# STUDY PROTOCOL

## EFFECTIVENESS AND SAFETY OF ATEZOLIZUMAB + BEVACIZUMAB PLUS LRTs AMONG PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA IN REAL-WORLD CLINICAL PRACTICE

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| **Leading site and sponsor** | Zhongda Hospital, Southeast University |
| **Country of study population:** | China and Asia-Pacific region |

# Study Synopsis

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| **Study Title** | Effectiveness and Safety of Atezolizumab + Bevacizumab Combined with Locoregional Therapies in Patients with Unresectable Hepatocellular Carcinoma in Real-world Clinical practice |
| **Background** | Unresectable hepatocellular carcinoma (uHCC) constitutes a significant health burden in the Asia-Pacific (APAC) region, particularly in China, where it is frequently associated with hepatitis B virus (HBV) infection and diagnosed at advanced stages. The combination of atezolizumab and bevacizumab (Atezo+Bev) has emerged as the established first-line standard of care, as evidenced by the IMbrave150 trial, which demonstrated statistically significant improvements in overall and progression-free survival. However, clinical trial populations are often selective, and not all patients achieve optimal responses, underscoring the need for additional therapeutic strategies.<br>Locoregional therapies (LRTs), including transarterial chemoembolization (TACE), transarterial radioembolization (TARE), hepatic arterial infusion chemotherapy (HAIC), ablation (e.g., RFA, MWA), and radiotherapy (e.g., external beam radiotherapy, iodine-125 brachytherapy), are integral to the management of uHCC, particularly in intermediate stages (BCLC B). However, their application is markedly heterogeneous across the APAC region due to variations in clinical guidelines and limited standardization. Robust evidence supporting specific combination strategies with systemic therapies like Atezo+Bev remains scarce.<br>This gap underscores the critical need for large-scale real-world evidence (RWE) to elucidate current practices, outcomes, and optimal timing of LRT+Atezo+Bev combinations in China and selected APAC regions. |
| **Leading Site** | Zhongda Hospital, Southeast University |
| **Clinical Sites** | Patient-level data will be retrospectively abstracted from medical records of approximately 35 study sites after approval by ethics committees. |
| **Objectives** | **Primary Objective:**<br>To describe the real-world overall survival (OS) in patients with unresectable hepatocellular carcinoma (uHCC) receiving first-line systemic therapy with atezolizumab plus bevacizumab (Atezo+Bev) in combination with locoregional therapies (LRTs).<br>**Secondary Objectives:**<br>To describe real-world progression-free survival (rwPFS), overall response rate (ORR), real-world disease control rate (DCR), time to discontinuation (TTD), time to next treatment (TTNT), and time to progression (TTP) in the cohort, stratified by locoregional therapy (LRT) categories.<br>***Definitions:***<br>a) *ORR: Propor*tion of patients achieving a complete response (CR) or partial response (PR), as assessed by investigators per RECIST v1.1 or mRECIST criteria using real-world imaging evaluations.<br>b) DCR: The proportion of patients who achieve complete response (CR), partial response (PR), or stable disease (SD) as assessed by investigators using real-world imaging evaluations in accordance with RECIST v1.1 or mRECIST criteria. Among these, stable disease (SD) must persist for at |

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| | least 6 weeks from the first documentation of SD, which helps exclude the interference of short-term disease fluctuations on assessment results and more objectively reflects the sustained control effect of treatment on tumors.<br>*c)* TTD: Time from initiation of Atezo+Bev to discont*inuation of Atezo+Bev therapy for any reason (e.g., toxicity, patient decision).*<br>*d) TTNT: Time from initiation of Atezo+Bev to initiation of any subsequent systemic therapy.*<br>*e) TTP: Time from initiation of Atezo+Bev treatment to radiological disease progression, as defined by investigator-assessed RECIST v1.1 or mRECIST criteria.*<br>**Safety Objectives:**<br>To describe the safety profile of the LRT+ Atezo+Bev cohort and its subgroups, including all treatment emergent adverse event (TEAE) , treatment-related AE (TRAE), and AEs of special interests such as bleeding, hypertension, liver dysfunction/ liver impairment, and immune-related AEs(irAEs).<br>**Exploratory Objectives:**<br>a) To describe associations between baseline patient/disease characteristics and clinical outcomes within specific LRT+ Atezo+Bev pattern.<br>b) To describe associations between specific LRT+ Atezo+Bev pattern and clinical outcomes.<br>c) To describe outcomes in specific subgroups (e.g., BCLC/CNLC stage, liver function [Child-Pugh, ALBI], AFP level, etiology (HBV vs. others)).<br>d) To describe and analyze factors influencing clinical effectiveness.<br>e) To describe subsequent treatment patterns after progression or discontinuation of LRT+ Atezo+Bev therapy. |
| **Study Design** | This is a retrospective, multicenter, cohort study. Approximately 1136 adult patients with uHCC treated with LRT+ Atezo+Bev between October 28, 2020, and October 31, 2025, will be included from 35 sites across China (including Mainland China, Hong Kong, Taiwan) and potentially the broader APAC region (Japan, Korea, Singapore, Malaysia).<br><br>**Key Definitions**<br>a) Index Date: First administration of atezolizumab or bevacizumab.<br>b) Baseline Period: 30 days prior to the index date.<br>c) Observation Period: From index date to death, last follow-up, new primary cancer diagnosis, or withdrawal of consent.<br>d) Sensitivity Analysis: Subgroup analyses will assess the optimal combination timing (e.g., LRT-first vs. concurrent) by adjusting for immortal time bias using time-dependent Cox models. |
| **Sample Size** | All patients who met the inclusion/exclusion criteria shall be included. To estimate the median OS in this unresectable HCC population (with an anticipated mOS of 30 months) with a 95% confidence interval that is approximately 5 months wide (i.e., a margin of error of ±2.5 months), the study would need to observe about 554 events (deaths). To achieve this number of events with a 48-month accrual period followed by 12 months of additional follow-up, and accounting for a 10% dropout rate. A total of |

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| | approximately 1,136 patients would need to be enrolled to achieve this precision. |
| **Population** | Study population will consist of adult patients with uHCC who initiated the study treatment of interest between 28 October 2020 and 31 October 2025. |
| **Inclusion Criteria** | Aged≥18 years at the initiation of Atezo+Bev<br>Initiated first-line Atezo+Bev between October 28, 2020, and July 31, 2025.<br>Received ≥1 LRT (TACE, TARE, HAIC, Ablation, Radiotherapy) within ±2 months of Atezo+Bev initiation (i.e., 2 months pre-initiation, during therapy, or 2 months post-discontinuation) , this window captures common clinical practice timing variations as observed in real-world cohorts.<br>Clinically or pathologically diagnosed uHCC before or at initiation. Evidence of unresectability includes:<br>Direct documentation of 'unresectable' or 'advanced' in medical records.<br>History of extrahepatic metastasis (confirmed by radiology, histology, or cytology).<br>Staging criteria: CNLC Stage IIIb, BCLC Stage B/C, or AJCC Stage IV, reflecting regional variations and broader applicability.<br>At least one visit record after the initiation of Atezo+Bev |
| **Exclusion Criteria** | Diagnosed with concomitant cancer except for basal cell carcinoma before or at the initiation of Atezo+Bev<br>Enrolled in interventional clinical trials at the initiation of Atezo+Bev.<br>Received any systemic therapy for HCC before the Atezo+Bev regimen. |
| **Treatment Definitions** | A. **Atezolizumab + Bevacizumab Regimen Definition:**<br>a) Index Date: Date of first administration of either atezolizumab or bevacizumab for uHCC.<br>b) Treatment Duration: Length of time from index date to date of last dose of either drug.<br>c) Discontinuation: Record date and reason for discontinuation (disease progression, toxicity, patient choice, death, completion |

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| | of planned course).<br>d) Dose Modifications/Interruptions: Record frequency and reason, especially for bevacizumab skipped doses.<br>B. **Locoregional Therapy (LRT) Definition:**<br>a) Modalities: Classified by records (TACE [cTACE/DEB-TACE], TARE, Ablation, HAIC, Radiotherapy).Combination LRT Definition: Administration of two or more distinct LRT modalities will be classified as a single "Combination LRT" episode, attributed to the date of the first LRT.<br>b) Timing Relative to Atezo+Bev Initiation: LRT exposure will be categorized based on its temporal relationship to the Atezo+Bev index date (first administration):<br>i. LRT-First: Completed within 2 months pre-Atezo+Bev (e.g., TACE 6 weeks before Bev infusion).<br>ii. Concurrent: Initiated within ±14 days of first Atezo+Bev dose (e.g., HAIC start 5 days post-initial Atezo).<br>iii. LRT-After: Completed within 2 months post-Atezo+Bev start (e.g., radiotherapy 1 month post-treatment). |
| **Study Endpoints** | **A. Primary Endpoint:**<br>Real-world overall survival (OS): defined as time from index date to death from any cause.<br>*Note: index date = first Atezo+Bev administration*<br>**B. Secondary Endpoints:**<br>a) **Real-world progression-free survival (rwPFS):** defined as the time from index date to clinician-documented disease progression (local progression, recurrence, new metastasis, or clinical progression) or death from any cause. Progression events are based on clinician judgment as recorded in medical documentation. Formal radiological reassessment or image archiving is not required due to the retrospective real-world nature of the study.<br>b) Real-world **Overall Response Rate (ORR):** defined as the percentage of patients who achieved complete response (CR) or partial response (PR) after the index date with at least one response assessment result. Both RECIST 1.1 and mRECIST will be used to evaluate tumor response.<br>c) Real-world **Disease Control Rate (DCR):** defined as the proportion of patients who achieve complete response (CR), partial response (PR), or stable disease (SD) as assessed by investigators using real-world imaging evaluations in accordance with RECIST v1.1 or mRECIST criteria. Among these, stable disease (SD) must persist for at least 6 weeks from the first documentation of SD, which helps exclude the interference of short-term disease fluctuations on assessment results and more objectively reflects the sustained control effect of treatment on tumors.<br>d) **Time to Discontinuation (TTD):** defined as time from the |

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| | initiation to discontinuation of Atezo+Bev.<br>e) **Time to next treatment (TTNT):** defined as time from the initiation of Atezo+Bev to the initiation of next systemic treatment.<br>f) **Time to Progression (TTP):** defined as the time from the Atezo+Bev index date to the first documented disease progression. Patients who died without progression may be censored in this endpoint analysis.<br>C. **Safety:** Describing the safety profile of the LRT+ Atezo+Bev cohort and its subgroups, including TEAE , TRAE ， and AE of special interests focusing on the incidence and severity of key adverse events (AEs) such as bleeding, hypertension, liver dysfunction/ liver impairment, and immune-related AEs(irAEs). |
| **Data Sources** | De-identified patient data will be retrospectively collected from all participated sites per institutional review board (IRB) approval:<br>**A. Electronic Medical Record Systems (EMR):**<br>a) Hospital Information System (HIS).<br>b) Laboratory Information System (LIS).<br>c) Picture Archiving and Communication System (PACS).<br>**B. Source Documentation:**<br>a) Clinician notes & consultation records.<br>b) Admission/discharge summaries.<br>c) Laboratory test results.<br>d) Medication/prescription records.<br>e) Radiology and pathology imaging reports.<br>f) Adverse event (AE) monitoring logs.<br>**C. Institutional follow-up tracking systems/databases independent of EMR (if available)**<br>**D. Investigator-completed reassessment forms (manual/hand-written documents) independent of EMR**<br>*Note: Each patient will be assigned a unique anonymized code to maintain data linkage while ensuring confidentiality, consistent with privacy protocols in real-world HCC studies. Pathology reports will be used solely for diagnostic verification (summary-level H&E/IHC findings); no human genetic resource samples or raw genetic data will be collected.* |
| **Data Analysis** | Any change to the data analysis methods described in the synopsis and protocol will not require an amendment unless this change substantially influences a principal feature of the study protocol. Any other changes to the data analysis methods described in the study protocol and the justification for making the change should be addressed in the statistical analysis plan (SAP) and will be described in the final study report. Missing data will in general not be imputed unless otherwise specified in the SAP. Study analyses will be performed using SAS® Version 9.2 or higher (SAS Inc., Cary, N.C., USA) or the latest stable version of R. All analyses will follow the intention-to-treat principle.<br>Continuous variables will be summarized using descriptive statistics, including mean, standard deviation (SD), median, interquartile range, minimum and maximum. Categorical variables will be summarized as |

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| | frequency and percentage.<br>Time-to-event variables will be estimated using Kaplan-Meier (KM) method. The median will be calculated along with two-sided 95% confidence intervals (CIs) by Brookmeyer-Crowley, and KM curve will be plotted and compared by log-rank test when subgroups are available. Event-free rate and/or time-to-event rate at month12, 24 and 36 will also be estimated using KM method and associated two-sided exact 95% CIs will be calculated using log (-log) transformation.<br>Subgroup analyses will be conducted for selected primary and secondary variables where sample size permits. Sensitivity analyses for selected primary and secondary variables will be conducted if appropriate/applicable. |

# 1. Background

## 2.1. Epidemiology and Clinical Burden of Unresectable Hepatocellular Carcinoma (uHCC) in China and the Asia-Pacific Region

Hepatocellular carcinoma (HCC) is a prevalent malignant tumor worldwide, characterized by high morbidity and mortality rates[1]. Notably, in Asia—particularly in China—it accounts for nearly half of the global incidence and mortality, presenting a significant public health challenge[2].

Unlike Western countries where HCC is primarily driven by hepatitis C virus (HCV) infection, alcohol abuse, and non-alcoholic fatty liver disease (MASLD) — which encompasses metabolic dysfunction-associated steatohepatitis (MASH) as a more advanced form — the main cause of HCC in China and most Asia-Pacific regions is chronic hepatitis B virus (HBV) infection. Although the proportion of MASLD-related HCC (including MASH-related cases) has increased in certain Asian regions recently, HBV infection remains the predominant etiological factor[3]. This distinct etiological background may not only influence the biological behavior of the disease but also result in differing treatment response patterns compared to Western cohorts. Moreover, HBV-related HCC is often more aggressive[4], with a significant proportion of patients in China being diagnosed at intermediate or advanced stages (e.g., Barcelona Clinic Liver Cancer(BCLC) stage B/C or China Liver Cancer(CNLC) stage IIb/IIIa/IIIb), thereby substantially limiting curative treatment options[5].

Therefore, conducting regional real-world evidence (RWE) studies that address the specific etiology and clinical characteristics of the region is essential for accurately evaluating treatment effectiveness within this unique biological context.

## 2.2. Current Standard of Care: Atezolizumab plus Bevacizumab (Atezo+Bev)

The Phase III IMbrave150 clinical trial showed that atezolizumab (an anti-PD-L1 antibody) combined with bevacizumab (an anti-VEGF antibody) has become the global first-line standard of care for patients with uHCC who have not undergone prior systemic therapy. The IMbrave150 trial demonstrated that the ATEZO+BEV regimen significantly improved overall survival (OS) (median OS: 19.2 months vs 13.4 months) and progression-free survival (PFS) (median PFS: 6.9 months vs

4.3 months) compared to sorafenib[6]. Furthermore, the Overall Response Rate (ORR) was notably enhanced (approximately 30% vs 11% according to RECIST 1.1 criteria)[7]. This regimen has been approved in China and other Asia-Pacific countries/regions, and Chinese subgroup analysis in IMbrave150 also revealed substantial efficacy benefits (OS HR: 0.44; PFS HR: 0.60)[8].

However, it should be noted that the patient population included in the IMbrave150 study was relatively selective, primarily comprising individuals with Child-Pugh A liver function and an ECOG performance status (PS) of 0-1. In contrast, in clinical practice, physicians may encounter patients with more compromised liver function, poorer PS, or other conditions that were excluded based on the IMbrave150 criteria. Moreover, despite the significant efficacy demonstrated by Atezo+Bev therapy, the Overall Response Rate (ORR) reported in the IMbrave150 study (approximately 30%) suggests that a considerable proportion of patients achieve only stable disease (SD) or experience progressive disease (PD).

These findings underscore the clinical imperative to explore strategies, such as the integration of appropriate Locoregional Therapies (LRTs), to further optimize and amplify the therapeutic efficacy of Atezo+Bev in a broader cohort of patients with uHCC.

### 2.3. Role and Types of Locoregional Therapy (LRT) in uHCC Management

LRT is a critical component in the management of HCC, particularly for localized but unresectable intrahepatic lesions. In the treatment of uHCC, the primary LRTs include commonly utilized LRTs primarily include:

Transarterial chemoembolization (TACE), including conventional TACE (cTACE) and drug-eluting bead TACE (DEB-TACE).

Transarterial radioembolization (TARE), typically performed using Y-90 microspheres.

Hepatic arterial infusion chemotherapy (HAIC), particularly in China, where FOLFOX-based HAIC is widely utilized.

Ablation Therapies including radiofrequency ablation (RFA) and microwave ablation (MWA).

Radiotherapy, including external beam radiotherapy and iodine-125 brachytherapy.

These LRTs not only play a pivotal role in the management of intermediate-stage HCC but also hold significant importance in advanced HCC. Their applications include tumor downstaging, bridging therapy for liver transplantation, local lesion control, palliative treatment, and combination with systemic therapy treatment.[9]

### 2.4. Overview of LRT Guideline Differences and Practice Heterogeneity in China and the Asia-Pacific Region

The application of LRT for uHCC varies significantly across clinical guidelines and practices in China and other Asia-Pacific (APAC) regions. This variability is driven by the primary etiology of HCC, regional staging systems, available medical resources, and local expertise.

The China Liver Cancer (CNLC) Guidelines[10] often advocate a more aggressive approach to locoregional therapy (LRT) in Chinese clinical practice. TACE is widely recommended for CNLC stages Ib to IIIa and, in certain cases, even for stage IIIb patients. HAIC based on the FOLFOX regimen is a unique recommendation for locally advanced HCC, particularly in cases involving major vascular invasion. Ablation is an important treatment option for earlier CNLC stages (Ia, Ib, IIa) and is sometimes combined with TACE in more complex scenarios. Compared to other LRT modalities, TARE is less frequently utilized in China.

The Asian Pacific Association for the Study of the Liver (APASL) guidelines[11], which hold significant influence across the Asia-Pacific region, also advocate for the active use of LRTs. While the importance of LRTs is universally recognized, regional variations exist in terms of emphasis on specific modalities. For instance, Japanese guidelines[12] provide more detailed criteria regarding tumor size and number as indications for TACE. In contrast, Korean guidelines[13] offer more extensive recommendations on TARE.

Overall, the APAC region demonstrates a more aggressive and diverse utilization of LRT compared to Western approaches. This study aims to clarify how varied LRT practices, particularly those emphasized in the CNLC and APASL guidelines (such as TACE, HAIC, TARE, ablation and radiotherapy), are combined with Atezo+Bev in real-world clinical settings. It also evaluates their impact on patient outcomes. The findings are expected to inform strategies for optimizing the clinical value of Atezo+Bev.

### 2.5. Rationale for Combining LRT with Atezo+Bev

LRTs can kickstart an immune response by releasing tumor antigens. Subsequently, systemic immunotherapies can amplify this response by unleashing T-cell activity. Additionally, anti-angiogenic agents can work to normalize the tumor environment, making it more conducive for both the LRTs to be effective and for the immune system to function optimally.[9]

Recent randomized controlled trials (RCTs), such as LEAP-012 , EMERALD-1 and Talentace, have demonstrated the feasibility and potential benefits of combining TACE with targeted therapies and immune checkpoint inhibitors for intermediate-stage HCC. These studies represent significant progress. However, these studies focus on one HCC stage—intermediate—and a single LRT modality, TACE, within defined protocols. This highlights a substantial evidence gap for the broader population of uHCC. In clinical practice, a wider range of LRTs—including TARE, ablation, and HAIC—is frequently utilized, alongside diverse patient characteristics that extend beyond those typically included in RCTs. Moreover, clinicians are actively exploring various combinations and sequences of these LRTs with targeted therapies plus immune checkpoint inhibitors in real-world settings.[14,15] This approach is driven by a strong biological rationale and aims to optimize outcomes for patients who may not achieve deep or durable responses to targeted therapy combined with immunotherapy alone.

## 2. Research Question and Objectives

**Research Question**: In clinical practice in China and selected Asia-Pacific regions, what is the effectiveness and safety for uHCC patients receiving first-line Atezo+Bev combined with LRT?

**Primary Objective**:

To describe real-world overall survival (OS) in uHCC patients receiving first-line Atezo+Bev in combination with any type of LRTs, with censoring defined as: loss to follow-up, withdrawal of consent, or diagnosis of new primary cancer (*critical for minimizing false follow-up bias*).

**Secondary Objectives**:

Describe

- real-world progression-free survival (rwPFS), Overall Response Rate (ORR [RECIST v1.1/mRECIST]), disease control rate (DCR), overall and stratified by key LRT categories.
- TTD: Time from Atezo+Bev initiation to discontinuation of Atezo+Bev monotherapy (*e.g., due to toxicity/patient decision*).
- TTNT: Time from Atezo+Bev initiation to subsequent systemic therapy.
- TTP: Time from treatment start to radiological progression (RECIST v1.1/mRECIST).

Describe the safety profile:

- TEAE,TRAE
- Grade 3-5 TEAE
- Grade 3-5 TRAE
- Incidence/severity of key AEs: bleeding, hypertension, hepatotoxicity, immune-related AEs (irAEs)
- In subgroup analyses (e.g., by LRT modality)

**Exploratory Objectives**:

To describe associations between baseline patient/disease characteristics and clinical outcomes within specific LRT+ Atezo+Bev pattern.

To describe associations between specific LRT+ Atezo+Bev pattern and clinical outcomes.

To describe outcomes in specific subgroups (e.g., BCLC/CNLC stage, liver function [Child-Pugh, ALBI], AFP level, etiology (HBV vs. others)).

To describe and analyze factors influencing clinical effectiveness.

To describe subsequent treatment patterns after progression or discontinuation of LRT+ Atezo+Bev therapy.

## 3. Study Design

This is a retrospective, multicenter, cohort study. Approximately 1136 adult patients with uHCC treated with Atezo+Bev plus LRT will be included from 35 sites across China and potentially broader APAC regions. The study period is strictly defined from October 28, 2020, to October 31, 2025. The study design schematic is presented in Figure 1.

**Key Definitions：**

Index Date: First administration of atezolizumab or bevacizumab.

Baseline Period: 30 days prior to the index date.

Observation Period: From index date to death, last follow-up, new primary cancer diagnosis, or withdrawal of consent.

Sensitivity Analysis:

- Subgroup analyses for LRT combination timing (LRT-first vs. concurrent).
- Adjustment for immortal time bias using time-dependent Cox models.

*Note: This study will utilize existing retrospective clinical data, and an exemption or waiver of informed consent will be sought, given the minimal risk and anonymized nature of the data analysis. Additionally, patients will be censored at the time of loss to follow-up, or upon diagnosis of a new primary malignancy, minimizing potential bias in follow-up data.*

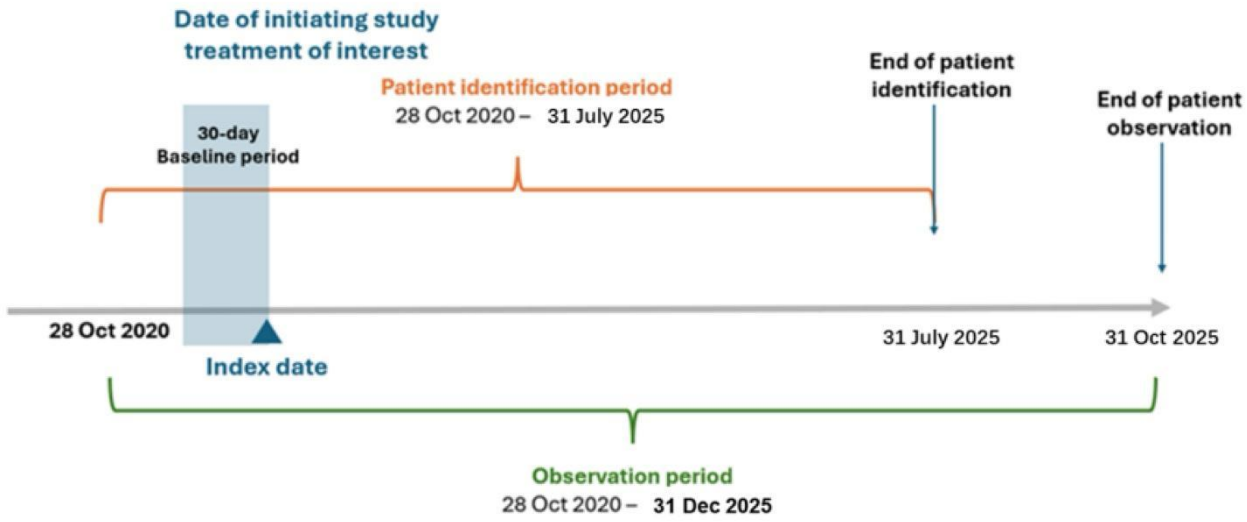


Figure 1. Study design schematic

*Note: End of patient observation is defined as 31 Oct 2025 or the day before the ethical approval from the leading site, whichever later.*

## 4. Selection Of Study Population

The effectiveness observation period varies among different effectiveness endpoints and is specified in section 6. The safety observation period is defined as from the date of initiating

Atezo+Bev to the earliest of 90 days post the later last dose of atezolizumab or bevacizumab, initiation of next systemic treatment, or end of observation. The study population will consist of adult patients with uHCC who initiated the study treatment of interest. These patients come from approximately 35 sites across China and potentially the broader APAC region. The eligibility criteria are shown below:

**Inclusion criteria:**

Aged≥18 years at the initiation of Atezo+Bev

Initiated first-line Atezo+Bev between October 28, 2020, and July 31, 2025.
Received ≥1 LRT (TACE, TARE, HAIC, Ablation, Radiotherapy) within ±2 months of Atezo+Bev initiation (i.e., 2 months pre-initiation, during therapy, or 2 months post-discontinuation) , this window captures common clinical practice timing variations as observed in real-world cohorts.
Clinically or pathologically diagnosed uHCC before or at initiation. Evidence of unresectability includes:

- Direct documentation of 'unresectable' or 'advanced' in medical records.
- History of extrahepatic metastasis (confirmed by radiology, histology, or cytology).
- Staging criteria: CNLC Stage IIIb, BCLC Stage B/C, or AJCC Stage IV, reflecting regional variations and broader applicability.

At least one visit record after the initiation of Atezo+Bev

**Exclusion criteria:**

Diagnosed with concomitant cancer except for basal cell carcinoma before or at the initiation of Atezo+Bev

Enrolled in interventional clinical trials at the initiation of Atezo+Bev.
Received any systemic therapy for HCC before the Atezo+Bev regimen.

## 5. Treatment Definitions

**Atezo+Bev Regimen Definition:**

Index Date: Date of first administration of either atezolizumab or bevacizumab for uHCC.

Treatment Duration: Length of Time from index date to date of last dose of either drug.

Discontinuation: Record date and reason for discontinuation (disease progression, toxicity, patient choice, death, completion of planned course).

Dose Modifications/Interruptions: Record frequency and reason, especially for bevacizumab skipped doses.

**LRT Definition:**

Modalities: Classified by records (TACE [cTACE/DEB-TACE], TARE, Ablation, HAIC, Radiotherapy).

**Combination LRT Definition**:

Administration of two or more distinct LRT modalities will be classified as a single "Combination LRT" episode, attributed to the date of the first LRT.

Timing Relative to Atezo+Bev Initiation: LRT exposure will be categorized based on its temporal relationship to the Atezo+Bev index date (first administration)

- LRT-First: Completed within ≤2 months pre-Atezo+Bev (e.g., TACE 6 weeks before Bev infusion).
- Concurrent: Initiated within ±14 days of first Atezo+Bev dose (e.g., HAIC start 5 days post-initial Atezo).
- LRT-After: Completed within ≤2 months post-Atezo+Bev start (e.g., radiotherapy 1 month post-treatment).

*Examples based on evidence: In clinical practice, concurrent LRT may enhance efficacy but requires careful AE monitoring (e.g., concurrent HAIC in GO30140).*

## 6. Data Source(s)

Patient treated with Atezo+Bev will be selected from hospitals across various provinces in China. After ethics committee (EC) approval, de-identified patient-level data will be retrospectively abstracted from medical records at approximately 35 sites. Data sources primarily include hospital information system (HIS), laboratory information system (LIS), and picture archiving and communication system (PACS). Each patient is assigned a unique, non-identifiable code to enable linkage. Source documents include clinician notes, admission/discharge summaries, laboratory results (including pathology reports for HCC diagnosis, as required without detailed genetic data), prescription records, imaging results, and communication documents. This approach ensures compliance with privacy regulations while capturing comprehensive real-world data.

## 7. Sample Size

To estimate the median OS in this unresectable HCC population (with an anticipated mOS of 30 months) with a 95% confidence interval that is approximately 5 months wide (i.e., a margin of error of ±2.5 months), the study would need to observe about 554 events (deaths). To achieve this number of events, the study will have a 48-month accrual period followed by 12 months of additional follow-up, accounting for a 10% dropout rate. A total of approximately 1136 patients would need to be enrolled in a prospective design.

However, in a retrospective design, all patients who met the inclusion/exclusion criteria shall be included. The exact sample size may be different from 1136. A post hoc power analysis will provide a retrospective assessment of whether the study had adequate power to estimate the primary endpoint (mOS) with the desired precision.

## 8. Data Analysis

Changes to the data analysis methods described in the synopsis and protocol will not require an amendment unless they substantially affect a principal feature of the study protocol. Any other changes and their justification should be documented in the statistical analysis plan (SAP) and described in the final study report. Analyses will be performed using SAS® Version 9.2 or higher (SAS Institute, Cary, NC, USA) or the latest stable version of R. All analyses will follow the intention-to-treat (ITT) principle. Missing data should be minimized and handled using appropriate imputation methods.

Continuous variables will be summarized using descriptive statistics, including the number of observations (n), mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), minimum, and maximum. Categorical variables will be summarized as frequency and percentage.

Time-to-event variables will be estimated using the Kaplan-Meier (KM) method. The median and two-sided 95% confidence intervals (CIs) will be calculated using the Brookmeyer-Crowley. KM curves will be plotted and compared using the log-rank test. Event-free rate and/or time-to-event rate at month 12,24 and 36 will also be estimated using KM method and associated two-sided exact 95% CIs will be calculated using log (-log) transformation. ORR will be calculated at 1, 3, and 6 months.

KM curves for OS and PFS will also be generated for pre-defined key subgroups. Median survival times and survival rates with 95% CIs will be presented for these subgroups. Exploratory comparisons between strata within a subgroup category (e.g., different LRT modalities, different BCLC stages) may be performed using the log-rank test, understanding its limitations due to confounding in an observational setting. ORR and DCR, along with their 95% CIs, will also be calculated and presented for pre-defined key subgroups. Exploratory comparisons of response rates between strata may be performed using Chi-square or Fisher's exact tests, as appropriate.

Missing values will be minimized and imputed with suitable statistical methods, detailed in the SAP.

## 9. Data Quality Assurance and Quality Control

The investigators must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, ICFs (if applicable), and documentation of Institutional Review Board (IRB)/EC and governmental approval (if necessary).

## 10. Management and Reporting of Adverse Events

All adverse events extracted from the data source for the study as specified in the protocol will be summarized as part of any interim safety analyses (if applicable) and in the final study report and final publication (if any).

## 11. Plans for Dissemination and Communication of Study Results

The results will be published in peer-reviewed journals and presented as abstracts/posters at medical congresses. Adherence to established guidelines is essential: Strengthening the Report of Observational Studies in Epidemiology (STROBE) for observational designs, Good Publication Practice 3 (GPP3), and International Committee of Medical Journal Editors (ICMJE). Publications will also comply with other top-tier standards like GRACE and CONSORT adaptations for observational data to ensure transparency and reproducibility.

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