against tumour-specific antigens
  - Specific expression patterns that may constitute gene signatures with prognostic and/or predictive power of response to Atezolizumab + Bevacizumab
  - Specific set of mutations associated with response to Atezolizumab + Bevacizumab
- Primer Extension Assay (PEA) identification of plasma cytokines and chemokines (384-plex, Olink), cfTNA Whole Exome Sequencing, Euroflow Panel, Whole Blood RNA sequencing andS5 Oncomine™ TCR Beta-SR Assay Sequencing to evaluate potential non-invasive biomarkers on blood, plasma or serum samples, such us:
  - Cytokines
  - cfDNA exome sequencing to capture mutations present in circulating DNA
  - Flow Cytometry and whole blood cell RNAseq to characterize circulating immune populations which changes could predict response to Atezolizumab + Bevacizumab
  - sequencing the TCRs of circulating T cells to detect specific antigenicity of tumour antigens

Exploratory Radiomic Analysis Plan

An exploratory Radiomic Analysis Plan will be performed to obtain a more precise evaluation of response to Atezolizumab + Bevacizumab in patients with unresectable hepatocellular carcinoma to correlate early changes in CT-radiomics signatures with PFS and OS. The Radiomic Analysis Plan will also evaluate the use of radiomics features for non-invasive prediction of immuno-oncologic characteristics based on biopsied lesions.

Target lesions corresponding to the primary tumour and metastases will be selected for radiomics features extraction. Target lesions will be selected based on size (≥ 1cm in large diameter for solid lesions and ≥ 1.5 cm in short diameter for nodes), preferably well-defined and avoiding for cystic changes and cavitation.

Multiple radiomics features from the target lesions will be extracted, including:

1. First order features (energy, entropy, minimum, percentiles, maximum, mean, median, interquartile range, range, standard deviation, skewness, kurtosis, among others).

2. Shape Features (volume, surface area, sphericity, among others).

3. Different filters for texture analysis will be applied for higher order statistics texture analysis, including: Gray Level Co-occurrence Matrix (GLCM) and Gray Level Run Length Matrix (GLRLM) features among others.

Interim Analyses

One interim analysis of safety is planned at the time of 50 recruited patients. This analysis is estimated to occur at approximately 6 months after the first patient was included in the study. The primary intent of the interim analysis is to allow the study to stop early if signs of safety risks for the patients are detected.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IIIB, SINGLE ARM, MULTICENTER STUDY OF ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB TO INVESTIGATE SAFETY AND EFFICACY IN SPANISH PATIENTS WITH UNRESECTABLE OR UNSUITABLE FOR LOCOREGIONAL TREATMENTS HEPATOCELLULAR CARCINOMA NOT PREVIOUSLY TREATED WITH SYSTEMIC THERAPY**
ACRONYM:	ATHECA study
PROTOCOL NUMBER:	ML42600
VERSION NUMBER:	2
EUDRACT NUMBER:	2020-005268-71
IND NUMBER:	Not applicable
NCT NUMBER:	NCT04732286
TEST PRODUCT:	Atezolizumab (RO5541267) Bevacizumab (RO4876646)
MEDICAL MONITOR:	[redacted]
SPONSOR:	Roche Farma S.A.

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 to the Sponsor or their designee. Contact details will be provided to the investigator prior to study start.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AASLD	American Association for the Study of Liver Diseases
AE	adverse event
ALBI	Albumin-Bilirubin
AP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BP	blood pressure
BID	twice a day
CD80	cluster of differentiation 80
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
Covid-19	Coronavirus Disease 2019
CR	complete response
CRC	colorectal cancer
CRS	cytokine-release syndrome
CRO	contract research organization
CT	computerized tomography
CTC	circulating tumour cells
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
EASL	European Association for the Study of the Liver
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EHG	extrahepatic growth
EOC	epithelial ovarian cancer

FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FoxP3	forkhead box P3
FTC	fallopian tube cancer
5-FU	5-fluorouracil
GBM	glioblastoma multiforme
GI	Gastrointestinal
GIDEON	Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HLH	hemophagocytic lymphohistiocytosis
ICF	informed consent form
ICH	International Council for Harmonisation
IgG1	immunoglobulin G1
IHG	intrahepatic growth
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IRB	Institutional Review Board
iRECIST	immunotherapy Response Evaluation Criteria in Solid Tumours
IL-2	interleukin 2
IRF	independent review facility
IRR	infusion related reaction
ITT	intent to treat
IxRS	Interactive Voice/Web Response System
IV	Intravenous
K-M	Kaplan Meier
LMWH	low molecular weight heparin
MAS	macrophage activation syndrome
MRI	magnetic resonance imaging
NAFLD	non-alcoholic fatty liver disease
NCI	National Cancer Institute

NE	not estimable
NSCLC	non-small-cell lung carcinoma
ORR	objective response rate
OS	overall survival
OS-RR	organ-specific response rate
PCR	polymerase chain reaction
PD	progressive disease
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PIVKA II	Protein induced by vitamin K absence-II
PK	Pharmacokinetic
PMBC	peripheral blood mononuclear cells
PPC	primary peritoneal cancer (PPC)
PPS	post progression survival
PR	partial response
PRO	patient-reported outcome
Q3W	every 3 weeks
RBC	red blood cell
RBR	Research Biosample Repository
RCC	renal cell cancer
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
16W-DCR	disease-control rate at 16 weeks
SHARP	Sorafenib HCC Assessment Randomized Protocol
SD	stable disease
T4	Thyroxine
T3	Triiodothyronine
TNF-α	tumour necrosis factor alpha
TTP	time to progression
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VEGF	vascular endothelial growth factor

WBC	white blood cell

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 due to 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).

1.1 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 overall survival (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. Food and Drug Administration (FDA) and is currently considered the global standard of care for the first-line treatment of patients with advanced HCC. The efficacy of sorafenib has been demonstrated in two large multicentre, randomized, double-blind, placebo-controlled Phase III trials: the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial and a trial conducted in the Asia-Pacific region. Both studies demonstrated a survival benefit of sorafenib versus placebo. In the SHARP trial, median OS was 10.7 months with sorafenib versus 7.9 months with placebo (hazard ratio [HR] = 0.69 [95% CI: 0.55, 0.87]); in the Asia Pacific trial, median OS was 6.5 months versus 4.2 months (HR = 0.68 [95% CI: 0.50, 0.93]). Benefit in median time to radiographic progression was also demonstrated: 5.5 months versus 2.8 months in the SHARP trial (HR = 0.58 [95% CI: 0.5, 0.7]) and 2.8 months versus 1.4 months in the Asia Pacific trial (HR = 0.6 [95% CI: 0.4, 0.8]).

The objective response rate per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0 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 Global Investigation of therapeutic Decisions in hepatocellular carcinoma and Of its treatment with sorafeNib (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]) was 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) in the phase III non-inferiority REFLECT trial (Kudo et al. 2018). In addition, lenvatinib showed statistically significant superiority compared to sorafenib in terms of PFS, time to progression (TTP), and objective response rate (ORR), as determined by the local investigator tumour 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 findings from the REFLECT trial were the basis for approval of lenvatinib in Japan, the US (July 2018) and the 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.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that targets programmed death-ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as cluster of differentiation 80 [CD80]), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by Atezolizumab enhances the magnitude and quality of tumour-specific T-cell responses, resulting in improved anti-tumour 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-tumour activity in nonclinical models. In the clinical setting, 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. Targeting the PD-L1 pathway with Atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including non-small-cell lung carcinoma (NSCLC), urothelial carcinoma, RCC, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. Atezolizumab is currently approved for the treatment of urothelial carcinoma, NSCLC, small-cell lung cancer, hepatocellular carcinoma, and triple-negative breast cancer.

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

1.3 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 intravenous (IV) 5-fluorouracil (5-FU)-based chemotherapy for the first-line treatment of patients with metastatic colorectal cancer (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.

1.4 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM OF ATEZOLIZUMAB AND BEVACIZUMAB AS MONOTHERAPIES IN HEPATOCELLULAR CARCINOMA

1.4.1 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 tumour types. No new safety signals related to Atezolizumab monotherapy were observed in the HCC population.

Study PCD4989g

Study PCD4989g is a Phase Ia, multicentre, 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 tumour 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 Tumours [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% confidence interval [CI]: 1.3, 3.4) months and median OS was 5.3 (95% CI: 2.4, not estimable [NE]) months.

Study YO29233

Study YO29233 is a Phase I, open-label, multicentre study evaluating the pharmacokinetics, safety, and preliminary anti-tumour activity of Atezolizumab as monotherapy in Chinese patients with locally advanced or metastatic gastric cancer, nasopharyngeal carcinoma, oesophageal cancer, HCC and other solid tumours, and the safety and preliminary anti-tumour 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).

1.4.2 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, Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2, and compensated liver function (Child-Pugh class A or B7),

received Bevacizumab 5 mg/kg or 10 mg/kg every 2 weeks (Q2W) until disease progression or treatment-limiting toxicity.

Of note, patients with extrahepatic disease, tumour 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 (intent to treat [ITT] group 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).

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.5.1 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 PD-L1/VEGF blockade may be clinically beneficial in a number of tumour types including HCC.

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, programmed cell death protein 1 (PD-1) and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumour cells has been reported to impede anti-tumour immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumour-specific T-cell immunity. In patients with advanced malignancies, therapies focused on enhancing T cell responses against cancer have been shown to give a significant survival benefit (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

HCC itself is a highly vascularised tumour type and several proangiogenic factors play a role in HCC pathogenesis. For example, in HCC, increased VEGF correlates with vascular density, tumour 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 tumour 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 tumour endothelial FasL expression and produced a significant increase in the influx of tumour-rejecting CD8+ over forkhead box P3 (FoxP3)+ T cells, which was FasL-dependent, and led to CD8-dependent tumour 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 tumours (Oelkrug and Ramage 2014; Wallin et al. 2016). In addition to increased trafficking of T cells into tumours (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 tumours (Roland et al. 2009; Voron et al. 2015).

The immunomodulatory effect of Bevacizumab is thus expected to enhance the effects of Atezolizumab by increasing CD8+ T-cell recruitment and relieving intratumoural immunosuppression.

1.5.2 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 was a Phase Ib, multicentre, open-label study of Atezolizumab in combination with Bevacizumab and/or chemotherapy as first-line therapy in patients with various metastatic cancers. 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 (60 patients) or Atezolizumab (59 patients) monotherapy. Results for Arm A and Arm F have been recently published (Lee et al. 2020).

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 ORR based on Independent-Review Facility (IRF) assessment per Response Evaluation Criteria in Solid Tumours, 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 PFS with the combination compared to Atezolizumab monotherapy.

Median PFS for the combination was 5.6 months compared to 3.4 months for the combination resulting in an 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, multicentre, 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. 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; Finn et al. 2020).

- 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.

1.5.3 Benefit-risk Assessment

Atezolizumab has been combined with Bevacizumab in patients with a range of different tumour 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 tumour types including HCC (Socinski et al. 2018; Rini et al. 2019).

This trial will enrol patients with unresectable or unsuitable for locoregional treatments HCC not previously treated with systemic therapy. 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.

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

In the setting of the COVID-19 pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from COVID-19. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of COVID-19.

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

Severe COVID-19 appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving Atezolizumab. At this time, there is insufficient evidence for causal association between Atezolizumab and an increased risk of severe outcomes from COVID-19.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with Atezolizumab and clinical and radiologic features for COVID-19– related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

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

2. OBJECTIVES AND ENDPOINTS

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 details on the study objectives and their corresponding endpoints are outlined below.

2.1 MAIN OBJECTIVES

This study is designed to evaluate the safety of Atezolizumab in combination with Bevacizumab in patients with unresectable HCC who have received no prior systemic treatment and are considered unsuitable for locoregional therapy. The primary endpoint is the incidence and severity of adverse events of grade ≥ 3 that lead to discontinuation of

study treatment. To further evaluate the safety of Atezolizumab in combination with Bevacizumab, secondary endpoints of severity of AEs (determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 [NCI CTCAE v5.0]), as well as changes from baseline in targeted vital signs and clinical laboratory test results will be evaluated during the patients' treatment.

As part of the secondary objectives of this study, the efficacy of Atezolizumab and Bevacizumab will be evaluated using the endpoint of overall survival ([OS] defined as the time from initiation of study treatment to death from any cause). Efficacy will also be examined using the following endpoints evaluated by RECIST v1.1 criteria (See Appendix 4): 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); objective response rate ([ORR], defined as a complete or partial response, on two consecutive occasions ≥ 4 weeks apart; time to progression ([TTP], defined as the time from initiation of study treatment to the first occurrence of disease progression) and 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). The endpoints of the number/rate of patients starting second line treatment and the changes from baseline in targeted vital signs and targeted clinical laboratory test results will also be used to further evaluate treatment efficacy.

During the study, deterioration in hepatic function will be monitored using the endpoints of:

- Changes in international normalized ratio (INR)
- Presence or absence of Ascites and /or Hepatic Encephalopathy
- Albumin-Bilirubin (ALBI) assessment grades of 1 to 3 (Johnson et al. 2015) based on calculated ALBI score (log10 bilirubin [µmol/L] × 0.66) + (albumin [g/L] × −0.0852) values as follows: ALBI score ≤ −2.60 = ALBI grade 1; > −2.60 to ≤ −1.39 =ALBI grade 2); and > −1.39 = ALBI grade 3

2.2 EXPLORATORY EFFICACY OBJECTIVES

This study also has exploratory objectives based on evaluating how patients' responses to study treatment influence survival from HCC. Tumour response will be primarily assessed by each investigational site, using RESIST 1.1 criteria and the efficacy findings by response in terms of OS and PFS will be reported accordingly. Tumour response will also be evaluated as additional exploratory objective over four different timepoints of the study (screening, week 6, week 12 and end of treatment) by a centralized assessment using the following criteria: HCC mRECIST, by measuring the sum of longest diameter of viable tumour (unidimensional measurement); the European Association for the Study of the Liver (EASL), by measuring the area of viable tumour (bidimensional measurement); and immunotherapy RECIST criteria (IRECIST), confirmed by taking into consideration tumour pseudoprogression. The patterns of tumour responses to Atezolizumab and Bevacizumab

treatment using these different criteria will be evaluated to analyze their exploratory impact on OS and PFS.

Another exploratory objective of this study is to evaluate whether the patterns of tumour progression (growth versus new lesion, intrahepatic versus extrahepatic) have different impacts on OS and PFS. Tumour Progression will be primarily assessed by RECIST 1.1 criteria (Appendix 4) and classified into three categories of progression which should all be confirmed at the next follow up visit:

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

ii. New intrahepatic lesion (NIH)

iii. New extrahepatic lesion and/or vascular invasion (NEH)

Within these three categories, OS and PFS will be evaluated.

In a secondary analysis, which will use HCC mRECIST criteria —taking into consideration the RECIST modifications described for SHARP (Reig et al. 2014)— the registration of tumour progression will also be categorized as follows:

i. New intrahepatic nodules will be considered progression if:

    a. They exceed 10 mm in diameter and present arterial enhancement at dynamic imaging.

    b. Non-specific non-hypervascular nodules ≥ 10 mm (absence of the above definitions) present a doubling tumour size reaching a diameter > 20 mm since its initial detection or showing hyperenhancement during the follow-up.

ii. Ascites and pleural effusion reflect progression only if malignant cells are pathology (cytology) proven.

iii. Vascular invasion may be classified as progression if expansive and/or displaying arterial enhancement at dynamic imaging.

iv. Hilar lymph nodes will be considered malignant if the smaller diameter exceeds 20mm and/or are hypervascular. Growth of existing nodes uses the same cut-offs as other lesions.

v. Lobar or segmental portal invasion with growth of the tumour thrombus reaching the main trunk of the portal vein or reaching the contralateral lobe.

OS and PFS will be evaluated within each of these five categories.

This study will explore how the factors underlying treatment withdrawal and post-study treatments impact patients by analysing OS according to the reason for treatment withdrawal (progressive disease [PD] versus AE versus deteriorating liver function/clinical conditions) and according to the type and duration of each post-study treatment given. This study will be performed over the same CT images used for the Radiomic exploratory analysis: Basal, week 6, week 12 and progression scan.

To investigate whether treatment efficacy varies across different metastatic sites, the organ-specific response rate (OS-RR) using RECIST 1.1 criteria, and the cumulative incidence probability of organ-specific progression will be measured. Comparison of OS-RR will be compared for target lesions including in the liver, lungs, and lymph-nodes as well as for non-target lesions in bones.

The final exploratory efficacy objective of the study will be to determine the applicability of depth of response (decrease in tumour burden) as a surrogate for OS. Tumour response according to RECIST 1.1, EASL, mRECIST and iRECIST criteria will be compared to baseline evaluations.

2.3 SAFETY OBJECTIVE

As described in Section 2.1, this study will primarily evaluate the safety of Atezolizumab in combination with Bevacizumab in patients with unresectable hepatocellular carcinoma who have received no prior systemic treatment and they are consider unsuitable for locoregional therapy.

This will be done by assessing the incidence and severity of adverse events grade ≥ 3 that lead to discontinuation of study treatment.

2.4 BIOMARKER AND RADIOMIC OBJECTIVES

In the Tissue & Blood Biomarker Plan, patients will have samples taken to identify Tissue and Blood based Biomarkers that might be associated with response patterns to Atezolizumab + Bevacizumab and patient outcomes under Atezolizumab+ Bevacizumab treatment. These samples will be obtained at three different study time points: Screening, Cycle 2 (week 3), Cycle 3 (week 6t

The following analyses will be conducted on blood, plasma, serum, and tumour biopsy samples taken from patients included in the project:

i. Multiplex Immunofluorescence T/B series & PDL1 (6-Plex+DAPI): S5 Oncomine™ TCR Beta-SR Assay Sequencing and RNA sequencing, will be performed on tumour biopsy samples to characterize:
   a. the tumour immune cell infiltrate
   b. the specificities of T lymphocyte receptors against tumour-specific antigens

c. Specific expression patterns that may constitute gene signatures with prognostic and/or predictive power of response to Atezolizumab + Bevacizumab

ii. ELISA Luminex HCYTA-60K-26 Human Cyto Panel A (48 cytokines), cfTNA Whole Exome Sequencing, Euroflow Panel, Whole Blood RNA sequencing andS5 Oncomine™ TCR Beta-SR Assay Sequencing to evaluate potential non-invasive biomarkers on blood, plasma or serum samples, such us:

a. Cytokines

b. cfDNA exome sequencing to capture mutations present in circulating DNA

c. sequencing the TCRs of circulating T cells to detect specific antigenicity of tumour antigens characterization of leukocyte subpopulations that could predict response

In addition, an exploratory Radiomic Analysis Plan will be performed and will aim to gain a more precise evaluation of response to Atezolizumab and Bevacizumab in patients with unresectable hepatocellular carcinoma. This Radiomic Analysis will be performed over the following CT images: Basal, week 6, week 12 and progression scan. The Radiomic Analysis Plan will also evaluate the use of radiomics features as a means of noninvasive prediction of immuno-oncologic characteristics based on biopsied lesions. To this end, the following analyses will be performed:

i. CT-radiomics signatures (including shape, first-order and higher-order texture features) at baseline will be correlated with the response to study treatment.

ii. Any early changes in CT-radiomics signatures during the study will be correlated with the response to study treatment.

iii. Any changes in inter- and intra- tumour CT-radiomics will be explored in relation to any differences in responder/non-responder lesions and to the patient clinical outcome.

iv. Any CT-radiomics features will be correlated with tumour mutational status in order to develop radiogenomic phenotypes.

v. Any CT-radiomics features will also be correlated with the tumour microenvironment on biopsied lesions including the tumour immunophenotype, RNA sequences, and vascularization.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase IIIb, one arm, multicentre, open-label study primarily designed to evaluate the safety of Atezolizumab + Bevacizumab in patients with unresectable or unsuitable for locoregional treatments for metastatic HCC not previously treated with systemic therapy.

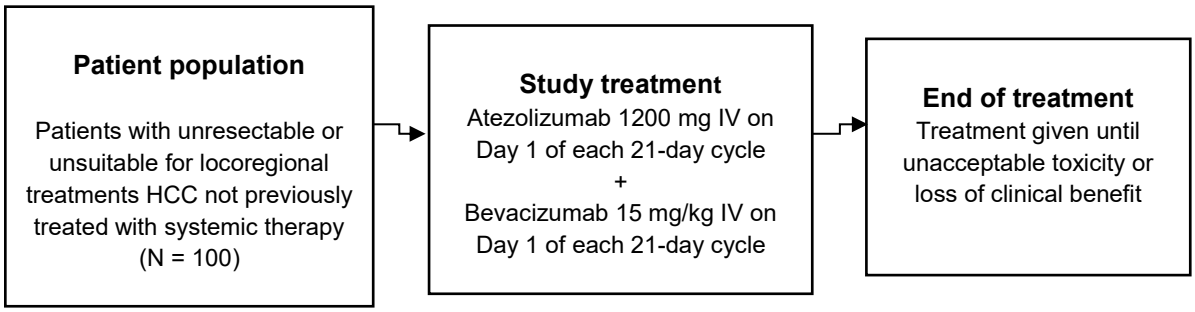
As part of its secondary objectives, this study is also designed to evaluate the efficacy of Atezolizumab and Bevacizumab in these patients.

The treatment schemed for all patients included in the study will be:

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

This study will enrol approximately 100 patients from 26 sites throughout Spain in one arm of treatment; Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



Patients treated with Atezolizumab + Bevacizumab, who transiently withhold or permanently discontinue either Atezolizumab or Bevacizumab, may continue on single-agent therapy as long as the patients are experiencing clinical benefit in the opinion of the investigator and after discussion with the Medical Monitor (i.e., patients transiently withhold or permanently discontinue 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).

For those patients clinically stable to continue on treatment beyond initial RECIST v1.1 defined progression, will be allowed to continue on treatment until next assessment (between 4 to 8 weeks later) to ensure patient's suitability for treatment, as is it recommended by immunotherapy (iRECIST) criteria.

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 tumour 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.

Tumour assessments will be performed at baseline and at regular intervals during study treatment. Additional scans will be performed as clinically indicated. Tumour assessments will continue until disease progression, regardless of whether treatment has been discontinued (e.g., for toxicity). Patients who meet RECIST v1.1 criteria for progression will undergo tumour assessments until loss of clinical benefit, whichever occurs later. In the absence of disease progression, tumour assessments should continue 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, including serum and plasma, will be collected for the exploratory biomarker assessments for the Tissue and Blood Biomarker Plan.

The regular tumour assessments will be performed at baseline, then every 6 weeks for the first 54 weeks and every 12 weeks thereafter. The CT images used for the Radiomic Analysis Plan will be the same as those for the regular tumour assessments performed at baseline, week 6, week 12 and patient's progression. The same images will be used for the exploratory efficacy analysis (see section 2.2). In these images, target lesions corresponding to the primary tumour and metastases will be selected for extraction of radiomic features and the exploratory efficacy analysis.

Assessment of response and progression

Registration of Response: Tumour Response will be primarily assessed locally by the study investigators using RECIST 1.1 criteria (Appendix 4) as a main assessment. Since activity may be detected by appearance of necrosis, an exploratory secondary analysis will include HCC mRECIST and EASL criteria. HCC mRECIST to measure the sum of longest diameter of viable tumour and EASL the area of viable tumour. This exploratory analysis will be performed over those scans shipped for the radiomic analysis: Screening, week 6, week 12 and progression scan (see section 2.2).

Registration of response will be also assessed by applying iRECIST rules and compared with other response criteria in terms of OS and PFS.

Bevacizumab induces vasoconstriction and this reduces splanchnic blood flow and thus, hepatic artery blood flow. This may reduce the intensity of contrast uptake that should not be registered as necrosis. In any case, registration of response or of stable disease will not affect in treatment maintenance.

Registration of progression: Tumour Progression will be primary assessed by RECIST 1.1 and the results in efficacy on terms of OS and PFS based on the following Patterns of progression:

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

- new intrahepatic lesion (NIH)

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

Secondary exploratory analysis will include HCC mRECIST, taking into consideration the RECIST modifications described for SHARP (Reig et al. 2014) for the capture of tumour progression to prevent over registration of progression and improper treatment interruption. Exploratory assessment on OS and PFS will be performed based on the following patterns of progression:

- New intrahepatic nodules will be considered progression if:

  - They exceed 10 mm in diameter and present arterial enhancement at dynamic imaging.

  - Non-specific non-hypervascular nodules ≥ 10 mm (absence of the above definitions) present a doubling tumour size reaching a diameter > 20 mm since its initial detection or showing hyperenhancement during the follow-up.

  - Ascites and pleural effusion reflect progression only if malignant cells are pathology (cytology) proven.

  - Vascular invasion may be classified as progression if expansive and/or displaying arterial enhancement at dynamic imaging.

  - Hilar lymph nodes are considered malignant if the smaller diameter exceeds 20mm and/or are hypervascular. Growth of existing nodes uses the same cut-offs as other lesions.

- Registration of progression will be also assessed by applying iRECIST rules and compared with other response criteria in terms of OS and PFS.

- Additional exploratory assessment of the depth of response by means of changes in TL tumour burden and its association with OS and PFS will be analysed.

- Finally, based on the hypothesis that treatment efficacy varies across different metastatic sites, a comparison of organ-specific response rates will be performed, including target lesions from the liver, lungs, lymph-nodes and non-target lesions in bones.

Criteria for treatment discontinuation

Safety events ≥ grade 3 related to treatment discontinuation is the primary endpoint of the study thus may be reached through several events.

- Development of AEs or SAEs ≥ grade 3 clinically significant considered related to any study treatment and irrespective of tumour evolution.

- **Tumour progression outside the liver:** this includes confirmed growth in sequential imaging, and metastasis spread in any location, new lymph nodes, new vascular invasion – note that vascular invasion should never be considered a target lesion.) assessed by RECIST v1.1 and confirmed by iRECIST.

- **Tumour progression within the liver:** assessed by RECIST v1.1as confirmed by iRECIST for target lesions. However, in case of new intrahepatic (NIH) tumour sites, treatment should not be interrupted upon detection of new nodules at first time. Further growth during follow-up should be registered to decide treatment interruption.

- **Liver function deterioration:**

  - Associated with progression will also represent a criterion for treatment interruption as it will also fit into SAEs ≥ 3.

  - Associated with the appearance of ascites in need of treatment, jaundice or encephalopathy will be considered also a criterion for treatment discontinuation.

According to these definitions, treatment may be maintained beyond progression under very specific circumstances following the iRECIST criteria and the refinements related to HCC per registration of progression and following confirmation with the medical monitor of the study.

3.2 END OF STUDY AND LENGTH OF STUDY

3.2.1 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 24 months since the last study patient is enrolled, whichever occurs first.

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

3.2.2 Length of Study

The total length of the study, from screening of the first patient to the end of the study is approximately 3 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-tumour 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).

Moreover, 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) (Finn et al. 2020) 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 one of the approved dosages for Bevacizumab (Avastin® local labels).

This dose schedule aligns with the Atezolizumab dose schedule used in combination with Atezolizumab in Study GO30140 and YO40245 (IMbrave150).

3.3.3 Rationale for Patient Population

This study will enrol patients with unresectable or unsuitable for locoregional treatments metastatic HCC not previously treated with systemic therapy. 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 YO40245, 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 locally advanced or metastatic HCC.

3.3.4 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.

3.3.5 Rationale for Primary Safety Endpoint

In this study, incidence and severity of safety events> grade 3 related to any study treatment discontinuation is the primary endpoint of the study.

In the YO40245 (IMbrave150) phase III trial (Finn et al. 2020), treatment-related events occurred in at least 10% of patients. The percentage of patients who discontinued any treatment component because of adverse events was 15.5% in the Atezolizumab–Bevacizumab group (7% discontinued both components) and 10.3% in the sorafenib group.

In the context of this protocol study, the safety events that will lead to any study treatment discontinuation may be reached through the occurrence of the following events:

- Development of AEs or SAEs $\geq$ grade 3 clinically significant considered related to any study treatment and irrespective of tumour evolution.

- **Tumour progression outside the liver:** this includes confirmed growth in sequential imaging, and metastasis spread in any location, new lymph nodes, new vascular invasion – note that vascular invasion should never be considered a target lesion.) assessed by RECIST v1.1 and confirmed by iRECIST.

- **Tumour progression within the liver:** assessed by RECIST v1.1as confirmed by iRECIST for target lesions. However, in case of new intrahepatic (NIH) tumour sites, treatment should not be interrupted upon detection of new nodules at first time. Further growth during follow-up should be registered to decide treatment interruption.

- **Liver function deterioration:**

    - Associated to progression will also represent a criterion for treatment interruption as it will also fit into SAEs $\geq$ 3.

- Associated to appearance of ascites in need of treatment, jaundice or encephalopathy will be considered also a criterion for treatment discontinuation.

Even though the safety profiles of Atezolizumab and Bevacizumab are well established, the additional information collected, using this endpoint will have the potential to reinforce the safety data already available for these treatments in the context of patients in Spain with unresectable or unsuitable for locoregional treatment HCC.

3.3.6 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 tumour burden. This initial increase in tumour 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 tumour growth followed by a response was observed in several tumour 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 assigned 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).

3.3.7 Rationale for the Use of iRECIST Criteria to Evaluate Tumour Response

Increasing clinical experience indicates that traditional response criteria (e.g., RECIST v1.1) may not adequately assess the activity of immunotherapeutic agents because initial radiographic evidence of disease progression does not necessarily reflect therapeutic failure. Patients can experience a response in the presence of new lesions or after an increase in tumour burden. Thus, this study will also employ iRECIST tumour response criteria (Seymour et al. 2017) that have been modified for unconventional tumour change patterns associated with cancer immunotherapy.

iRECIST was developed by the RECIST working group in an effort to create a common set of criteria that the cancer immunotherapy field could apply to clinical trials (Seymour et al. 2017). iRECIST accounts for responses that may occur following transient radiographic progression caused by immune-cell infiltration in tumours (leading to a transient increase in the size of existing lesions, including those that were previously undetectable and consequently appear as new lesions). iRECIST relies on collection of tumour assessment data after initial disease progression per RECIST v1.1.

Given the proposed immunomodulatory mechanism of action of Atezolizumab and the possibility of observing delayed responses, exploratory efficacy endpoints will include analyses based on iRECIST. These analyses will allow for exploratory analysis, the evaluation of iRECIST as an improved measure of the efficacy of immunotherapies relative to standard RECIST v1.1.

3.3.8 Rationale for the Use of HCC mRECIST Criteria to Evaluate Tumour Progression and Tumour Response

Increasing clinical experience indicates that traditional response criteria (e.g., RECIST v1.1) do have some limitations with regard to the evaluation of tumour response in hepatocellular carcinoma (HCC) treated with locoregional therapies and new targeted chemotherapy agents. For advanced hepatocellular carcinoma, the standard RECIST v1.1 criteria correlated poorly with the clinical benefits demonstrated in the SHARP trial for sorafeninb (Nexavar, a multikinase inhibitor of the vascular endothelial growth factor and platelet derived growth factor receptors) (Llovet JM 2008). Similar findings were seen after locoregional therapies for HCC such as radiofrequency ablation and chemoembolization (Forner A 2008). This is likely because these therapies reduce the vascularity of the tumour, producing necrosis which does not always reduce the overall tumour size. In addition, as HCC tumours enlarge, they show intranodular variability in their enhancement pattern on imaging which further complicates the evaluation of tumour size.

To address these issues and to provide a common framework for the design of clinical trials in HCC the American Association for the Study of Liver Diseases has proposed modified criteria (mRECIST), which quantify only the viable portions (characterized as arterially enhancing on imaging) of the tumour to provide an improved endpoint for assessment (Llovet JM, Di Bisceglie AM et al. 2008, Lencioni R 2012).

Secondary exploratory analyses in this study will therefore also include HCC mRECIST, taking into consideration the RECIST modifications described for SHARP (Reig et al. 2014) for the capture of tumour progression to prevent over registration of progression and improper treatment interruption. Further information on the HCC mRECIST criteria used to evaluate tumour progression can be found in Appendix 5.

3.3.9 Rationale for the Use of EASL Criteria to Evaluate Tumour Response

When specifically assessing tumour response in HCC lesions, the European Association of the Study of the Liver (EASL) guidelines were first developed in 2001 in order to account for the intranodular variability seen in imaging of HCC tumours. The EASL guidelines recommend measuring the viable and necrotic portions of the treated nodules and have been shown to allow early detection (within 1 to 2 months) of tumour necrosis (Riaz, A.,2009 Riaz A, Lewandowski RJ et al. 2009). Furthermore, the EASL guidelines recommend that only nodules exhibiting the typical characteristics of arterial wash-in followed by wash-out can be considered as new lesions. This recommendation addresses the peculiar

characteristic of the cirrhotic liver, in which a wide range of non-neoplastic lesions (such as large regenerative nodules) can develop during patient follow-up.

Secondary exploratory analyses in this study will therefore also include EASL guidelines (EASL 2018) for the evaluation of HCC response on imaging. Further information on the EASL criteria used to evaluate HCC response are provided in Appendix 6.

3.3.10 Rationale for Biomarker Assessments

In this study, exploratory biomarkers will be evaluated. This is part of the Tissue & Blood Biomarker Plan for patients included in translational research, to identify biomarkers that might be potentially associated with response patterns to Atezolizumab + Bevacizumab or the HCC disease evolution under Atezolizumab+ Bevacizumab treatment. Section 2.4 presents the details of the biomarkers that will be evaluated.

3.3.11 Rationale for Non-Standard Clinical Outcome Assessments

This study will include a Radiomic Analysis Plan aimed at providing a more precise evaluation of the response to Atezolizumab and Bevacizumab in patients with unresectable hepatocellular carcinoma. The CT-radiomic signatures identified will be correlated to various clinical outcomes of the study treatment. Details on the endpoints assessed in this Radiomic Analysis Plan are provided in Section 2.4.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 100 patients with unresectable or unsuitable for locoregional treatments metastatic HCC not previously treated with systemic therapy will be enrolled in approximately 25 Spanish 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.
- Locally advanced or metastatic and/or unresectable HCC with diagnosis confirmed by histology or radiologically, following the American Association for the Study of Liver Diseases (AASLD) criteria.

- 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 detected by computerized tomography (CT) scan.

- 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, transarterial radioembolization, 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.

- For those patients who received radioembolization as prior locoregional therapy should be necessary to wait at least 3 months before they could be included in this study.

- ECOG Performance Status of 0 or 1 within 7 days prior to recruitment.

- Child-Pugh class A with compensated ascites, within 7 days prior to recruitment.

- Patients should submit a pre-treatment tumour tissue sample. If tumour tissue is not available (e.g., depleted for prior diagnostic testing), it is **recommendable** to take a new biopsy if it´s clinically possible. If tumour tissue is available: A formalin-fixed, paraffin-embedded (FFPE) tumour specimen in a paraffin block (preferred) or a total of 28 slides (12 slides for histologic studies and 2x8 slides for genomic studies) containing unstained, freshly cut, serial sections should be submitted.

- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 7 days prior to recruitment, unless otherwise specified:

  – ANC ≥ 1.5 × 10^9/L (1500/μL) without granulocyte colony-stimulating factor support

  – Lymphocyte count ≥ 0.5 × 10^9/L (500/μL)

  – Platelet count ≥ 75 × 10^9/L (75,000/μL) without transfusion

    – Haemoglobin ≥ 90 g/L (9 g/dL).

    – Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) ≤ 5 × upper limit of normal (ULN)

  – Serum bilirubin ≤ 3 × ULN

  – Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault formula)

– Serum albumin ≥ 28 g/L (2.8 g/dL) without transfusion

– INR ≤ 1.5

– 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 and must demonstrate < 1 g of protein in 24 hours.

- Resolution of any acute, clinically significant treatment-related toxicity from prior therapy to Grade $\leq$ 1 prior to study entry, with the exception of alopecia

- Negative HIV test at screening

- Documented virology status of hepatitis, as confirmed by screening 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 with a failure rate of $<$ 1% per year during the treatment period and for at least 5 months after the last dose of Atezolizumab and 6 months after the last dose of Bevacizumab. Women must refrain from donating eggs during this same period.

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

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

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

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive 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:

- - Active or history of autoimmune disease or immune deficiency, including, but not limited to (full list of conditions presented in Appendix 7), 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 treatment 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 the 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 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 within the previous 12 months.

- 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, Stage I uterine cancer or bladder carcinoma in situ.

- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteraemia, or severe pneumonia.

- 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**.

- 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.

    - 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 enrolment. 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.

    - 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 that might require any treatment.

- 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 polymerase chain reaction (PCR) will be considered non-infected with HCV.

- Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases.

- Uncontrolled tumour-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 enrolment. 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 enrolment.

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

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

- Treatment with investigational therapy within 28 days prior to initiation of study treatment.

- Treatment with strong CYP3A4 inducers within 14 days prior to initiation of study treatment, including rifampin (and its analogues) or St. John's wort.

- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti−CTLA-4, anti−PD-1, and anti−PD-L1 therapeutic antibodies.

- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment.

- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumour necrosis factor alpha [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

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

    - Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose

corticosteroids (e.g., prednisone 10mg or equivalent) 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.

- 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 activated partial thromboplastin time (aPTT) is within normal limits within 14 days prior to initiation of study treatment.

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

- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to the first dose of Bevacizumab.

- History of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months prior to initiation of study treatment.

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

    - Patients with signs/symptoms of sub-/occlusive syndrome/intestinal obstruction at time of initial diagnosis **may be enrolled** if they had received definitive (surgical) treatment for symptom resolution.

- Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure.

- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture.

- Metastatic disease that involves major airways or blood vessels like vena cava, or centrally located mediastinal tumour masses (< 30 mm from the carina) of large volume.

    - Patients with vascular invasion of the portal or hepatic veins may be enrolled.

- History of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including but not limited to 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, transarterial radioembolization 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.

- If a diagnosis of COVID-19 infection is confirmed in a patient or if a patient has been in direct contact with a confirmed COVID-19 case within 2 weeks prior to the planned start of the study, the patient is excluded from the study.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is an open-label single-arm study. After written informed consent has been obtained, the study site will obtain the patient's identification number from the electronic Case Report Form (eCRF).

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 eCRF. Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 10 (Atezolizumab) and Appendix 9 (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 or applicable by clinical practice), 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 8. 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. • Atezolizumab should be infused over 60 (± 15) minutes. • **If clinically indicated**, vital signs should be measured every 15 (± 5) minutes during the infusion and at 30 (± 10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (± 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (± 10) minutes after the infusion.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 9 and Appendix 10.

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 8.

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) hours after the infusion. ● Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	● If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. ● Vital signs should be measured within 60 minutes prior to the infusion. ● Bevacizumab should be infused over 60 (± 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 90 (± 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (± 15) minutes thereafter. ● Vital signs should be measured at the end of infusion and 2 (± 1) hours after the infusion.

Guidelines for dosage modification and treatment interruption or discontinuation because of toxicities are provided in Appendix 9.

No dose modification for Bevacizumab is allowed.

4.3.3 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor (Roche Farma S.A) 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 interactive Voice/Web Response System (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 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.

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 metastatic HCC that is unresectable or unsuitable for locoregional treatments;
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for HCC that is unresectable or unsuitable for locoregional treatments;

- 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.
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin [LMWH]).
- 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 tumour 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 tumour 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:

        i. The patient has no evidence of progression or haemorrhage after completion of CNS-directed therapy.

        ii. The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

        iii. Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

        iv. 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); 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 Section 4.4.2 and Section 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). See Appendix 8.

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 10 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;

- 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 is allowed.

    - 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 despite anticoagulation treatment (see Section 4.1.2).

- Use of warfarin or Coumadin-like products (includes for prophylactic use) is prohibited.

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

- Concomitant chronic use of NSAIDs while receiving study drugs is prohibited, with the exception of chronic low-dose aspirin (< 325 mg/day). However, for the symptomatic relief of medical conditions (e.g., headache, fever) intermittent or short-term intake of oral NSAIDs is allowed, when co-administered with proton pump inhibitors to reduce potential GI damage.

4.4.4 Prohibited Food

Use of the following foods is prohibited as described below:

Consumption of grapefruit juice, a potent CYP3A4 enzyme inhibitor, is prohibited during the study and for 30 days after the final dose of study treatment.

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 (ICFs) 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 enrolment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

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

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

4.5.3 Physical Examinations

A complete physical examination, performed at screening 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 tumour 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

	Timing for Vital Sign Measurements	
Drug	First Infusion	Subsequent Infusions
Atezolizumab	• Within 60 minutes prior to the Atezolizumab infusion • Record patient's vital signs during or after the infusion. **If clinically indicated**, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion.	• 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 Tumour and Response Evaluations

Patients will undergo tumour assessments at baseline, every 6 weeks (± 1 week) for the first 54 weeks following treatment initiation, and every 12 weeks (± 1 week) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 criteria (see Appendix 4) 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,

tumour 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, tumour assessments may be repeated at any time if progressive disease is suspected.

All measurable and evaluable lesions should be assessed and documented at screening. Tumour assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening.

Screening assessments must include CT scans (with oral or IV contrast) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest 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 tumour assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

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

Objective response at a single timepoint will be determined by the Investigator according to RECIST v1.1 (see Appendix 4). 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, outlined in the schedule of activities (see Appendix 1), will be sent to the study site's local laboratory for analysis:

- **Haematology**: white blood cell (WBC) count, red blood cell (RBC) count, haemoglobin, haematocrit, 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), sodium, potassium, magnesium, chloride, glucose,

BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH, amylase, lipase and α-fetoprotein.

- Coagulation: INR, and aPTT.

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

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

4.5.7 Electrocardiograms

An electrocardiogram (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 Blood and Tissue Samples for Exploratory Tissue and Blood Biomarker Plan Study

The main ICF will contain information about the Tissue and Blood Biomarker plan.

The following samples will be stored locally, until shipment to a central laboratory identified by the Sponsor, for the exploratory Tissue and Blood Biomarker Plan:

- Blood samples for exploratory research on biomarkers.

- Tumour biopsy samples from screening (if available) to characterize the tumour immune cell infiltrate by multiparametric immunofluorescence.

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

For more details on the Tissue and Blood Biomarker Plan for patients included in the translational research, see Section 2.4. For a summary of the schedule for blood and tissue biomarker samples to be taken from patients, see Appendix 2.

Blood and tumour biopsy 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 analysed, 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.

4.5.9 Exploratory Radiomic Analysis Plan

The Informed Consent Form will contain information about the Radiomic Analysis Plan of the patient's CT scans. Patients with any contraindication to intravenous contrasts cannot be included in the Radiomic Analysis Plan.

The Radiomic Analysis Plan will not require additional CT Scans for patients who agreed to participate. All the radiomic analyses will be performed on the same images acquired for tumour assessment during the study treatment.

For collecting CT Scans procedures, storage conditions, and shipment instructions, see the Radiomic Analysis Plan protocol (Appendix 3).

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (Atezolizumab + Bevacizumab) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event.
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment.
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient.
- Use of another non-protocol anti-cancer therapy.
- Pregnancy.
- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). See Section 3.1.1 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 tumour response assessments (see Appendix 1).

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

4.6.2 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 enrolment 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 9 (Bevacizumab) and Appendix 10 (Atezolizumab). Refer to Section 5.2, Section 5.3, Section 5.4, Section 5.5, and Section 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 COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a

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

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, severe cutaneous adverse reactions, pericardial disorders, nephritis, and myositis. In addition, immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 10 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for Atezolizumab.

5.1.2 Risks Associated with Bevacizumab

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

Refer to Appendix 9 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 9 (Bevacizumab) and Appendix 10 (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 9 (Bevacizumab) and Appendix 10 (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 AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavourable 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 (CRS), HLH and MAS.
- Nephritis.
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis).
- Grade ≥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.

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 Section 5.4, Section 5.5, and Section 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 fulfils the criteria specified below. Evidence exists that the adverse event has an aetiology 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 (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, HLH, tumour 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 the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF 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 8.

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 time points 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 hypokalaemia) or a change in concomitant therapy.

- Is clinically significant in the investigator's judgment.

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

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

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

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

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

- Treatment-emergent ALT or AST >3×baseline value in combination with total bilirubin >2×ULN (of which ≥35% is direct bilirubin).

- Treatment-emergent ALT or AST >3×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 metastatic 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 as an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of metastatic 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.

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. Special situations and non serious AEs associated with special situations need to be reported to Roche within 30 calendar days. If the associated adverse event fulfils seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For Atezolizumab and Bevacizumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

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

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

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

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

- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong

dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.

- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

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

5.3.5.13 Patient-Reported Outcome Data

There will be no patient reported outcomes (PROs) collected in this study. Adverse event reports will therefore not be derived from PRO data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile patient reports of treatment-related symptoms with investigator reports of adverse events.

5.3.5.14 Biomarker Data

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)

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

- Pregnancies (see Section 5.4.3 for details on reporting requirements)

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

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

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

5.4.1 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Centre will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Centre 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 Centre, will be distributed to investigators.

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

5.4.2.1 Events that Occur Prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and 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 to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of Atezolizumab or 6 months after the last dose of Bevacizumab.

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 foetus. 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 foetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

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

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. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the foetus, 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 embryofoetal 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 embryofoetal toxicity is not considered an adverse event.

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, 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

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, 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

This is not a hypothesis testing study but an exploratory study with predefined precision of estimates for key safety parameters for sample size determination; there are no formal statistical hypotheses tests to be tested, and there will be no adjustments for multiplicity of endpoints or within-subgroups comparisons.

6.1 DETERMINATION OF SAMPLE SIZE

This study will enrol approximately a sample of convenience (Lohr 2010) of 100 patients across approximately 20 Spanish sites, possibly according to a competitive enrolment scheme (Kim et al. 2017). Approximately 100 patients will be recruited in 12 months and estimated 25 sites will participate in the study.

With this sample size, estimates of the observed frequencies exceeding 10-20% will have an acceptable precision (e.g., 95% confidence limit ± 5-6%), while for rare AE's, rather imprecise estimates will be obtained. For example, with an expected frequency of 1-2% (2-3 events in the 100 patients) the 95% CI of the observed proportion will cover a range of values compatible with the expected results with a 12-fold or greater of variation. For the same reason, a 2 to 3-fold increase over the expected frequencies might easily be observed by chance. As a consequence, the results for rare AEs in this study will have to be interpreted with caution.

The table below displays the confidence level and the width at observed frequencies of 10%, 15% and 20%. As shown, a sample size of 100 produces a two-sided 87% confidence interval with a width equal to 0.1 when the sample proportion is 10%, an 80% confidence interval with a width equal to 0.1 when the sample proportion is 15% and a 74% confidence interval with a width equal to 0.1 when the sample proportion is 20%.

Confidence Level	Sample size (N)	Target Width	Actual width	Proportion (P)	Lower limit	Upper limit	Width if p=0.5
0.866	100	0.1	0.1	0.1	0.05	0.15	0.16
0.792	100	0.1	0.1	0.15	0.1	0.2	0.136
0.739	100	0.1	0.1	0.2	0.15	0.25	0.123

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 SAS, 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, self-reported race/ethnicity) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Missing values will also be displayed, and they will be classified and managed using the methods outlined in the statistical analysis plan (SAP). Reproductive status and smoking history should also be captured. Summaries of patient's baseline cancer history will include stage, date of diagnosis, and any prior anti-tumour treatment. Demographic information includes age and self-reported race/ethnicity.

Missing values will be classified according to their underlying missing mechanism (missing completely at random; missing at random; missing not at random) and pattern (monotonic; generalized; univariate) (van Buuren et al. 1999; Little and Rubin 2002; van Buuren 2018). If necessary, 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).

6.4 SAFETY ANALYSES

This study is primarily a safety study. The safety analysis population of this single-arm study will consist of all enrolled patients who received at least one full or partial dose of study treatment.

6.4.1 Primary Analysis

The primary safety analysis will evaluate the incidence of treatment discontinuations of Atezolizumab and/or Bevacizumab due to adverse events of grade ≥ 3. Verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. Adverse event severity will be graded according to NCI CTCAE v5.0.

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

6.4.2 Other Safety Analyses Including Analyses of Exposure, Adverse Event Severity, Laboratory, Vital Sign, and Hepatic Function Data

Drug exposure will be summarized by descriptive statistics to include treatment duration, number of doses, and dose intensity. The following events occurring during or after the first dose of study treatment will be summarized by NCI CTCAE 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.
- Immune-related 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 events leading to temporary interruption of any component.
- All adverse events leading to temporary interruption of Atezolizumab.
- All adverse events leading to temporary interruption of Bevacizumab.

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

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

Additional analyses may be performed as indicated.

Missing data for items and patients will be summarized to improve results interpretation.

6.5 EFFICACY ANALYSES

6.5.1 Primary Efficacy Endpoints

This study is not designed to primarily evaluate efficacy. All baseline summaries and efficacy analyses will be based on the ITT analysis set defined as all recruited patients.

The main analysis of efficacy will be an analysis of OS, defined as the time from initiation of study treatment to death from any cause. Deaths with causes of death reported during the study will also be summarized.

Other efficacy endpoints for the study are as follows:

- 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

- ORR, defined as a complete or partial response, on two consecutive occasions, 4 weeks apart, as determined by the investigator according to RECIST v1.1

- 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

- 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.

- Number/Rate of patients starting second line treatment.

Time-dependent variables OS, PFS, TTP, DOR and PPS will be analysed using Kaplan-Meier (K-M) methods (Kaplan and Meier 1958) and Greenwood's formula (Greenwood 1926). Medians and quartiles with 95% confidence interval (CI) will be derived from the K-M curves. K-M plots with a 95% CI for OS, PFS, TTP, DOR and PPS will be prepared.

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

To evaluate whether the reason for treatment withdrawal has an impact on OS, OS based on the following reasons for treatment withdrawal will be described:

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

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

6.5.2 Exploratory Efficacy Endpoints

Exploratory efficacy analyses will be as follows:

- To further, evaluate whether the patterns of tumour responses to Atezolizumab + Bevacizumab treatment using different criteria have a different impact on OS and PFS. The different criteria for evaluation of tumour responses that will be compared are as follows: RECIST 1.1, HCC mRECIST, EASL and iRECIST criteria. Further details on the patterns of progression measured by these criteria are given in Section 2.2.

- - To further evaluate whether the patterns of tumour progression (growth versus new lesion, intrahepatic versus extrahepatic) have a different impact on OS and PFS. RECIST 1.1 criteria will be used to evaluate of tumour progression. Additionally, a secondary analysis for the registration of tumour progression will include HCC mRECIST, taking into consideration the RECIST modifications described for SHARP (Reig 2014). Further details on the patterns of progression measured by both these criteria are given in Section 2.2.

- To explore whether post-study treatments have an impact on OS. OS will be analysed according to type and duration of each post-study treatments.

- To evaluate whether reasons for treatment withdrawal (progressive disease or AE) have an impact on OS.

- To analyse the organ-specific response rate (OS-RR) using RECIST 1.1 and the cumulative incidence probability of organ-specific progression RR including target lesions from the liver, lungs, lymph-nodes and non-target lesions in bones.

- To determine the applicability of depth of response (decrease in tumour burden) as a surrogate for OS when compared to baseline measurement according to RECIST 1.1, EASL mRECIST and iRECIST criteria.

6.6 BIOMARKER AND RADIOMIC ANALYSES

The Tissue & Blood Biomarker Plan for patients included from the study included in translational research aims to identify biomarkers that might be potentially associated with response patterns to Atezolizumab + Bevacizumab or the HCC disease evolution under

Atezolizumab + Bevacizumab treatment. Further details of the exploratory biomarkers to be investigated are given in Section 2.6.

Although no formal statistical analysis of these exploratory biomarkers will be performed, data may be analysed in the context of this study and in aggregate with data from other studies.

This study includes CT Radiomic Analysis Plan designed to more precisely evaluate the tumour response to Atezolizumab and Bevacizumab in patients with unresectable HCC. Further details of the parameters to be evaluated in the CT Radiomic Analysis Plan are given in Section 2.6. Although no formal statistical analysis of these exploratory biomarkers will be performed, data may be analysed in the context of this study and in aggregate with data from other studies.

6.7 INTERIM ANALYSIS

6.7.1 Planned Interim Analysis

One 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.

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.

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) is entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD (IRB) OR ETHICS COMMITTEE (EC)

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).

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 and radiomic 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).

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).

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

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

and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate).

Site Inspections

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

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Roche Farma, S.A. (C/ Ribera del Loira 50, 28042 Madrid, Spain).

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

26 sites in Spain will participate in the study to enrol approximately 100 patients. Screening and enrolment 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.

The SC will monitor and evaluate patient safety throughout the study. Tumour response and progression will be evaluated by an IRC.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

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

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective

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 multicentre trials only in their entirety and not as individual centre data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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APPENDIX 1 – SCHEDULE OF ACTIVITIES

Assessment Window (Days) [a]	Screening [b]			Treatment Phase (Q3W)	Treatment Discontinuation [c]	Survival Follow-Up
	–28 to –1	–14 to –1	-7 to -1	Day 1 of Each Cycle [c]	≤ 30 Days after Last Dose	
Signed Informed Consent Form(s) [b]	x					
Review of eligibility criteria	x					
Medical, surgical, and cancer histories, including demographic information [d]	x					
Complete physical examination [e]	x					
Limited physical examination [f]				x [g]	x	
ECOG Performance Status [g]			x	x [g]	x	
Child Pugh			x			
Radiological tumour 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		
Oesophageal and/or gastric varices assessment (EGD [l])				Perform as clinically indicated		
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 [p]	x [p]	
Alpha fetoprotein (local laboratory)	x			x	x	
Coagulation panel (aPTT, 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**	
Concomitant medications [t]		**x**		**x**	**x**	
Adverse events [u]	**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**		
Survival and anti-cancer therapy follow-up [w]						**x**
Tumour biopsy sample (if available) for biomarker plan	**x**					
Blood samples for biomarker plan	**x**			**Day 1 of Cycle 2 and then Day 1 of Cycle 3**		
CT Scan for Radiomic plan	**x**			**Week 6 (prior cycle 3) & week 12 (prior cycle 5)**	**x**[x]	

CT = computed tomography; EGD = esophagogastroduodenoscopy; 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; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours, 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-tumour treatment. Demographic information includes age and self-reported race/ethnicity. Reproductive status and smoking history should also be captured.

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

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

[g] ECOG Performance Status at screening must be recorded between day -7 and day -1 before Day 1 of Cycle 1. 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. Tumour assessments will be performed at baseline, every 6 weeks (± 1 week) for the first 54 weeks following the initiation of study treatment, and every 12 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 tumour evaluation. Tumour response will be evaluated by the investigator using RECIST Version 1.1. In the absence of disease progression, tumour 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.

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

[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.

[k] The dose of Bevacizumab will be based on the patient's weight (in kilograms) measured ≤ 14 days prior to baseline (the initiation of study treatment) and will remain the same throughout the study unless there is a weight change of > 10% from baseline. If re-baseline is needed the latest baseline weight should always be used to calculate percent change in weight for all subsequent doses.

[l] All patients must undergo an EGD within 6 months of starting the study and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrolment.

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

Appendix 1. Schedule of Activities

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

[o] All patients will be tested for HIV locally prior to the inclusion into the study and if not in contradiction with local legislation; HIV-positive patients will be excluded from the clinical study. HBsAg, 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 serologically 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.

[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 and must demonstrate < 1 g of protein in 24 hours.

[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. Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new anti-cancer therapy, whichever occurs first. After this period, investigators should report any serious adverse events and adverse events of special interest that are believed to be related to prior treatment with study drug. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, new *systemic* anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it is determined that the study treatment or participation is not the cause of the adverse event. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-related procedures until a final outcome can be reported.

[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 tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 (± 10) minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. 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 the study treatment until there is evidence of disease progression or lack of clinical benefit.

[w] 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.

[X] Progression Scan.

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

APPENDIX 2 – SCHEDULE OF SAMPLES FOR TISSUE AND BIOMARKER PLAN

Visit	Timepoint	Sample Type
Screening (Day −28 to Day –1)	Prior to first infusion of Atezolizumab	**Tumour biopsy sample** if available to characterize: (1) Tumour immune cells infiltrate by immunofluorescence. (2) The specificities of T lymphocyte receptors against tumour-specific antigens. (3) Specific expression patterns that may constitute gene signatures with prognostic and/or predictive power of response to Atezolizumab + Bevacizumab.
● **Screening** (Day −28 to Day –1) ● Cycle 2 (week 3) ● Cycle 3 (week 6)	Prior to first infusion of Atezolizumab	Biomarker (blood, plasma, and serum) sample to evaluate: (1) Cytokines. (2) cfDNA exome sequencing to capture mutations present in circulating DNA. (3) Sequencing the TCRs of circulating T cells to detect specific antigenicity of tumour antigens. (4) Flow cytometry to see leukocyte subpopulations that can predict response.

APPENDIX 3 – RADIOMIC ANALYSIS PLAN

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Appendix 3. Radiomic Analysis Plan

1. Background and rationale

Medical imaging allows for non-invasive oncologic diagnosis and treatment guidance. Radiomics converts imaging data into large number of quantifiable features from tumour tissue using automatically extracted data-characterization algorithms. Radiomics can i) facilitate a deeper understanding of tumour biology, ii) capture tumour heterogeneity and iii) monitor tumour evolution and response to therapy (1-3). Moreover, with the development of high-throughput methods to extract and correlate multiple imaging parameters with genomics data, a new opportunity in medical research has emerged. Radiogenomics aims to correlate imaging features (i.e., the imaging phenotype) with gene expression patterns, gene mutations, and other genome-related data. Radiogenomics can be used to develop imaging surrogates for specific genetic signatures to predict outcome and assess response to anticancer targeted therapy such antiangiogenics and immunotherapy in hepatocarcinoma (HCC) towards a more precise patient care (4, 5).

The most widely used medical imaging modality in oncology is computed tomography (CT), which assesses tissue density. CT is performed as standard of care in the vast majority of patients with HCC before starting treatment and routinely for assessing response (6). Due to the non-invasive nature of CT, its capacity of study the whole body in just a few seconds and its broad use in clinical practice, CT-radiomics is a promising tool for radiogenomics signatures development and the identification of novel predictive and response biomarkers to immunotherapy and anti-angiogenic treatments (7-9).

2. Objectives of the analysis

i. To explore the correlation CT-radiomics signatures (including shape, first-order and higher-order texture features) at baseline with response to atezolizumab and bevacizumab, in patients with untreated unresectable hepatocellular carcinoma included in the study (ML42600).

ii. To explore early changes in CT-radiomics signatures as response to atezolizumab and bevacizumab, in patients with untreated unresectable hepatocellular carcinoma included in the study (ML42600).

iii. To explore inter- and intra-tumour heterogeneity changes in CT-radiomics signatures in relation to differences in responder/non-responder lesions to atezolizumab and bevacizumab, in patients with untreated unresectable hepatocellular carcinoma included in the study (ML42600).

iv. To evaluate the correlation of radiomics features with tumour mutational status to develop radiogenomics phenotypes, in patients with untreated unresectable hepatocellular carcinoma included in the study (ML42600).

v. To evaluate the correlation of CT-radiomics features with the tumour microenvironment on biopsied lesions including tumour immunophenotype by RNA seq and vascularisation from tumour samples in patients with untreated unresectable hepatocellular carcinoma included in the study (ML42600).

Appendix 3. Radiomic Analysis Plan

3. Imaging protocol

Patients included in the study ML42600 will have a CT scan at baseline, before starting treatment with Atezolizumab and Bevacizumab (within 28 days of Cycle 1, Day 1), and every 6 weeks (± 1 week) during the first 54 weeks of treatment with Atezolizumab and Bevacizumab and every 12 weeks (± 1 week) thereafter. This will continue until PD defined by RECIST 1.1/iRECIST criteria, or loss of clinical benefit defined by the response criteria defined in the main study protocol, whichever occurs last, even if starting a new anticancer therapy. If disease progression is documented prior to week 6, CT will be done at this point.

For the Radiomic plan, no additional scans are required. Only the CT scans performed at baseline, week 6, week 12 and at disease progression will be required to ship for central radiomic evaluation.

The CT acquisition protocol will include:

Scan phase/delay	**Pre-contrast**	**Post contrast chest**	**Arterial phase (late arterial phase strongly preferred)**	**Portal venous phase**	**Delayed venous phase**
Scan Locations/Coverage:	Abdomen and pelvis performed in one breathhold	Chest	Entire liver performed in one breathhold	Abdomen and Pelvis in one breath-hold	entire liver performed in one breathhold
FOV	Large				
Slice thickness	5 mm or lower				
Reconstruction interval (distance between slice locations)	5 mm				
Gap (slice spacing)	No				
Contrast media					
Oral contrast	Not required				
Iv contrast	Required 100 - 150 mL Non-ionic only 150-300 mg/mL				
Dose	1.5-2mL/kg body weight				
Rate of injection	4 cc / sec (power injector)				
Reconstruction algorithm	- Convolution kernels B20f, B20s, B30f and B30s from Siemens (Erlangen, Germany) - B from Philips Electronics (Eindhoven, Netherlands) - Soft from General Electric (Boston, USA)				

Appendix 3. Radiomic Analysis Plan

Timing of multiphase sequences for the chest and liver

Multiphase acquisitions	Phase	Specifications
Fixed time delay	Chest CT scan	25 seconds after starting injection at 3 mL/s
	Arterial phase	45 seconds after starting injection at 3 mL/s
	Portal venous phase	60-80 s after the start of injection at 3 mL/s
	Delayed venous phase	4-5 minutes after the start of injection
Bolus tracking (recommended)	Chest CT scan	Aortic triggering is performed at ascending aorta. After threshold aortic enhancement of 100-120 HU is reached, a scan delay of 6 seconds is suggested for chest CT scan.
	Arterial phase	After the chest CT scan had been acquired, a scan delay of 10 seconds is suggested for late arterial phase acquisition.
	Portal venous phase	30-35 seconds after late arterial phase acquisition
	Delayed phase	4-5 minutes after the start of injection

4. Health and Safety considerations

Local health and safety requirements should be followed at all times.

CT images will be acquired after intravenous contrast administration, the procedure is almost entirely safe. The CT scans will be reviewed by radiology staff and made available to the clinical units in the standard way, so the CT scans will contribute to patient management.

5. Imaging data collection

Acquisition and analysis CT data will be collected at each centre and uploaded into a server after anonymization and linked to an alphanumeric code assigned in the protocol ML42600 Anonymization will be performed on-site by the owner of the information, and to make it feasible to trace it back). Defined investigators at each of the recruiting centres will be in charge of the scans upload into the server. The clinical investigator team at each clinical centre will compromise to keep the identity of the subjects' confidential code. The link between the anonymization code and real personal data will be safely stored at the clinical centre, and only the local investigator will have access to it. The collection and processing of CT scans from enrolled subjects will be limited to those data that are necessary to fulfil the objectives of the study. These data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection European and National regulations. Appropriate technical and organizational measures to protect the

personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration will be put in place. Given the complexity and exploratory nature of the exploratory analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche's policy on study data publication.

6. Quality control and quality assurance

The overall monitoring of safety issues related to the Radiomic Analysis Plan will be performed by the study management group CT acquisition and post-processing are subject to internal validation and standardization processes. It is the responsibility of the participating centres to inform the Radiomic Analysis Plan team of any upgrades to the CT scanner hardware or software.

7. Imaging analyses

Target lesions corresponding to the primary tumour and metastases will be selected for radiomics features extraction. Target lesions will be selected based on size (≥ 1 cm in large diameter for solid lesions and ≥ 1.5 cm in short diameter for nodes), preferably well-defined and avoiding for cystic changes and cavitation.

Multiple radiomics features from the target lesions will be extracted, including:

i) First order features (energy, entropy, minimum, percentiles, maximum, mean, median, interquartile range, range, standard deviation, skewness, kurtosis, among others).

ii) Shape Features (volume, surface area, sphericity, among others).

iii) Different filters for texture analysis will be applied for higher order statistics texture analysis, including Gray Level Co-occurrence Matrix (GLCM) and Gray Level Run Length Matrix (GLRLM) features among others.

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APPENDIX 4 – RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS, VERSION 1.1 (RECIST V1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumours, 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]

TUMOUR MEASURABILITY

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

DEFINITION OF MEASURABLE LESIONS

Tumour Lesions

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumour 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.

Appendix 4. Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST V1.1)

METHODS FOR ASSESSING LESIONS

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

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

CLINICAL LESIONS

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

CHEST X-RAY

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

CT AND MRI SCANS

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

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOUR MARKERS, CYTOLOGY, HISTOLOGY

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

ASSESSMENT OF TUMOUR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumour 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 tumour. 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 tumour. 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 x 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 tumour assessment as a measure of tumour 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, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

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

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

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

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

Measuring Lesions That Split or Coalesce on Treatment

When non-lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce,

a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

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

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

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

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

  All lymph nodes must be non-pathological in size (< 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumour marker level above the normal limits.

- PD: Unequivocal progression of existing non-target lesions.

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumour 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 tumour (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table A4-1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table A4-1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

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

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

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an

objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table A4-1.

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

REFERENCES

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

APPENDIX 5 – MODIFIED RECIST (mRECIST) ASSESSMENT FOR HEPATOCELLULAR CARCINOMA

The Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma can be found at the following website:

https://imaging.cancer.gov/clinical_trials/docs/mRECIST%20for%20HCC%202010.pdf

APPENDIX 6 – EASL GUIDELINES FOR THE CLINICAL MANAGEMENT OF HEPATOCELLULAR CARCINOMA

The EASL guidelines for the clinical management of hepatocellular carcinoma, including imaging assessments to evaluate for disease progression can be found at the following website:

https://www.sciencedirect.com/science/article/pii/S0168827818302150

APPENDIX 7 – 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.

Appendix 7. Preexisting Autoimmune Diseases and Immune Deficiencies

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anaemia • Autoimmune haemolytic anaemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myelitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • 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 anaemia • 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

APPENDIX 8 – ANAPHYLAXIS PRECAUTIONS

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

REQUIRED EQUIPMENT AND MEDICATION

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

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

PROCEDURES

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

1. Stop the study treatment infusion.

2. Call for additional medical assistance.

3. Maintain an adequate airway.

4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.

5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.

6. Continue to observe the patient and document observations.

7. Collect serum and plasma samples for immunogenicity testing.

8. Ask the patient to return for immunogenicity sample collection at the time of washout, if appropriate.

APPENDIX 9 – GUIDELINES FOR MANAGEMENT OF ADVERSE EVENTS ASSOCIATED WITH BEVACIZUMAB

1. Dose Modifications

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

2. Treatment Interruption

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.

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

If Bevacizumab treatment is withheld or discontinued, Atezolizumab can be continued as long as the patient is experiencing clinical benefit, as determined by the investigator per medical judgment.

3. Management Guidelines

Guidelines for management of patients who experience adverse events associated with atezolizumab are provided in Appendix 10.

For cases in which management guidelines are not covered in the bevacizumab Investigator Brochure or this protocol, patients should be managed as deemed appropriate by the investigator according to their best medical judgment.

Table A9-1 provides guidelines for the management of patients who experience adverse events associated with Bevacizumab.

Appendix 9. Guidelines for Management of Adverse Events Associated with Bevacizumab

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

Event	CTCAE Version 5.0 Grade	Action to be Taken
Allergic reactions or Infusion-related reactions Or Anaphylaxis	Grade 1	Systemic intervention not indicated – continue bevacizumab.
	Grade 2	Oral intervention indicated – slow infusion to 50% or interrupt if clinically indicated (re-start infusion at 50% and increase in 50% increments if well tolerated). Infusion can be re-started at the full rate for subsequent infusions.
	Grade 3	Bronchospasm (allergy-related oedema/angioedema; hypotension); hospitalization for clinical sequelae; intravenous intervention indicated – discontinue bevacizumab.
	Grade 4	Life-threatening consequences; urgent intervention indicated - discontinue bevacizumab.
Thromboembolic Event (arterial)	Any Grade	Discontinue bevacizumab
Thromboembolic Event (Venous)	Grade 3	Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2weeks, bevacizumab should be held until the full-dose anticoagulation period is over. The use of direct oral anticoagulants is not recommended. If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed during full-dose anticoagulation IF all the criteria below are met: - The patient must not have pathological conditions that carry high risk of bleeding (e.g., tumour involving major vessels or other conditions). - The patient must not have had haemorrhagic events > grade 2 while on study.

Appendix 9. Guidelines for Management of Adverse Events Associated with Bevacizumab

Event	CTCAE Version 5.0 Grade	Action to be Taken
		- The patient must be on stable dose of heparin, low molecular weight heparin, or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab.
	Grade 4	Discontinue bevacizumab.
Hypertension	[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice.]	
	Grade 1 (SBP 120-139 mmHg or DBP80-89 mm Hg)	Consider increased BP monitoring; start anti-hypertensive medication if appropriate.
	Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg)	Begin (or modify baseline anti-HTN therapy) anti-hypertensive therapy and continue bevacizumab.
	• Grade 2 symptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg)	• Start or adjust anti-hypertensive medication.
	• Grade 3 • (≥ SBP 160 mmHg or ≥ DBP 100 mmHg	• Modify existing anti-HTN therapy (more than one drug or more intensive therapy than previously indicated. • Hold bevacizumab until symptoms resolve AND BP < 160/90 mm Hg.
	Grade 4 (e.g., hypertensive crisis or malignant hypertension)	Discontinue bevacizumab.
Heart Failure or left ventricular dysfunction	Grade 3	Discontinue bevacizumab.
	Grade 4	Discontinue bevacizumab.
Proteinuria*	1+ proteinuria (≥ ULN - < 1.0 g/24h)	Continue bevacizumab.

Appendix 9. Guidelines for Management of Adverse Events Associated with Bevacizumab

Event	CTCAE Version 5.0 Grade	Action to be Taken
	2+ and 3+ proteinuria (1.0 - < 3.5g/24h)	2+ - administer bevacizumab and obtain 24-hour urine protein before next administration. 3+ - obtain 24-hour urine protein and administer bevacizumab if < 2.0 g/24h.
	4+ proteinuria (≥ 3.5 g/24h)	Obtain 24-hour urine protein and administer bevacizumab only when < 2.0 g/24h.
Nephrotic syndrome		Grade 3 or 4 Discontinue bevacizumab.
Haemorrhage (CNS)	Any grade	Discontinue bevacizumab.
Haemorrhage (haemoptysis)	Grade 1	Trace haemoptysis; continue bevacizumab.
	Grade 2 - 4	≥2.5 mL bright red blood per episode; discontinue bevacizumab.
Haemorrhage (other)	Grade 3 - 4	Discontinue bevacizumab.
RPLS (Reversible Posterior Leukoencephalopathy syndrome or PRES (Posterior Reversible Encephalopathy Syndrome)		Discontinue bevacizumab.
Wound dehiscence requiring medical or surgical intervention		Discontinue bevacizumab.
Perforation (GI, or any other organ)		Discontinue bevacizumab.
Fistula (GI, pulmonary or any other organ)		Discontinue bevacizumab.
Obstruction of GI tract	G2 requiring medical intervention	Hold bevacizumab until complete resolution.
	G3-4	Hold bevacizumab until complete resolution. If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion.
Febrile neutropenia	Grade 3	Continue bevacizumab.
	Grade 4	Hold bevacizumab until resolution or return to baseline.
Platelet count decreased	Grades 1 - 3	Continue bevacizumab.
	Grade 4	Hold bevacizumab until resolution or return to baseline.
Other Unspecified bevacizumab-related AEs (except controlled nausea/vomiting).	Grade 3	Hold bevacizumab until symptoms resolve to ≤grade 1 or baseline.
	Grade 4	Discontinue bevacizumab. Upon consultation with the study chair/medical monitor, resumption of bevacizumab may be considered if a patient is benefiting from

Event	CTCAE Version 5.0 Grade	Action to be Taken
		therapy, and the G4 toxicity is transient, has recovered to ≤grade 1 (or baseline) and unlikely to recur with retreatment.

*Institutional protocols acceptable

APPENDIX 10 – RISKS ASSOCIATED WITH ATEZOLIZUMAB AND GUIDELINES FOR MANAGEMENT OF ADVERSE EVENTS ASSOCIATED WITH ATEZOLIZUMAB

Table of Contents

Appendix 10. Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

1. Background

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 aetiology.

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

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

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

- In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.

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

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

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

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

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of Atezolizumab. 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 assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

2. Dose Modifications

There will be no dose modification for Atezolizumab in this study.

3. Treatment Interruption

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

4. Management Guidelines

4.1 Pulmonary Events

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnoea 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 tumour assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported aetiologies 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 A10-1.

Appendix 10. Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Table A10-1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue Atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab.
Pulmonary event, Grade 2	• Withhold Atezolizumab for up to 12 weeks after event onset. [a] • Refer patients 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, with no improvement after 48–72 hours of corticosteroids, treat as treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue Atezolizumab and contact the Medical Monitor. [c] • 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 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.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to 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 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.

4.2 Hepatic Events

Patients eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table A10-2.

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 aetiologies 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. • For events of > 5 days' duration, consider initiating treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to baseline or to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to baseline or to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
AST or ALT increases to > 10 × ULN or total bilirubin increases to > 3 × ULN	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish aetiology 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.

4.3 Gastrointestinal Events

Management guidelines for diarrhoea or colitis are provided in Table A10-3.

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 (Diarrhoea or Colitis)

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

GI = gastrointestinal.

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

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

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

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

4.4 Endocrine Events

Management guidelines for endocrine events are provided in Table A10-4.

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

Event	Management
Grade 1 hypothyroidism	• Continue Atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Grade 2 hypothyroidism	• Consider withholding atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume Atezolizumab when symptoms are controlled, and thyroid function is improving.

Grade 3 and 4 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer to an endocrinologist. • Admit patient to the hospital for developing myxoedema (bradycardia, hypothermia, and altered mental status). • Resume atezolizumab when symptoms are controlled, and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Medical Monitor for life threatening immune-mediated hypothyroidism. c
Grade 1 hyperthyroidism	• **TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue Atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. • **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism. • Consider patient referral to endocrinologist.
Grade 2 hyperthyroidism	• Consider withholding Atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume Atezolizumab when symptoms are controlled, and thyroid function is improving.
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Refer to an endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Medical Monitor for life threatening immune-mediated hyperthyroidism.[c]
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold Atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume Atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding Atezolizumab, permanently discontinue Atezolizumab and contact Medical Monitor. [c]
Hyperglycaemia, 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.

Hyperglycaemia, Grade 3 or 4	• Withhold Atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume Atezolizumab when symptoms resolve, and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold Atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1– 2 mg/kg/day IV methylprednisolone and convert to 1– 2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement 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 Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging

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

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

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

4.5 Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table A10-5.

Table 5 Management Guidelines for Ocular Events

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

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

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

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

4.6 Immune-mediated Cardiac Events

Management guidelines for cardiac events are provided in Table A10-6.

4.6.1 Immune-Mediated Myocarditis

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnoea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on pericardial disorders below) and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who

reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate aetiology, should be treated according to the guidelines in Table A10-6.

4.6.2 Immune-mediated Pericardial Disorders

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

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

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

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

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate aetiology, should be treated according to the guidelines in Table A10-6. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the aetiology and manage accordingly.

Table A10-6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2–4 Immune-mediated pericardial disorders, Grades 2–4	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

4.7 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, antipyretics, 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 (Reigler et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including Atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for the medical management of IRRs and CRS are provided in Table A10-7.

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

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 A10-7.

Table A10-7 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, antipyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.

Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. [e] • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue Atezolizumab, and contact Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of Atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretics, 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 Medical Monitor.
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue Atezolizumab and contact Medical Monitor. [f] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. [e] • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.

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 Medical Monitor. [f] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. [e] For patients who are refractory to anti-cytokine therapy, experimental treatments [g] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

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

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

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

[b] Fever is defined as temperature $\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, antipyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnoea, 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 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, antipyretics, 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) for information on experimental treatments for CRS.

4.8 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 A10-8.

Table A10-8 Management Guidelines for Pancreatic Events, Including Pancreatitis

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

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

GI = gastrointestinal.

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

[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 investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

4.9 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 A10-9.

Table A10-9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue Atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue Atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.

Dermatologic event, Grade 3	• Withhold Atezolizumab for up to 12 weeks after event onset.[a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1−2 mg/kg/day if event does not improve within 48−72 hours. • If event resolves to Grade 1 or better, resume Atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding Atezolizumab, permanently discontinue Atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue Atezolizumab and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to 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 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.

4.10 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. Management guidelines for neurologic disorders, with specific guidelines for myelitis are provided in Table A10-10.

Table A10-10 Management Guidelines for Neurologic Disorders

Appendix 10. Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate aetiology. • 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 aetiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • For general immune-mediated neuropathy: – If event resolves to Grade 1 or better, resume atezolizumab. [b] – If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] • For facial paresis: – If event resolves fully, resume atezolizumab [b] – If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

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

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

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

Table A10-11 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 a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue tiragolumab/placebo and atezolizumab/placebo and contact the Medical Monitor. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue tiragolumab/placebo and atezolizumab/placebo and contact the Medical Monitor. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

4.12 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 oedema. 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 aetiology, should be treated according to the guidelines in Table A10-12.

Table A10-12 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact 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.

4.13 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 aetiologies (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 aetiology, should be treated according to the guidelines in Table A10-13.

Table A10-13 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue Atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold Atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume Atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding Atezolizumab, permanently discontinue Atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue Atezolizumab and contact Medical Monitor.[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.

[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.

4.14 Immune-Mediated Myositis

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate aetiology, should be treated according to the guidelines in Table A10-14.

Table A10-14 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 Medical Monitor. [c]
Immune-mediated myositis, Grade 3	• Withhold Atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist.

	• Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume Atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue Atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. Permanently discontinue atezolizumab and contact the Medical Monitor.
Immune-mediated myositis, Grade 4	• Permanently discontinue Atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

4.15 Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if 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:
  - Haemoglobin $<$90 g/L (9 g/dL) ($<$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)
- Haemophagocytosis 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 $\geq$2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin $>$684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq 181 \times 10^9$/L (181,000/μL)
  - AST $\geq$ 48 U/L
  - Triglycerides $>$1.761 mmol/L (156 mg/dL)
  - Fibrinogen $\leq$3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table A10-14.

Table A10-15 Management Guidelines for Suspected Haemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue Atezolizumab and contact Medical Monitor. • Consider patient referral to haematologist. • 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 Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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