PROTOCOL

TITLE:	Prophylactic endoscopic variceal ligation in patients with high-risk esophageal varices receiving atezolizumab plus bevacizumab for hepatocellular carcinoma : A phase II, multicenter, single-arm trial (ESCOAT trial)
VERSION NUMBER:	1.1
REGISTRATION:	To be determined
AUTHOR:	Ju Hyun Shim, MD, PhD Department of Gastroenterology, Liver Center Asan Medical Center, University of Ulsan College of Medicine 88, Olympic-ro 43-gil, Songpa-gu, Seoul, 05505, Republic of Korea Tel.: +82-2-3010-3190 E-mail: s5854@amc.seoul.kr
DATE FINAL:	IRB approval state ~ March 31, 2029
IRB No.	2024-1524
Document date	2024.12.26

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL SYNOPSIS

TITLE:	Prophylactic endoscopic variceal ligation in patients with high-risk esophageal varices receiving atezolizumab plus bevacizumab for hepatocellular carcinoma : A phase II, multicenter, single-arm trial (ESCOAT trial)
VERSION NUMBER:	1.1
REGISTRATION:	To be determined
PHASE:	Phase II
INDICATION:	Hepatocellular carcinoma with high-risk varix

- **Objectives and Endpoints**

This study aims to evaluate the efficacy and safety of prophylactic endoscopic variceal ligation (EVL) in reducing the risk of variceal bleeding among hepatocellular carcinoma (HCC) patients with high-risk esophageal varices, as identified through endoscopy, who are undergoing combination therapy with atezolizumab and bevacizumab (Atezo/Bev). Additionally, the study seeks to analyze the impact of prophylactic EVL on patient survival and quality of life, as well as to identify potential biomarkers that can predict the risk of variceal bleeding and therapeutic response.

- **Study design**
- **Description of Study**

A multicenter, single arm, phase II trial

- **Number of patients**

Total of 44 patients are expected to be enrolled

- **Target study population**

Inclusion Criteria for Participants:

- Patients aged 19 years or older and under 80 years.
- Patients with liver function are classified as Child-Pugh Class A.
- Barcelona Clinic Liver Cancer stage C patients with no prior systemic anticancer therapy for hepatocellular carcinoma.
- Patients with an Eastern Cooperative Oncology Group performance score of 0-1.
- Adequate Hematologic and Liver Function:
  A. Hemoglobin: ≥ 9.0 g/dL
  B. Absolute Neutrophil Count : ≥ 1,000/mm³
  C. Platelet Count: ≥ 70,000/μL

D. Prothrombin Time: ≥ 70% (or Prothrombin Time INR ≤ 1.2)

- Patients with upper gastrointestinal endoscopy performed within six months prior to the start of anticancer treatment.
- No plans for breastfeeding, and if of childbearing potential, using contraception or no plans for spouse's pregnancy or practicing contraception.
- Patients who have received an explanation of the treatment purpose and methods and have provided informed consent for the treatment.

Exclusion Criteria:

- Participants who have previously received systemic anticancer therapy for advanced hepatocellular carcinoma.
- Patients with a prior history of liver transplantation.
- with uncontrolled malignant tumors other than HCC at the time of enrollment (participation is allowed if disease-free survival exceeds two years).
- Patients with uncontrolled or serious underlying diseases requiring treatment.
- Patients with a history of esophageal or gastric variceal bleeding.
- Previous Variceal Treatments: Patients who have undergone any of the following treatments for variceal bleeding:
  A. Endoscopic Variceal Obliteration (EVO)
  B. EVL
  C. Transjugular Intrahepatic Portosystemic Shunt (TIPS)
  D. Percutaneous Approach for Retrograde Transvenous Obliteration (PARTO)
  E. Surgical procedures
- Patients who have used anticoagulants or antiplatelet agents within one week prior to the study.
- Presence of grade 2 or higher isolated gastric varices or Red Color Signs confirmed by baseline endoscopy (EGD).
- Patients who are pregnant.
- Patients who are unable to understand or provide written informed consent.
- Patients deemed unsuitable for clinical study participation based on the investigator’s judgment.

- End of the study

The end of the study will be the date from which the last information of the last patient is recorded in the study database: Until one year after the last patient enrollment (Expected by March 31, 2029)

- Length of Study

The study start date will be the date of the first data collection: the date from which information on the first study patient is recorded in the study database: March 1, 2025 (planned).

This study will be conducted for 2 years approximately. (Enrollment phase: 24 months, minimal follow-up of enrolled period, 1-year minimal follow-up period of 12 months from enrollment)

- **Statistical Methods**

Primary Analysis

- Incidence of esophageal varix bleeding after initiation of Atezo/Bev

  [Timepoint for evaluation: either 6 months from the first Atezo/Bev treatment date or the time of Atezo/Bev treatment discontinuation, whichever occurred first]

Secondary Analysis

- Cumulative incidence of esophageal varix bleeding
- Cumulative incidence of non-variceal GI bleeding
- Overall survival
- Cumulative incidence of liver-related complications (except for varix bleeding)
- Incidence of complications related to endoscopic varix ligation
- Quality of Life Assessment Related to Treatment
- Development of biomarker predicting occurrence of variceal bleeding and clinical outcome

  [Timepoint for evaluation of second anaylsis: either the time from the first Atezo/Bev treatment date to the discontinuation of Atezo/Bev treatment or last follow-up date, whichever occurred first]

  *Liver-related complications are defined as ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy.

- **Determination of Sample size**

Based on previous studies, the incidence of variceal bleeding in liver cancer patients has been reported to be between 9-10%. In patients receiving atezolizumab and bevacizumab for liver cancer, variceal bleeding occurred in 1.3-17.0% during treatment. Notably, Larrey et al. focused on a high-risk patient population with a high prevalence of high-risk varices, where the incidence of esophageal variceal bleeding exceeded 10%.[1]

According to their findings, the incidence of esophageal variceal bleeding at 6 months following the initiation of atezolizumab and bevacizumab treatment was 26% in patients with high-risk varices, compared to 11% in those without varices or with low-risk varices. Based on these results, we hypothesize that prophylactic EVL can reduce the incidence of esophageal variceal bleeding in high-risk varix patients to 8%.

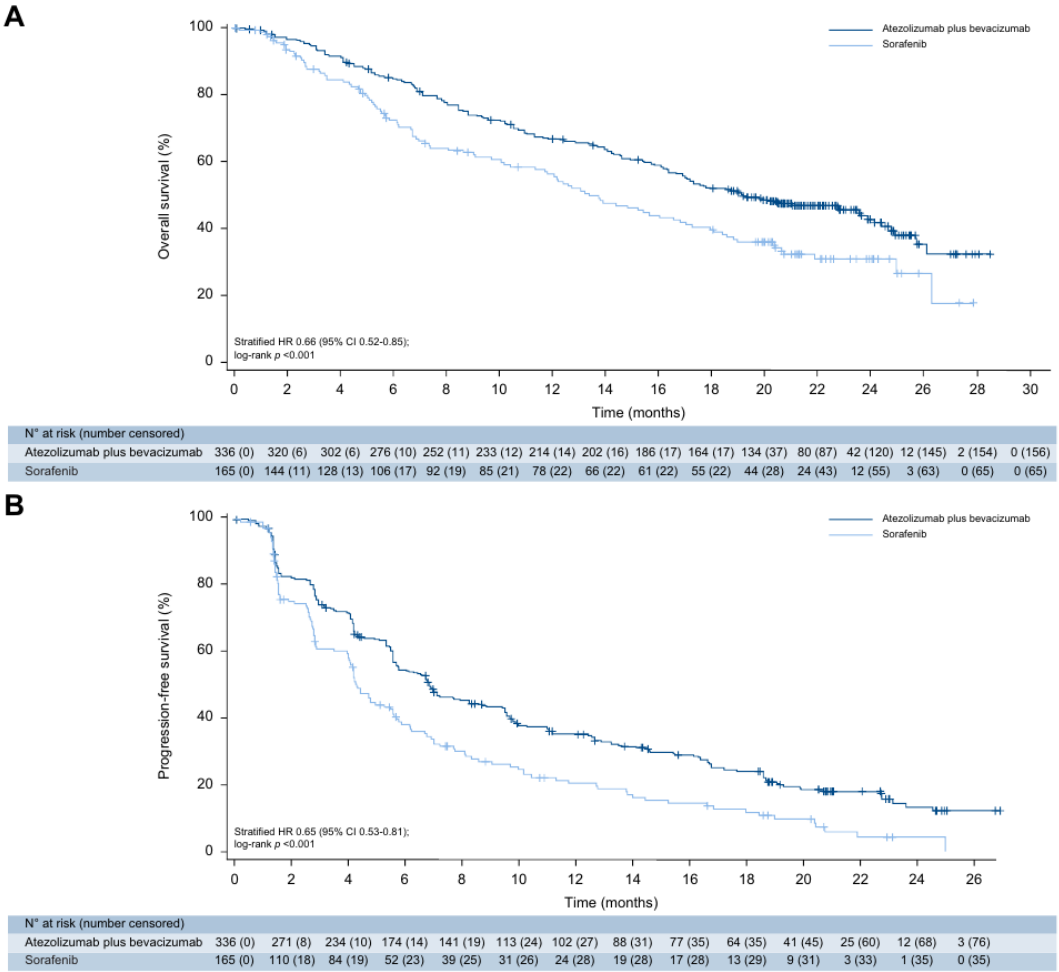
Assuming a recruitment period of 24 months and a follow-up period of 12 months from the last patient enrollment, we calculated the sample size needed to achieve a Type I error rate (α) of 0.05 and 80% power (Type II error, $\beta = 0.20$). The required sample size is 37 patients per group. Considering a 15% drop-out rate, we determined that each group should include 44 participants.

1. BACKGROUND

Atezolizumab plus bevacizumab (Atezo/Bev) is the first-line standard treatment for advanced hepatocellular carcinoma (HCC). Atezolizumab is an immune checkpoint inhibitor, while bevacizumab is a monoclonal antibody that specifically inhibits VEGF (vascular endothelial growth factor).

The combination of atezolizumab and bevacizumab demonstrated significant improvements in overall survival (OS) and progression-free survival (PFS) compared to the previous first-line treatment, sorafenib (SOR), in the phase 3 IMbrave150 study (median OS: 19.2 [95% CI, 17.0–23.7] months vs. 13.4 [95% CI 11.4–16.9] months; PFS: 6.9 [95% CI 5.7–8.6] vs. 4.3 [95% CI 4.0–5.6] months, p<0.001, Figure 1).[2]

Figure 1. Overall and Progression-free survival in atezolizumab plus bevacizumab and sorafenib group. (A) Kaplan-Meier estimates of OS (B) Kaplan-Meier estimates of PFS



Additionally, the objective response rate was higher in the atezolizumab-bevacizumab group (30%) compared to sorafenib (11%, Table 1).[2] This evidence supports the superior efficacy of

Atezo/Bev in improving patient outcomes in advanced HCC.

Table 1. Clinical response in atezolizumab plus bevacizumab and sorafenib group

	Atezolizumab plus bevacizumab (n = 326)	Sorafenib (n = 159)
Objective response, n (%) [95% CI]	97 (30) [25-35]	18 (11) [7-17]
Complete response, n (%)	25 (8)	1 (<1)
Partial response, n (%)	72 (22)	17 (11)
Stable disease, n (%)	144 (44)	69 (43)
Disease control rate, n (%)	241 (74)	87 (55)
Progressive disease, n (%)	63 (19)	40 (25)
Patients with ongoing response, n (%)	54 (56)	5 (28)
Duration of response, median (95% CI), months*	18.1 (14.6-NE)	14.9 (4.9-17.0)
Range, months	2.5-25.6†	2.5†-21.8
Responders with duration of response, %		
≥12 months	69	65
≥18 months	51	22

However, despite the confirmed superior efficacy of Atezo/Bev, concerns regarding safety have been raised. As shown in Table 2, while the incidence of treatment-related adverse events (AEs) and grade 3/4 AEs was lower compared to the sorafenib group, the occurrence of grade 5 or higher AEs, though rare, was higher in the Atezo/Bev group (Treatment-related grade 3/4 [Atezo/Bev vs. SOR]: 43% vs. 46%; Grade 5: 2% vs. <1%). Moreover, the rate of serious treatment-related adverse events was higher in the Atezo/Bev group, with 23% of patients experiencing serious AEs, compared to the sorafenib group (Treatment-related severe AEs: 23% vs. 16%).

Table 2. Safety summary of atezolizumab plus bevacizumab and sorafenib group

	Atezolizumab plus bevacizumab (n = 329)*	Sorafenib (n = 156)*
Treatment duration, months	Atezolizumab: 8.4 (3.5-18.3) Bevacizumab: 7.0 (3.4-15.9)	2.8 (1.4-6.9)
All-cause all grade AE	322 (98)	154 (99)
Treatment-related all grade AE	284 (86)	148 (95)
Grade 3/4 AE†	207 (63)	89 (57)
Treatment-related Grade 3/4 AE†	143 (43)	72 (46)
Serious AE	160 (49)	51 (33)
Treatment-related serious AE	76 (23)	25 (16)
Grade 5 AE	23 (7)	9 (6)
Treatment-related Grade 5 AE	6 (2)	1 (<1)
AE leading to withdrawal from any component	72 (22)	18 (12)
AE leading to withdrawal from both components	34 (10)	0
AE leading to dose interruption of any study treatment	195 (59)	68 (44)
AE leading to dose modification of sorafenib‡	0	58 (37)

AE, adverse event. Data are median (interquartile range) or n (%).
*Safety-evaluable population (defined as patients who received study treatment).
†Highest grade experienced.
‡No dose modification was allowed for atezolizumab or bevacizumab.

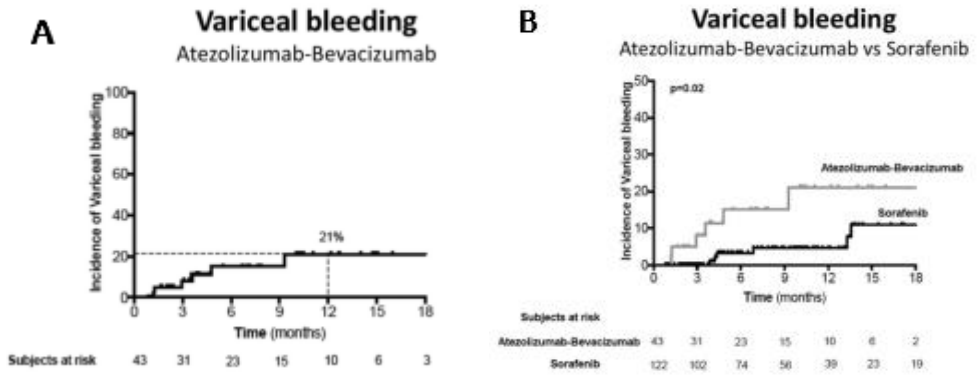
These findings highlight the need for careful monitoring and management of adverse events, especially given the increased risk of serious complications associated with Atezo/Bev treatment, despite its efficacy advantages.

Although the IMbrave150 trial reported a low incidence of gastrointestinal bleeding among treatment-related adverse events, this outcome should be interpreted with caution, as patients with high-risk esophageal varices were excluded from the trial at the time of enrollment. Bevacizumab, which targets circulating VEGF and inhibits the VEGF signaling pathway, affects several critical coagulation processes, leading to either thrombotic or

hemorrhagic complications depending on the patient's condition and the delicate balance of various physiological factors.[3,4] Thus, while bevacizumab offers therapeutic benefits, careful monitoring for vascular complications is essential, particularly in patients at higher risk of bleeding.

Since the IMbrave150 trial, several clinical studies have reported cases of gastrointestinal (GI) bleeding, including variceal bleeding and non-GI bleeding, in liver cancer patients treated with Atezo/Bev. An observational study published in *Liver International* evaluated the incidence of variceal bleeding in liver cancer patients receiving Atezo/Bev therapy. The study found that 14% of patients experienced variceal bleeding, with the 12-month cumulative incidence rising to 21% (Figure 2A).[1] These findings demonstrated a significant increase in the incidence of bleeding compared to the sorafenib-treated group, indicating that while Atezo/Bev offers improved efficacy, it also carries an increased risk of bleeding complications, particularly in patients with varices (Atezo/Bev vs. SOR: 21% vs. 5%, p=0.02, Figure 2B).

Figure 2. Incidence of acute variceal bleeding in the patients treated with atezolizumab plus bevacizumab and in patients (A) Incidence of acute variceal bleeding in the whole population of patients treated with Atezo/Bev; (B) Incidence of acute variceal bleeding in patients treated with Atezo/Bev vs. SOR



The most recent meta-analysis also confirmed a significantly increased incidence of variceal bleeding in liver cancer patients treated with atezolizumab and bevacizumab (Atezo/Bev). According to the analysis, the incidence of variceal bleeding was reported to be 4.31% (95% CI, 2.42–6.63, $p < 0.01$, Table 3), highlighting the bleeding risks associated with this treatment.[5] These findings reinforce concerns raised in prior studies about the potential for bleeding complications in patients undergoing Atezo/Bev therapy, particularly those with preexisting varices.[6,7] This further emphasizes the importance of screening for high-risk varices and considering prophylactic interventions like endoscopic variceal ligation (EVL) to minimize bleeding risks in this population.[8]

Table 3. Prevalence of bleeding event after Atezo/Bev in HCC patients

Outcome	No. of studies	Prevalence,%	95% CI	I^2	*p* for heterogeneity
Any type of bleeding	28	8.42	5.72–11.54	89	<0.01
Grade of bleeding					
Grade III–IV bleeding	19	4.42	2.64–6.10	76	<0.01
Grade V bleeding	6	2.06	0.56–4.22	58	0.04
Bleeding site					
Gastrointestinal bleeding	26	5.48	3.98–7.17	69	<0.01
Variceal bleeding	12	4.31	2.42–6.63	72	<0.01
Non-gastrointestinal bleeding	10	4.27	1.99–7.24	80	<0.01

2. OBJECTIVES AND ENDPOINTS

This study aims to evaluate the efficacy and safety of prophylactic EVL in reducing the risk of variceal bleeding among patients with HCC and high-risk esophageal varices, as identified through endoscopy, who are undergoing combination therapy with Atezo/Bev. Additionally, the study seeks to analyze the impact of prophylactic EVL on patient survival and quality of life, as well as to identify potential biomarkers that can predict the risk of variceal bleeding and therapeutic response.

2.1. EFFICACY OBJECTIVES

2.1.1. Primary Efficacy Objective

- The incidence of esophageal variceal bleeding at 6 months following treatment in patients with HCC receiving atezolizumab and bevacizumab as standard therapy. [Timepoint for evaluation: either 6 months from the first Atezo/Bev treatment date or the time of Atezo/Bev treatment discontinuation, whichever occurred first]

2.1.2. Secondary Efficacy Objective

- Cumulative incidence of acute esophageal varix bleeding after initiation of Atezo/Bev: acute esophageal varix bleeding is defined as:
  i) Current oozing or spurting type bleeding on the esophageal varix
  ii) Stigmata suggesting recent bleeding (pin-point ulceration on the varix, adherent clot, or white protrusion in the setting of hematemesis but no other cause of UGI bleeding)
  iii) Post-EVL ulcer bleeding is also considered esophageal varix bleeding

  [Timepoint for evaluation: either the time from the first Atezo/Bev treatment date to the discontinuation of Atezo/Bev treatment or last follow-up date, whichever occurred first]

- Cumulative incidence of non-variceal GI bleeding: non-variceal GI bleeding is defined as new-onset hematemesis, melena or both combined with overall hemorrhage from the upper GI tract except for esophageal varix bleeding.

  [Timepoint for evaluation: either the time from the first Atezo/Bev treatment date to the discontinuation of Atezo/Bev treatment or last follow-up date, whichever occurred first]

- Overall survival

[Timepoint for evaluation: either the time from the first Atezo/Bev treatment date to the discontinuation of Atezo/Bev treatment or last follow-up date, whichever occurred first]

- Cumulative incidence of liver-related complications (except for esophageal varix bleeding)
  : liver-related complication is defined as ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy.

  [Timepoint for evaluation: either the time from the first Atezo/Bev treatment date to the discontinuation of Atezo/Bev treatment or last follow-up date, whichever occurred first]

- Incidence of EVL-related complications
  [Timepoint for evaluation: either the time from the first Atezo/Bev treatment date to the discontinuation of Atezo/Bev treatment or last follow-up date, whichever occurred first]

- Quality of Life Assessment Related to Treatment
  [Timepoint for evaluation: at every outpatient visit starting from the initiation of the first Atezo/Bev treatment]

- Development of biomarker predicting occurrence of variceal bleeding and clinical outcome
  [Timepoint of evaluation: Assessment will be conducted at the end of study]

3. STUDY DESIGN

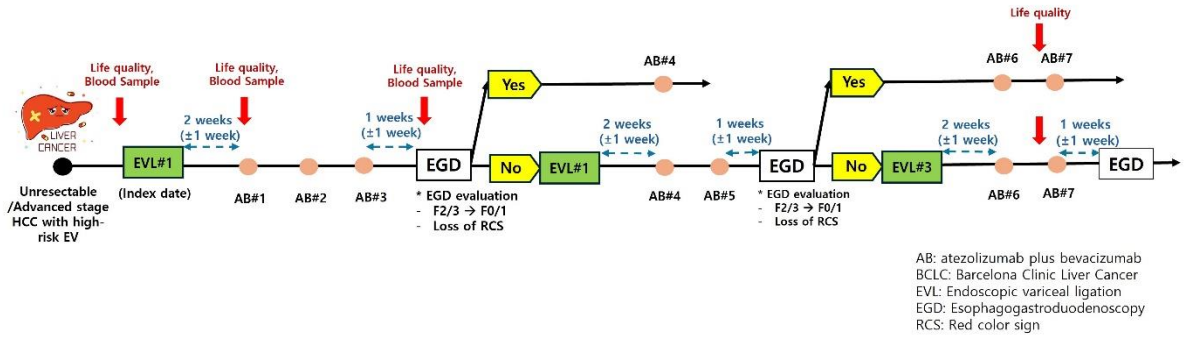
3.1. DESCRIPTION OF THE STUDY

A multicenter, phase II trial of Atezo/Bev for hepatocellular carcinoma with high-risk varix.

3.1.1. Overview of Study Design

This study will initially enroll 44 patients across all sites in South Korea. Figure 1 presents an overview of the study design.

Figure 3. Study Schema



- The pre-treatment EGD will be performed before the first cycle of Atezo/Bev within 2 weeks (± 1 week).
- If high-risk varices are detected via EGD, prophylactic EVL will be performed. Two weeks (± 1 week) after EVL, the first cycle of Atezo/Bev therapy will begin.
- Atezolizumab will be administered by IV, 1200 mg on day 1 of each 21day cycle.
- Bevacizumab will be administered by IV, 15 mg/kg on day 1 of each 21day cycle.
- Follow-up EGD will be performed one week after 3rd, 5th, and 7th consecutive doses of Atezo/Bev therapy to monitor varices and assess response to EVL.
    - If varices show improvement, patients will continue Atezo/Bev therapy and EGD follow-ups only without additional intervention.
    - If varices show no improvement or progression, on-demand EVL will be performed and then the next session of Atezo/Bev continues.

3.2. END OF STUDY AND LENGTH OF STUDY

The study start date will be the date of the first data collection: the date from which information on the first study patient is recorded in the study database: 01-Jan-2025 (planned)

This study will be conducted for 2 years approximately. (Enrollment phase: 24 months, minimal follow-up of enrolled period, 1-year minimal follow-up period of 12 months from enrollment)

4. MATERIALS AND METHODS

4.1. PATIENTS

Approximately 44 HCC participants with high-risk varix will be enrolled in this study.

4.1.1. Inclusion Criteria

- Patients aged 19 years or older and under 80 years.
- Patients with liver function are classified as Child-Pugh Class A.
- BCLC stage C patients with no prior systemic anticancer therapy for hepatocellular carcinoma.
- Patients with an Eastern Cooperative Oncology Group performance score of 0-1.
- Adequate Hematologic and Liver Function:
  A. Hemoglobin: ≥ 9.0 g/dL

B. Absolute Neutrophil Count: ≥ 1,000/mm³
C. Platelet Count: ≥ 70,000/μL
D. Prothrombin Time: ≥ 70% (or Prothrombin Time INR ≤ 1.2)

- Patients who underwent upper gastrointestinal endoscopy within six months prior to the initiation of anticancer treatment, where high-risk varices were identified.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of <1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab, 6 months after the last dose of bevacizumab. Women must refrain from donating eggs during this same period.

  A. 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).

  B. 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.

  C. 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:

  A. 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.

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

  C. 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.

- Patients who have received an explanation of the treatment purpose and methods and have provided informed consent for the treatment.

4.1.2. Exclusion Criteria:

- Participants who have previously received systemic anticancer therapy for advanced hepatocellular carcinoma.
- Patients with a prior history of liver transplantation.
- Patients with uncontrolled malignant tumors other than hepatocellular carcinoma at the time of enrollment (participation is allowed if disease-free survival exceeds two years).
- Patients with uncontrolled or serious underlying diseases requiring treatment.
- Patients with a history of esophageal or gastric variceal bleeding.
- Previous Variceal Treatments: Patients who have undergone any of the following treatments for variceal bleeding:
  A. Endoscopic Variceal Obliteration
  B. EVL
  C. Transjugular Intrahepatic Portosystemic Shunt
  D. Percutaneous Approach for Retrograde Transvenous Obliteration
  E. Surgical procedures
- Patients who have used anticoagulants or antiplatelet agents within one week prior to the study.
- The presence of grade 2 or higher isolated gastric varices or Red Color Signs confirmed by baseline EGD.
- Patients who are pregnant.
- Patients who are unable to understand or provide written informed consent.
- Patients deemed unsuitable for clinical study participation based on the investigator's judgment.

4.2. STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products for this study are Atezo/Bev.

4.2.1. Study Treatment Dosage, Administration, and Compliance

- Atezolizumab will be administered by IV, 1200 mg on day 1 of each 21day cycle.
- Bevacizumab will be administered by IV, 15 mg/kg on day 1 of each 21day cycle
- Patients will receive treatment as outlined in Table 4 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 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 IRR with any previous infusion, premedication with antihistamines, anti-pyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an IRR, or 60 (±15) minutes if the patient experienced an IRR with the previous infusion. • If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion.

IRR = infusion-related reaction.

4.2.1.2. Endoscopic variceal ligation

4.2.2. Investigational Medicinal Product Handling and Accountability

All investigational medicinal products will be used by commercial products. It will be handled at the study site according to the study site's institutional standard operating procedure.

4.2.3. Concomitant therapy (Permitted therapy, Prohibited therapy and other restrictions)

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

4.2.3.1. 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)
- Vaccinations (such as influenza, COVID-19)
  **Live, attenuated vaccines are not permitted (see Section 4.1.2).*

- 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
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:
  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy. Bevacizumab must be held during palliative radiotherapy treatment. Upon completion of palliative radiotherapy treatment, continuation of bevacizumab treatment may be allowed at the investigator's discretion.
- Other local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:
  Patients experiencing a mixed response requiring local therapy for control of 3 or fewer lesions may still be eligible to continue study treatment at the investigator's discretion. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.
- Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.
- Anti-emetic prophylaxis may be administered at the treating physician's discretion according to local practice.
- In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.2.3.2 and 4.2.3.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and beta2-adrenergic agonists; see Appendix 2 [anaphylaxis precautions]).

4.2.3.2. Cautionary Therapy for Atezolizumab-Treated Patients

- Corticosteroids, Immunosuppressive Medications, and TNFα 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.

- Herbal Therapies

  Concomitant use of herbal therapies is not recommended because their PK, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.2.3.3 Prohibited Therapy) may be used during the study at the discretion of the investigator.

4.2.3.3. 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, for various time periods prior to starting study treatment, depending on the agent (see Section 4.2.3.1), and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see Section 4.2.3.1 for details)
- Investigational therapy within 4 weeks prior to Day 1 of Cycle 1 and during study treatment Live, attenuated vaccines (e.g., FluMist®) within 4 weeks prior to Day 1 of Cycle 1, during atezolizumab treatment, and for 5 months after the final dose of atezolizumab
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to Day 1 of Cycle 1 and during study treatment because these agents could potentially increase the risk of autoimmune conditions when given in combination with atezolizumab
- Current use of full dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purposes or anti-platelet therapy are prohibited within 10 days prior to Day 1 of Cycle 1 and during study treatment
  - **Local label recommended doses for prophylactic use of anticoagulants or thrombolytic therapies are allowed.*
  - **Low-dose aspirin (< 325 mg/day) is permitted. Coadministration of proton-pump inhibitors is strongly recommended to reduce potential GI damage.*
  - **If a patient experiences a venous thromboembolism event while still receiving study treatment, it may still be possible for the patient to continue study treatment despite anticoagulation treatment (see Section 4.2.3.1).*
- Use of warfarin or warfarin-like products is not permitted (includes for prophylactic use)

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

4.3. STUDY ASSESSMENT

4.3.1. Informed Consent Forms

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

4.3.2. Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, endoscopic findings, history of gastrointestinal bleeding, endoscopic bleeding control 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, antiplatelet agents, anticoagulant agents, 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 or ethnicity.

4.3.3. 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 CRF.

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

4.3.4. 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 CRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event CRF.

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

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

	Timing for Vital Sign Measurements	
Drug	First Infusion	Subsequent Infusions
Atezolizumab	● Within 60 minutes prior to the infusion ● Record patient's vital signs during or after the infusion if clinically indicated.	● Within 60 minutes prior to the infusion ● Record patient's vital signs during or after the infusion if clinically indicated
Bevacizumab	● Within 60 minutes prior to the infusion ● Record patient's vital signs during or after the infusion if clinically indicated	● Within 60 minutes prior to the infusion ● Record patient's vital signs during or after the infusion if clinically indicated

4.3.5. Tumor and Response Evaluations

Patients will undergo tumor assessments at screening, every 3-4 treatment cycle, regardless of dose delays, until radiographic disease progression per RECIST v1.1[9] or loss of clinical benefit as determined by the investigator. Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

All measurable and/or evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 14 days prior to initiation of study treatment do not have to be repeated at screening, so long as they meet criteria outlined below.

4.3.5.1. Radiologic Assessment

Screening assessments must include CT scans with contrast or MRI scans of the abdomen. A spiral CT scan of the chest may be obtained but is not a requirement. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

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

4.3.5.2. Response Evaluation

Objective response will be determined by the investigator at specified timepoints according to RECIST v1.1. Assessments should be performed by the same individual, if possible, to ensure internal consistency across visits.

4.3.6. Laboratory, Biomarker, and Other Biological Samples

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), magnesium, sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, LDH and serum alpha-fetoprotein (AFP)
- Coagulation: INR, and aPTT
- Thyroid-function testing: TSH, free T3 (or total T3) and free 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 for all patients; HCV RNA for patients with a positive HCV antibody test
- C-reactive protein
- Pregnancy test: All women of childbearing potential will have a urine or serum pregnancy test performed at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

4.3.7. Electrocardiograms

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

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. 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 CRF.

4.3.8. Endoscopy

Endoscopic examinations will be performed by experienced endoscopists certified in gastroenterology endoscopy, using video endoscopes (GIF Q-240, GIF-XQ260, or GIF-

Q260; Olympus, Tokyo, Japan) to evaluate the esophageal varices. If high-risk esophageal varices are identified in the EGD performed two weeks prior to the first anticancer treatment, EVL will be conducted. For ligation, either the 6 Shooter® Universal Saeed® Multi-Band Ligator (COOK Medical) or Speedband Superview Super 7TM (Boston Scientific) will be used.

A follow-up EGD will be conducted one week after the first anticancer treatment. If any of the following criteria are met, additional EVL will not be performed, and anticancer treatment will proceed two weeks later. Otherwise, an additional on-demand EVL session will be conducted:

- The esophageal varices have improved to F1 or less.
- The red color sign has disappeared.

On-demand EVL will be considered after 3rd, 5th, and 7th consecutive doses of Atezo/Bev, with EGD follow-up performed to assess eligibility. The maximum number of EVL sessions is limited to three sessions. Once the maximum of three EVL sessions is completed, a follow-up EGD will be performed one month later. If no abnormalities are found, follow-up EGD will be scheduled every three months for two sessions, every six months for two sessions, and then annually thereafter.

4.4. TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.4.1. Study Treatment Discontinuation

Patients must permanently discontinue study treatment if any of the following criteria are met:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator 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)
- Radiographic disease progression per RECIST v1.1 or symptomatic deterioration attributed to disease progression

4.4.2. 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

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 with or without external beam radiotherapy in completed and ongoing studies.

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 treatments (i.e., atezolizumab, bevacizumab, external beam radiotherapy) 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. The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

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

Note: Based on the most recent version of NCI CTCAE (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 5.1.8 for reporting instructions), per the definition of serious adverse event in Section 5.1.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.1.8 for reporting instructions), per the definition of serious adverse event in Section 5.1.2.

5.1.1. Procedures for Recording Adverse Events

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

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

5.1.2. Serious Adverse Events

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
- 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)
- Results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- 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 (according to NCI CTCAE criteria; see Table 6); 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 CRF.

5.1.3. 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 CRF.

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 to the Principal Investigator. After initiation of study treatment, all serious adverse events and adverse events of special interest, regardless of relationship to study treatment, will be reported until 90 days after the last dose of study treatment or initiation of non-protocol systemic anti- cancer therapy, after the last dose of study treatment whichever occurs first.

5.1.4. 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 drug or study-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 CRF and in the patient’s medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event CRF.

5.1.5. Post-Study Adverse Events

Investigators are instructed to report all serious adverse events or adverse events of special interest that occur after the end of the adverse event reporting period (defined as 30 days after the last dose of study treatment for adverse events or 90 days after the last dose of study treatment for serious adverse events and adverse events of special interest or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first), if the event is believed to be related to prior study drug treatment, regardless of time after study.

The investigator should report these events directly to Principal Investigator or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to

investigators.

5.1.6. Adverse Events of Special Interest

- Adverse events of special interest are required to be reported by the investigator to the Principal Investigator. Adverse events of special interest for this study include the followings:
  - Systemic lupus erythematosus
  - Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, HLH, and MAS
  - Nephritis
  - Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
  - Grade $\geq$ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
  - Vasculitis
  - Autoimmune hemolytic anemia
  - Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
  - Hemorrhage
  - Any grade CNS bleeding
    - Grade $\geq$ 2 GI bleeding
    - Grade $\geq$ 2 hemoptysis
    - Other Grade >=3 hemorrhagic event

The following event also require immediate reporting:

- Cases of potential drug-induced liver injury that includes an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice. (see Section 5.1.7)
- Suspected transmission of an infectious agent by the study drug, 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 who was exposed to a medicinal product. This term applies only when contamination of the study drug is suspected.

In addition, the following Special Situations Reports should be collected even in the absence of an AE;

- Data related to the Product usage during pregnancy or breastfeeding, data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- Data related to a “suspected transmission of an infectious agent via a medicinal product” (STIAMP), reasonable attempts should be made to obtain and submit the age or age group of the patient in order to be able to identify potential safety signals specific to a particular population.

5.1.7. Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 5 x baseline value) in combination with either an elevated total bilirubin (> 3 x ULN) or clinical jaundice in the absence of cholestasis or other

causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST > 5 x baseline value in combination with total bilirubin > 3 x ULN
- Treatment-emergent ALT or AST > 5 x 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 CRF and reported to the Principal Investigator.

5.1.8. Reporting Requirements From Investigator To Principal Investigator

Certain events require immediate reporting to allow the Principal Investigator to take appropriate measures to address potential new risks in a clinical study. The investigator must report such events to the Principal Investigator; The following is a list of events that the investigator must report to the Principal Investigator after learning of the event, regardless of relationship to study drug:

- Serious Adverse Event/ Adverse events of special interest/ Pregnancy: within 30 working days

The principal investigator must report to Roche after learning of the event

- SAEs (related and not related to the Product): within 30 calendar days
- Non-Serious AESIs: within 30 calendar days
- Special Situation Reports (with or without AE): within 30 calendar days
- Product complaints (with or without an AE): within 30 calendar days

The investigator must report new significant follow-up information for these events to the Principal Investigator. New significant information includes the following: 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

Principal investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1. DETERMINATION OF SAMPLE SIZE

Previous studies have reported that the incidence of variceal bleeding in liver cancer patients is 9-10%. Among liver cancer patients undergoing treatment with atezolizumab and bevacizumab, variceal bleeding was observed in 1.3-17.0% of cases. In particular, we

referred to the study by Larrey et al.[1], which focused on patients with an esophageal variceal bleeding rate above 10% and a high proportion of high-risk varices.

According to Larrey et al., the incidence of esophageal variceal bleeding at six months following the initiation of atezolizumab and bevacizumab therapy was 26% in patients with high-risk varices, while it was 11% in patients with no varices or low-risk varices.

Based on the hypothesis that prophylactic EVL could reduce the incidence of esophageal variceal bleeding to 8% in high-risk varix patients, we assumed an enrollment period of 24 months and a follow-up period of 12 months from the last subject enrolled. The sample size required to achieve a significance level (Type I error) of 0.05 and power of 80% (Type II error) was calculated to be 37 patients. Considering a dropout rate of 15%, the target sample size for each group was set at 44 patients.

6.2. STATISTICAL ANALYTIC PLAN

Baseline characteristics of the patients will be summarized for the following variables: age, sex, clinical center, ECOG performance status, Child-Pugh classification, extrahepatic spread of disease, baseline alpha fetoprotein and PIVKA-II level, HCC etiology, presence of cirrhosis, presence and types of varices, presence of red color sign, type of vascular invasion, tumor size, number of tumors, prior local therapy for HCC, history of comedication including antiplatelet agents or anticoagulants, and the number of bands used in EVL during treatment. Other laboratory findings will be included: white blood cell count, hemoglobin, platelets, creatinine, prothrombin time, alanine aminotransferase, aspartate aminotransferase, albumin, and total bilirubin.

The incidence of esophageal variceal bleeding and survival rate during treatment will be calculated using the Kaplan-Meier method. Factors influencing the incidence of esophageal variceal bleeding and survival rate during treatment will be analyzed using the log-rank test or the Cox regression hazard model.

The factors in Cox proportional-hazard model will include the followings: age, sex, BMI, ECOG performance status, Child-Pugh classification, tumor size, extrahepatic spread of disease, baseline alpha fetoprotein and PIVKA-II level, HCC etiology, type of varices, presence of cirrhosis, comedication with beta blocker, the number of sessions of EVL, type of vascular invasion, and prior local therapy for HCC. Hazard ratio (HR) and 95% confidence interval (CI) will be calculated using a Cox proportional-hazards model. P values ≤0.1 will be considered statistically significant.

We will record and report all reasons for study drop out as much as possible to assess the missing data mechanism (missing completely at random, missing at random, or non-ignorable missingness, meaning the data missingness is related to the actual value).

6.3. ELECTRONIC CASE REPORT FORMS

All CRFs should be completed by designated, trained site staff. CRFs should be reviewed and electronically signed and dated by the investigator

7. ETHICAL CONSIDERATIONS

7.1. COMPLIANCE WITH LAWS AND REGULATIONS

The investigational institutions should make sure that the necessary personnel and facilities to conduct the study are appropriately provided. The investigators should do their best for the safety of the study subjects. If serious adverse events occur during the trial, the investigators should notify IRB after taking adequate therapeutic measures. The responsible conduct of the study will be regularly monitored by the Human Research Protection Center of each participating site.

7.2. INFORMED CONSENT

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

The investigator is responsible for obtaining written informed consent from each participant after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the IRB-approved consent form for the written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining the consent

A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative. If the subject or representative cannot read, **an impartial witness is needed.**

7.3. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

In addition to the requirements for reporting all adverse events to the investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB. 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 and archived in the site's study file.

7.4. CONFIDENTIALITY

The investigator must ensure that subjects' anonymity will be strictly maintained. The subjects should be accessed by only subject initials or an identification code. Their identities have to be protected from unauthorized parties.

Only the investigators, study coordinators, those who conduct inspections, IRB, can review the data of the subjects to verify the reliability and the study process within the range prescribed by the relevant provisions and without violating the confidentiality of research

subjects.

8. References

1. Larrey E, Campion B, Evain M, et al. A history of variceal bleeding is associated with further bleeding under atezolizumab-bevacizumab in patients with HCC. *Liver Int*. Dec 2022;42(12):2843-2854. doi:10.1111/liv.15458
2. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. Apr 2022;76(4):862-873. doi:10.1016/j.jhep.2021.11.030
3. Patel JN, Jiang C, Owzar K, et al. Pharmacogenetic and clinical risk factors for bevacizumab-related gastrointestinal hemorrhage in prostate cancer patients treated on CALGB 90401 (Alliance). *The Pharmacogenomics Journal*. 2024/03/04 2024;24(2):6. doi:10.1038/s41397-024-00328-z
4. Jaiswal V, Jain E, Hitawala G, et al. Bevacizumab and Sinus Venous Thrombosis: A Literature Review. *Cureus*. Nov 2021;13(11):e19471. doi:10.7759/cureus.19471
5. Song Y-G, Yeom K-M, Jung EA, Kim SG, Kim YS, Yoo J-J. Risk of Bleeding in Hepatocellular Carcinoma Patients Treated with Atezolizumab/Bevacizumab: A Systematic Review and Meta-Analysis. *Liver Cancer*. 2024:1-11. doi:10.1159/000539423
6. Ha Y, Kim JH, Cheon J, Jeon GS, Kim C, Chon HJ. Risk of Variceal Bleeding in Patients With Advanced Hepatocellular Carcinoma Receiving Atezolizumab/Bevacizumab. *Clin Gastroenterol Hepatol*. Aug 2023;21(9):2421-2423.e2. doi:10.1016/j.cgh.2022.07.035
7. Ben Khaled N, Möller M, Jochheim LS, et al. Atezolizumab/bevacizumab or lenvatinib in hepatocellular carcinoma: Multicenter real-world study with focus on bleeding and thromboembolic events. *JHEP Rep*. Jun 2024;6(6):101065. doi:10.1016/j.jhepr.2024.101065
8. Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology*. 2023;78(6):1922-1965. doi:10.1097/hep.0000000000000466
9. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. Jan 2009;45(2):228-47. doi:10.1016/j.ejca.2008.10.026

Appendix 1
Schedule of Activities

Assessment/Procedures	Screening	Baseline	Baseline+2 weeks (±1 week)	Atezo/Bev #3/#5/#7+1 weeks (±1 week)	End of the Study
	Baseline ≤ 4weeks	EVL#1	Atezo/Bev#1	2 weeks before initiation of Atezo/Bev	Overall survival
Informed consent	O				
Medical History	O		(O)	(O)	
Inclusion/Exclusion criteria	O				
EGD (with or without EVL)[1]	O	O		O	
Physical examination[2]	O				
Vital signs[3]	O	(O)	(O)	(O)	
Hematology[4]	O	(O)	(O)	(O)	
Chemistry[5]	O	(O)	(O)	(O)	
Prothrombin time	O	(O)	(O)	(O)	
Urinalaysis	O				
Electrocardiogram	O				
HBsAg/anti-HCV	(O)				
Alpha-fetoprotein/PIVKA II	O				
Chest CT	O				
Liver dynamic CT or MRI[6]	O				
Compliance check		(O)		(O)	
Concomitant medications	O		(O)	(O)	
Quality of life evaluation[8]		O	O	O	
Blood sample collection[9]		O	O	(O)	

1. An EGD must be performed within six months based on baseline criteria, including endoscopic images. Patients with small varices classified as F2 or higher, or those showing a red color sign, are eligible for study enrollment. Two weeks before the initiation of the first dose of Atezo/Bev, EVL is performed. Subsequently, EGD follow-ups are conducted two weeks (±1 week) prior to each chemotherapy session to perform on-demand EVL as per the study protocol. If the criteria for EVL are not met, ligation is not performed, and censoring is done at that endoscopy time point

2. The physical examination includes assessing physical activity and identifying any notable signs.

3. Vital signs include blood pressure, pulse, and weight measurements. Height is measured once during screening.

4. Hematology: Hemoglobin, red blood cell count, white blood cell count and differential, and platelet count.

5. Chemistry: Sodium, potassium, BUN, creatinine, total protein, albumin, AST, ALT, ALP, GGT, total/direct bilirubin, amylase, phosphorus, and calcium.

6. A CT or MRI scan performed as standard liver dynamic imaging within four weeks of screening can be used.

7. At six months after initiation of Atezo/Bev, the incidence of esophageal variceal bleeding is assessed, along with the cumulative incidence of esophageal variceal bleeding, non-variceal gastrointestinal bleeding, and liver-related complications throughout the study period. Overall survival is also evaluated at the end date of the study. Additionally, all patients who have undergone EVL, the incidence of EVL-related complications is assessed.

8. To assess changes in quality of life related to treatment, the EORTC QLQ-C30 and EORTC QLQ-HCC18 will be evaluated at the time of study enrollment and periodically thereafter. Deterioration is defined as a decrease of 10 points or more compared to baseline in two consecutive assessments, or a decrease of 10 points or more followed by death.

9. A total of 20 mL of peripheral blood will be collected. If these samples are not collected during the scheduled visits, they may be obtained at any time during the clinical trial. Additional samples may also be collected depending on the patient's clinical condition.

- Participants meeting the inclusion/exclusion criteria during screening may complete the baseline visit on the same day. Baseline test items may utilize results from screening tests.

Appendix 2
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 administration in a clinical setting:

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

Procedures

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

1. Stop the study treatment administration, if possible.
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.