Participant Information Sheet and Consent Form for Clinical Trial

IRB No. 2024-1524

Document date: 2024.12.26

Study 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)

You are being invited to participate in a study evaluating the effectiveness of prophylactic endoscopic variceal ligation in reducing the incidence of esophageal variceal bleeding in patients with hepatocellular carcinoma who have high-risk esophageal varices and are starting standard treatment with atezolizumab and bevacizumab. Participation in this study is entirely voluntary, and there is no obligation or pressure to participate.

This study aims to compare the additional efficacy of a medically validated and approved treatment. Therefore, it is important that you fully understand the purpose of this study, the procedures involved, and the potential discomfort or inconvenience you may experience if you decide to participate.

The following text provides answers to questions you may have about the study. Please read it carefully. If there is anything unclear or if you have additional questions, feel free to ask the researcher conducting the study.

After receiving answers to all your questions and deciding that you wish to participate in the study, you (or your legal representative) must sign the consent form to begin your participation. The researcher who explained the study to you (or a person authorized by the principal investigator) will also sign the consent form and write the date in handwriting.

Your signature confirms that you have received and understood explanations about the study, including its procedures and associated risks. It also indicates your (or your legal representative's) decision to participate in the study.

The objectives for this clinical trial

Version 1.2

You have been diagnosed with unresectable hepatocellular carcinoma (HCC) and identified as having high-risk esophageal varices. The combination therapy of atezolizumab and bevacizumab has been approved by the U.S. FDA for the treatment of advanced HCC.

Atezolizumab is an antibody (a protein similar to those naturally produced by the immune system) that blocks the programmed death-ligand 1 (PD-L1) pathway. The PD-L1 pathway is involved in regulating the body's natural immune response, but tumors can exploit this mechanism to partially resist or evade the immune system. By blocking the PD-L1 pathway, atezolizumab helps the immune system suppress or halt tumor growth.

Bevacizumab is an antibody that helps slow the growth of new blood vessels, which can aid in stopping tumor proliferation in your body. However, bevacizumab is also involved in signaling pathways related to tumor angiogenesis, and previous studies have reported a low incidence of bleeding side effects. As a result, international guidelines recommend performing upper endoscopy before initiating cancer therapy in patients with high-risk esophageal varices. If necessary, prophylactic endoscopic variceal ligation (EVL) is advised.

Despite this recommendation, there is currently no clear guideline on how much EVL reduces the incidence of esophageal variceal bleeding during treatment compared to not performing EVL, or the optimal timing for initiating cancer therapy after EVL.

This study is a phase II clinical trial designed to evaluate the effectiveness of atezolizumab and bevacizumab in reducing the incidence of esophageal variceal bleeding in HCC patients with high-risk esophageal varices. The goal is to strengthen the clinical evidence for prophylactic EVL before treatment with atezolizumab and bevacizumab, and to contribute to establishing critical treatment strategies for advanced HCC.

This research will be conducted across six university hospitals in South Korea: **Asan Medical Center (Seoul), Seoul National University Hospital, Bundang Seoul National University Hospital, Hanyang University Guri Hospital, National Cancer Center, and Samsung Medical Center (Seoul).**

What treatment or procedures will I receive if I participate in this study?

Participants in this study will receive combination therapy with **atezolizumab** and **bevacizumab**, which is an FDA- and Korean Ministry of Food and Drug Safety-approved

treatment for advanced HCC with demonstrated survival benefits. If high-risk esophageal varices are identified during the pre-treatment upper endoscopy, **prophylactic EVL** will be performed to reduce the risk of bleeding during cancer therapy.

This study aims to assess the effectiveness of prophylactic EVL in reducing the risk of esophageal variceal bleeding and ensuring the safety and efficacy of atezolizumab and bevacizumab in advanced HCC patients.

Who will participate in this study?

This study plans to enroll a total of 44 clinical trial participants, with 30 participants being recruited at Asan Medical Center.

Eligibility criteria for participation include:

- A diagnosis of unresectable, advanced HCC.
- The presence of high-risk esophageal varices with a risk of bleeding.
- No plans for pregnancy during the study period.
- Ability to remain active and comply with the study's drug regimen and other requirements.
- Willingness to voluntarily provide informed consent prior to participation.

Participants meeting these criteria will be considered for inclusion in the study.

The length of study and Study procedures

Once the consent form is signed, the study will begin. The total study duration is expected to last until **March 31, 2029**, with the completion date estimated to be 12 months after the last patient is enrolled.

Study Procedures:

- Participants will receive **atezolizumab** and **bevacizumab** treatments every 3 weeks, starting from the screening visit.
- One week after the **3rd dose** of atezolizumab and bevacizumab, an upper endoscopy

will be performed to assess the condition of the esophageal varices. If necessary, **endoscopic variceal ligation (EVL)** will be performed.

- Subsequent endoscopies will be conducted **one week after the 5th and 7th doses** to evaluate the improvement of the esophageal varices.

Limitations on EVL Sessions:

- To minimize the risk of bleeding associated with repeated EVL procedures, the **maximum number of consecutive EVL sessions** during the treatment period will be restricted to **three sessions** in total.

This structured approach is designed to ensure the safety and effectiveness of the treatment while minimizing the risks of complications from repeated procedures.

How Will the Study Be Conducted If I Participate?

This study is designed for patients diagnosed with liver cancer who are starting standard treatment with atezolizumab and bevacizumab and have high-risk esophageal varices. Patients meeting the eligibility criteria will be provided with a detailed explanation of the study. Upon understanding the study and providing informed consent, participation in the clinical trial will begin based on the patient's voluntary decision.

Screening and Eligibility

Before starting the study, participants will undergo a thorough medical examination, including a consultation with the researcher, a review of medical history, physical exams, and laboratory tests. Past illnesses and concomitant medications will also be assessed. If all detailed eligibility criteria are met, the patient will be enrolled in the study. If any criteria are not met, participation in the study will not be possible, even if the patient wishes to participate.

Study Procedures

1. **Pre-Treatment Endoscopy**
    - Two weeks before the first dose of atezolizumab and bevacizumab, an upper endoscopy will be performed.
    - If high-risk esophageal varices are identified, endoscopic variceal ligation (EVL) will be conducted as a preventive measure.

2. **Treatment and Follow-Up**
    - Participants will receive atezolizumab and bevacizumab every three weeks.
    - At each visit, side effects of the medication will be monitored.
3. **Endoscopic Monitoring**
    - After the **3rd dose** of atezolizumab and bevacizumab, an upper endoscopy will be performed to assess the improvement in esophageal varices.
    - If no improvement is observed, additional EVL will be performed.
    - Follow-up endoscopies will also be conducted one week after the **5th** and **7th doses** to evaluate the condition of esophageal varices.
    - EVL will be performed a maximum of three times during the study.
4. **Routine Tests and Assessments**
    - Every 3-4 treatment cycles, participants will undergo blood tests, urine tests, liver CT (or MRI), and patient-reported outcomes assessments (health-related quality of life evaluation).
    - These tests, including imaging and tumor evaluations, are standard procedures in regular care and will help assess treatment efficacy and guide future treatment plans.
5. **Screening Tests**
    - Screening blood tests will include complete blood count, biochemistry, coagulation tests, tumor markers, and tests for hepatitis B and C. Approximately 15-20 mL of blood will be collected.
    - The results will determine whether the patient currently or previously carried these viruses.
6. **Patient-Reported Outcomes**
    - Health-related quality of life will be assessed using the EORTC QLQ-C30 tool, taking about 5 minutes to complete.

Transition to Alternative Treatment

If the cancer worsens or new metastases are identified in other organs at any point during the study, participation in this trial will end. Treatment will then transition to therapies based on international guidelines.

All blood samples collected in this study will be used solely for research purposes and discarded afterward. The study aims to ensure that participants receive the most appropriate and effective treatment while minimizing risks.

What participants do

If you decide to participate in the study and sign the consent form in your own handwriting, the study will begin. During your participation, you will be required to follow these guidelines:

- **Attend Scheduled Visits**:
  You must visit the hospital on the planned treatment dates to undergo the necessary tests and procedures.
- **Report Your Condition**:
  Inform the research team about your health status and any medications you are taking.
- **Notify About External Medical Visits**:
  If you visit another medical institution for consultation or treatment during the study, you must inform the research team. Failure to adhere to these requirements or cooperate with the research team may make it difficult to continue your participation in the study.
- **Compliance with Study Requirements**:
  While participating in the clinical trial, you must adhere to the specified requirements outlined by the research team.

- **For Female Participants**:
  - If you have childbearing potential, you must use a reliable method of contraception during the clinical trial and for **5 months after the last dose of atezolizumab** and **6 months after the last dose of bevacizumab**. Please discuss with your clinical trial physician to determine the best contraceptive method for you.
  - If you become pregnant, notify your clinical trial physician immediately. The physician may wish to follow up with you until the outcome of your pregnancy is known.
  - During this period, you must not donate eggs.

- **For Male Participants:**
  - If your partner is pregnant or of childbearing potential, you must use condoms during the clinical trial and for **6 months after the last dose of bevacizumab**.
  - You must not donate sperm during this period.
  - If your partner becomes pregnant, notify your clinical trial physician immediately.

The physician may request permission to collect information about the pregnancy and the baby from you and your partner.

- Regardless of your decision regarding such follow-up, your participation in the clinical trial can continue.

Your cooperation is essential to ensure the success of the study and your safety throughout the process.

What Are the Potential Side Effects, Risks, and Discomforts of Participating in the Study?

In general, all medications and procedures carry risks and may cause adverse reactions, making it difficult to predict all possible side effects.

The medications, procedures, and treatment methods used in this study are approved for use both domestically and internationally, and their safety is supported by accumulated data. Therefore, they are considered safe. However, the following are known adverse reactions associated with these treatments:

(*Provide a detailed list of known adverse reactions here, specific to the medications and procedures involved in the study, such as atezolizumab and bevacizumab*.)

* **Atezolizumab**

Frequency	Potentially Serious Adverse Reactions
Very Common (≥10% of patients)	• Fatigue • Itching (Pruritus) • Joint Pain (Arthralgia) • Weakness (Asthenia) • Nausea • Fever • Loss of Appetite • Rash • Diarrhea • Vomiting • Shortness of Breath (Dyspnea) • Urinary Tract Infection • Cough • Muscle and Bone Pain (Myalgia, Musculoskeletal Pain, Bone Pain) • Headache
Common (1%-10% of patients)	• Chills • Inflammation of the intestines (Colitis) • Difficulty swallowing (Dysphagia) • Increased liver enzymes indicating liver inflammation • Shortness of breath due to reduced oxygen supply (Dyspnea) • Flu-like symptoms • Allergic reactions or drug intolerance (Hypersensitivity) • Low potassium levels in the blood (Hypokalemia) • Low sodium levels in the blood (Hyponatremia)

	• Infusion-related reactions • Inflammation of the lungs (Pneumonitis) • Low blood platelet count causing bruising or bleeding (Thrombocytopenia) • Low blood pressure (Hypotension) • Liver inflammation (Hepatitis) • Hypothyroidism • Abdominal pain • Nasal congestion • Dry skin • Increased creatinine levels (normally excreted by the kidneys) • High blood sugar levels (Hyperglycemia) • Pain in the back of the throat (Oropharyngeal pain)
Uncommon (<1% of patients)	• Decreased adrenal hormone production (Adrenal insufficiency) • Diabetes • Hyperthyroidism • Inflammation of the brain, surrounding membranes, and spinal cord (Meningo encephalitis) • Inflammation of the pituitary gland (Hypophysitis) • Inflammation of the heart muscle (Myocarditis) • Inflammation of the kidneys (Nephritis) • Severe skin or mucosal reactions (Severe skin adverse reactions) • Nerve damage causing muscle weakness and/or paralysis (Guillain-Barré Syn drome) • Nerve damage causing muscle weakness (Myasthenic Syndrome/Myasthenia Gravis) • Inflammation of the pancreas, including elevated pancreatic enzymes (Pancre atitis) • Critically high levels of sugar and acid in the blood or urine (Diabetic ketoaci dosis) • Inflammation and damage to the muscles (Myositis)

Allergic Reactions

Allergic reactions associated with atezolizumab may occur, typically during or shortly after intravenous infusion. Symptoms may include:

- Nausea
- Vomiting
- Skin reactions (hives or rash)
- Shortness of breath
- Low blood pressure

These reactions can range from mild to severe and, in rare cases, may lead to death or permanent disability. If you experience any of these symptoms, your clinical trial physician may temporarily or permanently discontinue the infusion of atezolizumab. The physician may also administer specific medications to treat these symptoms.

Immune Reactions

In rare cases, atezolizumab may cause immune-related reactions. These reactions can lead to severe inflammation and/or adverse effects associated with serious infections. Multiple organs in the body (e.g., liver, kidneys, lungs, and bone marrow) may be involved, potentially

resulting in hospitalization, life-threatening situations, or death.

Symptoms may include:

- Extremely low blood pressure that does not respond to standard treatment
- High fever
- Cough
- Severe shortness of breath requiring oxygen therapy and/or intubation
- Severe dizziness, confusion, or weakness
- Decreased urination and kidney failure
- Liver dysfunction
- Extremely low blood counts and/or bleeding within organs

If you experience any of these symptoms, it is critical to notify your physician immediately, as immediate treatment and hospitalization may be necessary. Your clinical trial physician may provide medications to manage these symptoms.

* **Bevacizumab**

Frequency	Potentially Serious Adverse Reactions
Very Common (≥10% of patients)	• High blood pressure • Tingling or numbness in fingers or toes • Low white blood cell counts potentially associated with fever • Low platelet count • Weakness, fatigue • Diarrhea, nausea, vomiting, and abdominal pain
Common (1%-10% of patients)	• Infections, presence of bacteria in the blood, or abscess formation in tissues or organs • Intestinal perforation or tears • Abnormal connections between gastrointestinal tract, skin, or other tissues (fi stulas) • Low red blood cell count • Bleeding, including tumor-associated bleeding and nosebleeds • Pulmonary embolism • Arterial blockages due to clots, including stroke or heart attack • Venous thrombosis • Urinary tract infection • Abdominal pain • Intestinal obstruction • Dehydration • Pain, redness, tenderness, or blistering in fingers or toes • Decreased consciousness, drowsiness, fatigue • Fainting • Allergic reactions, including infusion-related allergic reactions • Shortness of breath, low oxygen levels in the blood • Wound healing issues • Heart failure, especially in patients who received specific chemotherapy

Rare (<0.1% of patients)	• Symptoms of reversible posterior leukoencephalopathy syndrome (headache, vision changes, confusion, or seizures), often associated with high blood press ure • Hypertensive encephalopathy with similar symptoms (headache, vision chang es, confusion, or seizures)

*** Potential Side Effects of EVL**

Following EVL, the following side effects may occur:

- Chest pain lasting 2-3 days
- Difficulty swallowing
- Other potential complications include:
    - Failure to stop bleeding
    - Re-bleeding
    - Infection
    - Stricture at the esophagogastric junction
    - Abscess
    - Ulcers
    - Shortness of breath
    - Sepsis

What Benefits Can I Expect from Participating in This Study?

By participating in this study, you will receive treatment for liver cancer and high-risk esophageal varices, which may have a positive impact on your health and symptoms.

During the study, you will benefit from the research team's continuous attention and care, potentially improving the quality of your medical treatment. While there may not be direct personal benefits from participating in the study, the information you provide can contribute to developing optimal clinical guidelines for treating patients with similar conditions. This advancement in medical knowledge could benefit future patients.

Your participation in this study helps improve treatment strategies and supports the development of better care for individuals with liver cancer and esophageal varices.

What Are the Alternative Treatment Options Outside of This Study?

If you choose not to participate in this study, the following treatment options are available:

1) **For HCC:** Standard treatments for liver cancer include

- **Liver Transplantation**: While effective in some cases, it is contraindicated for cancers with vascular invasion due to the high recurrence rate.
- **Partial Hepatectomy (Liver Resection):** This procedure is often not feasible for advanced cases and carries a high risk of recurrence after surgery.
- **Radiofrequency Ablation (RFA):** This option is generally contraindicated for advanced-stage cancers due to the associated risks.

2) **For HCC with vascular invasion**, effective treatment options are very limited. Even if you do not participate in the study, the recommended treatment in clinical practice remains the combination therapy of atezolizumab and bevacizumab, as it has been shown to be effective.

3) **For Esophageal Varices:** To prevent bleeding, the following options are available:

- **Beta-Blockers**: These medications reduce blood flow to the esophageal varices, lowering the risk of bleeding.
- **Endoscopic Variceal Ligation (EVL):** This procedure mechanically ligates varices to prevent bleeding.

Recent randomized trials have shown that EVL significantly reduces the risk of bleeding compared to beta-blockers alone. Observational studies also suggest that combining EVL with beta-blockers is more effective at preventing bleeding than either treatment alone.

In this study, participants will receive a combination of EVL and beta-blockers for esophageal varices, providing a comprehensive approach to bleeding prevention alongside atezolizumab and bevacizumab therapy for liver cancer. These alternative therapies may also be pursued as part of standard clinical care if you choose not to join the study.

What Compensation or Treatment Is Available If I Experience Harm or Injury During the Study?

The study does not cover medical costs for the progression of your existing condition (liver cancer), complications arising from the treatment with atezolizumab and bevacizumab, or any other treatments administered during the study.

If you carefully follow all study guidelines and procedures, and the study is conducted

accurately, but you suffer an injury or illness directly related to the research, the investigator will provide information and arrange for the medical treatment necessary for your recovery. However, if the injury is caused by your failure to follow the study guidelines, the investigator will not be responsible for covering the costs.

This study is covered by liability insurance. If any unexpected complications or injuries directly related to the study treatments occur, compensation will be provided in accordance with the terms of the insurance policy.

If you experience any physical harm during the clinical trial, you must report it to the investigator immediately. Furthermore, if you have any related questions or concerns, you are encouraged to contact the research team.

Will I Receive Any Financial Compensation for Participating in This Study?

Participants in this study are eligible for financial compensation under the following conditions: After completing the screening tests and being deemed eligible for the study, participants will receive a participation fee of **200,000 KRW** following randomization.

Upon completing the study at **the endpoint**, participants will receive an additional participation fee of **200,000 KRW**. If you withdraw from the study before the endpoint of study, compensation will be provided proportionally based on the duration of your participation.

Will I Incur Any Costs for Participating in This Study?

There are some costs associated with participating in this study: The screening tests (blood tests, urine tests, imaging studies, etc.) and procedures conducted during the study are standard procedures for liver cancer patients and would be performed even if you were not participating in this study. As these are part of routine care, no financial support is provided for these tests, and the costs will need to be covered by you or your caregiver.

The costs of the treatment drugs (atezolizumab and bevacizumab) and any radiation therapy are covered under insurance benefits. However, you or your caregiver are responsible for paying the remaining costs not covered by insurance.

Is Participation in the Study Voluntary, and Can I Withdraw at Any Time?

Whether or not you participate in this study is entirely your or your caregiver's voluntary decision. There will be no disadvantages or discrimination in your future treatment regardless of your choice to participate. Even if you choose to participate, you may withdraw from the

study at any time during its course. Withdrawing from the study will have no impact on the standard care and treatment you receive.

Will the Study Continue If I Don't Withdraw My Participation?

Although your participation in the study will generally continue unless you choose to withdraw, there are specific circumstances in which the investigator may decide to terminate your participation.

1. If the principal investigator determines that adverse reactions require you to stop participating for your safety
2. If the investigator judges that the study drug is not effective, or your condition worsens to a point where continuing in the study is not beneficial.
3. If it becomes evident after the study starts that you are not suitable to continue participation due to safety concerns or other factors.
4. If the principal investigator concludes that continuing the study for you would be inappropriate for any reason.

How Will My Information Be Handled, and Will My Privacy Be Protected?

If you agree to participate in this clinical trial, the following procedures will ensure the confidentiality and proper handling of your information: Your medical information, such as age, gender, weight, medical history, surgical history, medication use, and test results related to the study, will be recorded in specific formats (paper or electronic). This information will be accessible only to authorized researchers involved in the study. It will be protected through secured measures such as password encryption or locked storage.

Authorized individuals, such as members of our Institutional Review Board (IRB), Clinical Research Protection Center, or government representatives, may review your data to ensure the study is conducted properly. No one else will have access to your information without explicit permission.

If you withdraw from the study, the information collected up to the point of withdrawal will still be used for research purposes. All information obtained during this study will be processed in compliance with national and local laws. Your information will not be shared with your insurance company, employer, or any other third party unless required by law. If the results of this study are published in medical journals or presented at scientific conferences, your identity will remain confidential.

The data collected will be stored at the trial site for **15 years after the trial concludes** or for the duration required by applicable laws (whichever is longer). After this period, the data will be securely destroyed in accordance with legal regulations.
By signing the consent form, you agree to the above terms. Your privacy and confidentiality will be protected throughout the study and beyond.

Will I Be Informed If New Information or Risks Are Discovered During the Study?

During the study, you will be informed about any new information related to the study drugs or associated risks that might influence your decision to participate or continue in the study, or that could negatively impact your health and well-being.
If new findings emerge about the study drugs (e.g., severe side effects experienced by other participants), this information will be communicated to you either orally or in writing. In addition to updates on the study drugs, any new treatments or relevant information about your condition will also be shared with you, either orally or in writing. This ensures that you remain fully informed throughout your participation and can make well-informed decisions about continuing in the study.

Who Should I Contact If I Have Questions or Issues During the Study?

If you have questions about the study, need more information, or experience any health concerns during the study (e.g., illness, accidents, hospitalization, fractures, etc.), you can contact the following individuals at any time

Principal Investigator – Name: Prof. Ju Hyun Shim, Phone Number: 02-3010-3190

Research Coordinator – Name: Jiwon Ku, Phone Number: 010-3251-0409

If you have any questions about your rights as a participant in this clinical trial, concerns about the study itself, or if you wish to speak with someone not directly involved in the study, you may contact the following.

Human Research Protection Center Phone Number: 02-3010-7285

Institutional Review Board of Asan Medical Center, Seoul Phone Number: 02-3010-7166

Signature

I confirm that I have read or have had this consent form read to me. I understand the information provided and have had my questions answered. I understand that I will receive a copy of this consent form, signed and dated, covering all pages. I voluntarily agree to participate in this study as described above, and I authorize Seoul Asan Medical Center to use and share my information as outlined in this consent form.

Participant Name: _____

Signature: _____

Date of Signature: _____ / _____ / _____ (YYYY/MM/DD)

Please sign the following section only if applicable:

I, as the legal representative (parent, spouse, or guardian), confirm that the participant is unable to provide consent due to lack of capacity for self-expression. Therefore, I consent to the participant's involvement in this clinical trial on their behalf.

Legal Representative Name: _____

Signature: _____

Date of Signature: _____ / _____ / _____ (YYYY/MM/DD)

I confirm that, in a situation where the clinical trial participant is unable to comprehend the consent form and other documented information, the responsible physician has adequately explained the clinical trial to the participant (or their legal representative). The participant (or their legal representative) has understood the explanation and agreed to participate in the clinical trial (and provided a handwritten signature if possible).

Witness

Name: _____

Signature: _____

Date of Signature: _____ / _____ / _____ (YYYY/MM/DD)

I, the undersigned, confirm that I have thoroughly explained this informed consent form to the participant named above and/or their legal representative.

Name of Principal Investigator or co-investigator: _____

Signature of Principal Investigator or co-investigator: _____

Date of Signature: _____ / _____ / _____ (YYYY/MM/DD)