Clinical Study Protocol (Interventional)

Official Title: Single-Center, Single-Arm, Two-Stage, Prospective Phase II Clinical Study of AK112 Combined with GAP Regimen as Conversion Therapy for Locally Advanced Gallbladder Cancer

NCT number: Not yet assigned

Protocol Version: V2.1

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1 Research Background

Gallbladder cancer ranks first in incidence among biliary tract malignancies, characterized by high malignancy, aggressive biological behavior, and an extremely poor long-term prognosis [1]. Radical surgical resection remains the only potentially curative treatment modality to date. However, due to insidious onset and non-specific early symptoms, most patients are diagnosed at advanced stages and lose the opportunity for radical resection [2]. Conversion therapy delivers potent, comprehensive anti-tumor treatment preoperatively to achieve tumor downstaging, providing patients with initially unresectable locally advanced gallbladder cancer potential access to radical curative surgery, and ultimately improving their long-term survival outcomes [3].

With rapid advances in precision medicine and tumor immunology, the Health China Initiative—Cancer Prevention and Control Implementation Plan (2023–2030) jointly issued by 13 national authorities, including the National Health Commission of China [4], clearly proposes to strengthen early diagnosis, early treatment, and scientific research breakthroughs for malignant tumors, concentrating superior resources to achieve key breakthroughs in core prevention and treatment technologies. The Action Plan for Improving Tumor Diagnosis and Treatment Quality, also released by the National Health Commission [5], emphasizes optimizing tumor diagnosis and treatment models, elevating scientific decision-making capacity, and promoting the innovative implementation of the "single-disease, multidisciplinary team (MDT)" diagnosis and treatment model. These policy guidelines provide clear guidance and strong support for clinical research and innovative clinical practice of conversion therapy for gallbladder cancer.

Conversion therapy for gallbladder cancer is still in the exploratory stage, with most relevant studies limited to small-sample retrospective analyses lacking high-level evidence-based medical evidence. The landmark ABC-02 clinical trial established gemcitabine plus cisplatin (GC) chemotherapy as the cornerstone systemic regimen for advanced biliary tract malignancies [6]. Recent studies demonstrate that conventional chemotherapy regimens achieve conversion-to-resectability rates generally lower than 30% [7,8].

The systemic treatment landscape for biliary tract malignancies has shifted toward combined modalities integrating immunotherapy, chemotherapy, and targeted therapy. Two landmark Phase III trials, TOPAZ-1[9] and KEYNOTE-966[10], validated the prominent clinical survival benefits of immunotherapy combined with chemotherapy as first-line treatment for advanced biliary tract malignancies. A 2024 retrospective study by Wang et al. [11] reported that the GC regimen combined with PD-1/PD-L1 inhibitors enabled radical resection in 50% of gallbladder cancer patients after conversion therapy. The 2025 Phase II ZSAB-TransGOLP trial [12] reported that tislelizumab plus lenvatinib and GEMOX regimen achieved tumor downstaging in 66.7% of gallbladder cancer patients.

AK112 is a bispecific antibody co-targeting PD-1 and VEGF. Compared with separate sequential administration of anti-PD-1 and anti-VEGF monoclonal antibodies,

AK112 exerts dual blockade of the PD-1 and VEGF signaling pathways via a single agent. VEGF serves as a major immune-suppressive factor within the tumor microenvironment and simultaneously upregulates PD-1 expression on immune cells. Concurrent inhibition of PD-1 and VEGF therefore generates synergistic anti-tumor immunotherapeutic effects within the tumor microenvironment.

A domestic Phase II clinical study evaluating AK112 combined with chemotherapy as first-line therapy for advanced biliary tract cancer (BTC) enrolled 22 subjects with a data cutoff date of February 29, 2024. Investigator-assessed objective response rate (ORR) reached 63.6% (14/22), disease control rate (DCR) 100.0% (22/22), median progression-free survival (PFS) 8.5 months, median overall survival (OS) not yet reached, 9-month OS rate 81.8%, and 12-month OS rate 62.2%. Collectively, AK112 combined with chemotherapy demonstrated favorable safety, acceptable tolerability, and robust anti-tumor efficacy in patients with advanced BTC.

Against this clinical background, there is an urgent unmet clinical need to conduct gallbladder cancer-specific Phase II clinical trials to further validate the efficacy and safety of AK112 plus GAP regimen as conversion therapy for locally advanced gallbladder cancer.

2 Research Objectives and Endpoints

2.1 Research Objectives

Overall Objective:

This study aims to explore the clinical translational value of AK112 combined with the GAP regimen as conversion therapy for initially unresectable locally advanced gallbladder cancer, and generate high-quality evidence-based medical data to improve radical surgical resection rates and long-term survival outcomes in this patient population.

Primary Objective:

Evaluate the anti-tumor efficacy of AK112 plus GAP conversion therapy for locally advanced gallbladder cancer, with the primary core endpoint defined as the R0 radical resection rate following conversion therapy.

Secondary Objectives:

Assess short-term anti-tumor efficacy: Objective Response Rate (ORR) and Disease Control Rate (DCR) per RECIST v1.1 criteria;

Evaluate pathological response magnitude: Major Pathological Response (MPR) rate and Pathological Complete Response (pCR) rate;

Analyze survival benefits: Track Progression-Free Survival (PFS) and Overall Survival (OS);

Evaluate safety and treatment tolerability: Monitor the nature, frequency, and severity of Adverse Events (AEs).

Explore predictive biomarkers: Dynamically detect changes in PD-L1 expression, tumor mutational burden (TMB), and VEGF pathway-related molecular alterations.

2.2 Study Endpoints

Primary Endpoint and Definition

R0 Resection Rate: The proportion of subjects who receive radical resection after multidisciplinary team (MDT) comprehensive assessment following AK112+GAP conversion therapy, with postoperative histopathological confirming no residual tumor cells at microscopic surgical margins.

Secondary Endpoints and Definitions

Objective Response Rate (ORR): The proportion of subjects achieving Complete Response (CR) or Partial Response (PR) per RECIST v1.1 criteria, with a minimum sustained response duration of ⩾4 weeks;

Pathological Complete Response (pCR) Rate: The proportion of subjects with no viable tumor cells identified on postoperative histopathological specimens;

Major Pathological Response (MPR) Rate: The proportion of subjects with viable tumor cell proportion ⩽ 10% within postoperative histopathological specimens;

Overall Survival (OS): Time interval from the first administration of study treatment to death from any cause;

Progression-Free Survival (PFS): Time interval from the first administration of study treatment to the first documented Progressive Disease (PD) or death from any cause, whichever occurs earlier;

Disease Control Rate (DCR): The proportion of subjects achieving CR, PR, or Stable Disease (SD);

Postoperative Recurrence-Free Survival (RFS): Time interval from radical curative surgery to the first documented tumor recurrence or death from any cause;

Safety Endpoints: Incidence and maximum severity of all AEs and Serious Adverse Events (SAEs).

Exploratory Endpoints and Definitions:

Correlation between intratumoral PD-L1 expression level, TMB, VEGF pathway molecular alterations, and treatment efficacy or acquired therapeutic resistance.

3 Trial Design

3.1 Overall Trial Design

This is a single-center, single-arm, open-label, prospective, Phase II conversion clinical trial. All enrolled subjects receive uniform AK112+GAP conversion therapy without a randomized control arm.

The trial adopts the Simon optimal two-stage design:

Stage I: Plan to enroll 11 eligible patients with locally advanced gallbladder cancer (LAGBC) to receive AK112+GAP conversion therapy. If ≤1 patient achieves R0 resection after conversion therapy and surgical evaluation, the regimen is deemed insufficiently effective, and the trial will be terminated early. If ≥2 patients achieve R0 resection, the trial proceeds to Stage II.

Stage II: Cumulative enrollment target of 18 patients total. If the final total number of R0 resected patients ≥5, the null hypothesis (H_0: $p \leq 10\%$) will be rejected, confirming that the regimen meets the primary endpoint with clinical application value.

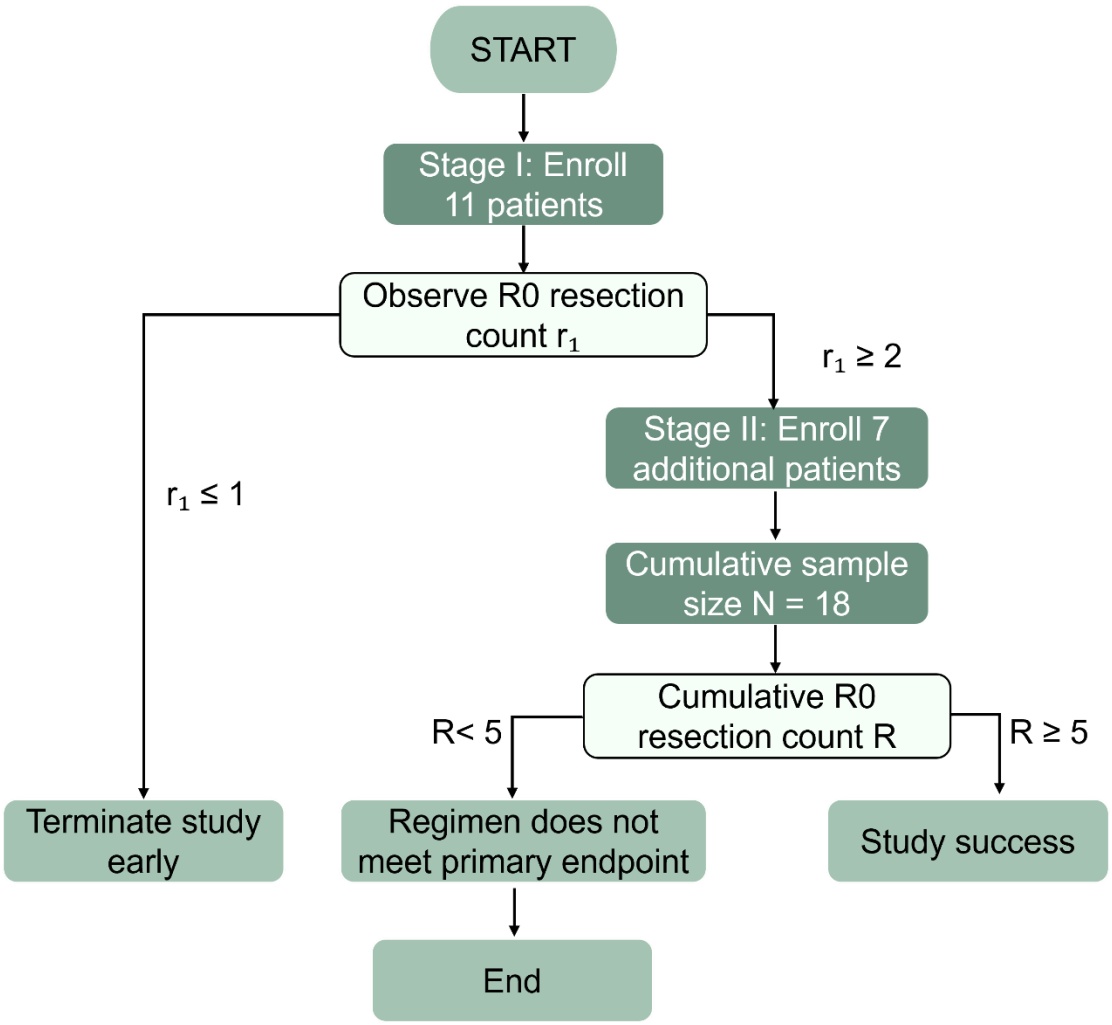
Intervention and Assessment Logic: Each treatment cycle spans 21 days (Q3W),

with a planned treatment duration of 4–6 cycles. Radiological efficacy assessment per RECIST v1.1 is performed every 2 cycles, and the MDT team dynamically evaluates surgical eligibility throughout the treatment period.

3.2 Trial Duration

Study period: June 2026 – June 2028

3.3 Simplified Trial Flowchart



4 Study Population

Patient Source: Patients with initially unresectable locally advanced gallbladder cancer evaluated by the MDT team.

4.1 Eligibility Criteria

(1) Voluntarily provide written informed consent;
(2) Age ≥18 years and ≤75 years at enrollment;
(3) Histologically or cytologically confirmed gallbladder adenocarcinoma;
(4) Radiological assessment meeting any of the following criteria: a. Hepatic invasion requiring extensive hepatectomy that the patient cannot tolerate; b. Biliary tract invasion extending beyond the bifurcation threshold requiring extensive hepatectomy that the patient cannot tolerate; c. Regional lymph node metastasis with fused bulky lymph nodes (maximum short-axis diameter >2 cm) compressing or invading critical blood vessels/biliary tracts, precluding radical lymphadenectomy; d. Primary tumor vascular invasion: main portal vein or left portal branch invasion without feasible vascular reconstruction; proper hepatic artery/common hepatic artery invasion >180°, or invasion <180% combined with mandatory portal vein reconstruction; right portal vein/right hepatic artery invasion with intolerance to extensive hepatectomy; e. Direct invasion of adjacent organs (pancreas, stomach, duodenum, colon);
(5) MDT consensus confirming initial non-resectability, with anticipated feasibility of radical resection after conversion therapy;
(6) Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1;
(7) No prior systemic anti-tumor therapy for locally advanced gallbladder cancer;
(8) At least one measurable target lesion per RECIST v1.1 suitable for repeated accurate quantitative measurement;
(9) Adequate organ function to tolerate the conversion regimen;
(10) Estimated survival ≥3 months;
(11) Willing and able to comply with scheduled visits, treatment regimens, laboratory testing, and all other study requirements;
(12) Adequate hematologic, renal, hepatic, coagulation, and cardiac function confirmed by screening laboratory tests (no blood product/growth factor support within 7 days prior to screening lab draws):

a. Hematology:

i. Absolute Neutrophil Count (ANC) ≥1.5 × 10^9/L (1,500/mm^3)

ii. Platelet count ≥100 × 10^9/L (100,000/mm^3)

iii. Hemoglobin ≥90 g/L;

b. Renal function:

i. Calculated Creatinine Clearance (CrCl) ≥50 mL/min via the Cockcroft-Gault formula:

$$CrCl\ (mL/min) = [(140 - Age) \times Weight\ (kg) \times F] / [Serum\ Creatinine\ (mg/dL) \times 72]$$

F = 1 for males, F = 0.85 for females; SCr = serum creatinine.

ii. Urine protein ≤1+ or 24-hour urine protein quantification <1.0 g;

c. Hepatic function:
i. Total bilirubin (TBil) ⩽ 2 × the upper limit of normal (ULN);
ii. AST and ALT ≤2.5 × ULN;
iii. Serum Albumin (ALB) ≥28 g/L;
d. Coagulation function: International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (APTT) ≤1.5 × ULN;
e. Cardiac function: Left Ventricular Ejection Fraction (LVEF) ≥50% on echocardiogram.

4.2 Exclusion Criteria

(1) Histological or cytological confirmation of gallbladder non-adenocarcinoma: squamous cell carcinoma, neuroendocrine neoplasm, lymphoma, sarcoma;
(2) Presence of distant metastatic disease at screening;
(3) Prior radiotherapy, chemotherapy, targeted therapy, or immunotherapy for gallbladder cancer;
(4) Concurrent other malignant tumors besides gallbladder cancer;
(5) Severe uncontrolled biliary tract infection or untreated obstructive jaundice;
(6) Major surgery or severe trauma within 30 days prior to first study drug administration:

a. Definitions:
Major surgery: All open/laparoscopic procedures requiring general endotracheal anesthesia entering thoracic, abdominal, or pelvic cavities (e.g. exploratory laparotomy, gastrointestinal resection, hernia repair, partial hepatectomy);
Severe trauma: Deep tissue injury, visceral rupture requiring hospitalization or surgical repair (e.g., fractures, extensive soft-tissue contusion, closed abdominal trauma);
b. Minimally invasive/interventional procedures permitted with mandatory washout intervals:
Diagnostic biopsy (lymph node, liver/gallbladder fine needle, EUS biopsy): minimum 7 days between the procedure and the first drug administration, no active hemorrhage/hematoma;
Biliary decompression (PTCD, ERCP stent/ nasobiliary drainage): a minimum of 14 days between the procedure and the first drug administration, no active hemorrhage, peritonitis, or biliary leakage confirmed by clinical and radiological evaluation;

(7) Active autoimmune disease, active inflammatory bowel disease, congenital or acquired immunodeficiency, active pulmonary tuberculosis, active syphilis infection, prior solid organ or allogeneic hematopoietic stem cell transplantation, or non-infectious interstitial lung disease requiring long-term systemic corticosteroid therapy;
(8) Severe bleeding diathesis or coagulation disorder history:

a. Screening lab abnormalities: PLT <100 ×10^9/L; INR >1.5 (without anticoagulation); APTT >1.5 × ULN; Fibrinogen <1.5 g/L;
b. CTCAE Grade ≥2 active bleeding event within 3 months before enrollment, or uncontrolled major vascular complications;

(9) Confirmed hypersensitivity to any excipient or active component of the study

drugs;

(10) Pregnant or lactating female patients;

(11) Severe psychiatric disorder, history of substance dependence, or other medical conditions that may impair trial compliance throughout study participation.

4.3 Discontinuation Criteria

(1) Subject to voluntary withdrawal (withdrawal of informed consent): Subjects may withdraw at any stage for any reason, without penalty.

(2) Medically indicated permanent discontinuation: Documented progressive disease (PD), intolerable treatment-related toxicities, rapid clinical deterioration, or confirmed perioperative contraindications to radical curative surgery;

(3) Discontinuation due to protocol non-compliance or regulatory issues: Poor study visit adherence, major protocol deviation, erroneous subject enrollment;

(4) Other administrative reasons: Early trial termination initiated by the sponsor/investigator, institutional ethics committee or regulatory authority requirements.

5 Treatment Groups

This is a single-arm clinical trial with no randomized control arm. All eligible enrolled subjects receive uniform AK112 + GAP conversion therapy.

6 Study Procedures

6.1 Screening Period

The time interval from written informed consent signature to the first administration of study drug shall not exceed 28 calendar days. Screening assessments include collection of demographic data, past medical history, prior oncologic treatment history, height, weight, complete physical examination, vital signs, ECOG performance status, 12-lead ECG, transthoracic echocardiogram, comprehensive laboratory testing (complete blood count, serum biochemistry, coagulation profile, thyroid function panel), infectious disease screening (HBV, HCV, HIV), serum pregnancy test (for female subjects of childbearing potential), cross-sectional tumor imaging (chest/abdomen/pelvis CT/MRI, brain CT/MRI, whole-body bone scan), and collection of tumor tissue biospecimens for predictive biomarker testing.

6.2 Treatment Period

6.2.1 Drug Preparation

Study drugs shall be prepared by qualified designated staff using aseptic technique.

AK112 preparation protocol:

Undiluted AK112 stock solution shall not be administered intravenously directly. Calculate the required dose (20 mg/kg), dilute in a 250–500 mL 0.9% sodium chloride (normal saline) infusion bag to achieve a final concentration range of 1.0–8.0 mg/mL. Remove an equal volume of diluent from the infusion bag prior to adding AK112 solution from one or multiple drug vials. Mix gently by slow inversion of the bag; vigorous shaking is prohibited. Visually inspect the final diluted solution; discard the solution if turbidity, particulate matter or precipitation is observed, and document the disposal in the drug accountability log.

Diluted AK112 solution must be administered immediately after preparation. If administration is delayed, the total storage time (including infusion duration) shall not exceed 4 hours either at room temperature or refrigerated storage (2–8°C).

Chemotherapy agents (gemcitabine, albumin-bound paclitaxel, cisplatin) are commercially marketed products purchased by the trial sponsor; all storage, handling, intravenous administration, and waste disposal procedures shall comply with local hospital pharmacy guidelines and the manufacturers' full prescribing information. Refer to the respective manufacturer package inserts for detailed handling specifications.

6.2.2 Treatment Regimen

(1) Pre-conversion supportive management: Subjects with obstructive jaundice and TBil >2×ULN receive sequential jaundice reduction and hepatoprotective therapy. All active biliary tract infections must be fully controlled prior to initiation of study treatment.

(2) AK112 Administration

Dose: 20 mg/kg IV on Day 1 of each 21-day cycle (Q3W).

Administration setting: Inpatient/outpatient clinic under trained study staff supervision; prohibited for at-home self-administration.

Infusion duration: 60–70 minutes; may extend to a maximum of 120 ±15 minutes for infusion intolerance.

Infusion reaction management: No primary prophylaxis permitted; secondary prophylaxis allowed. Emergency supplies (epinephrine, IV diphenhydramine, resuscitation equipment) must be readily available during infusion.

Filtration: Administer the entire diluted solution through a 0.2 μm / 0.22 μm inline filter. Post-infusion normal saline flush to clear all drug from the IV tubing.

(3) Chemotherapy Dosing

Body Surface Area (BSA) formula: BSA (m^2) = 0.20247 × Height(m)^0.725 × Weight(kg)^0.425; maximum capped BSA = 2.0 m^2 for all patients with calculated BSA >2.0 m^2.

Gemcitabine: 1000 mg/m^2 IV on Day 1 and Day 8 of each Q3W cycle;

Cisplatin: 25 mg/m^2 IV on Day 1 and Day 8 of each Q3W cycle;

Albumin-bound paclitaxel: 125 mg/m^2 IV on Day 1 and Day 8 of each Q3W cycle.

Premedication for chemotherapy: 5-HT3 receptor antagonists, dexamethasone (or equivalent), and antihistamines (e.g. diphenhydramine).

(4) Infusion sequence:

AK112 IV infusion first, with a minimum 15-minute interval before sequential administration of gemcitabine, albumin-bound paclitaxel, and cisplatin.

(5) Treatment duration:

Standard planned course of 4–6 cycles; may be extended to 6–8 cycles for subjects with confirmed clinical tumor benefit who remain ineligible for radical surgery after 6 cycles.

Radiological efficacy assessment per RECIST v1.1 will be performed every 2 cycles, with repeated MDT surgical eligibility reassessment after each imaging evaluation.

6.3 Follow-Up Period

Safety follow-up: Complete physical examination, vital signs, laboratory testing, and tumor imaging 30 days after the last study drug administration.

Survival follow-up: Every 90 days after safety follow-up until death, loss to follow-up, withdrawal of consent, or trial closure; collect survival status and subsequent anti-tumor treatment records.

Postoperative follow-up (surgical patients): Synchronized with survival follow-up frequency, with additional recurrence data collection.

6.4 Dose Modification and Delay Rules

AK112: No dose reduction permitted; administration may be delayed up to a maximum of 4 weeks.

Chemotherapy agents: Dose reduction or administration delay (maximum 2 weeks) is permitted per grade of treatment-related toxicity. Discontinue the respective chemotherapy agent permanently if two sequential dose reductions fail to resolve intolerable toxicities.

6.5 Concomitant Medications

No other anti-tumor therapy (targeted agents, immunotherapy, radiotherapy) was permitted during study participation. Standard supportive care (anti-emetics, granulocyte colony-stimulating factors, etc.) is allowed per institutional guidelines.

7 Efficacy and Safety Assessment

7.1 Efficacy Assessment

Primary efficacy endpoint: R0 radical resection rate. Radiological tumor assessment per RECIST v1.1 every 2 cycles; final comprehensive efficacy evaluation upon completion of conversion therapy, with MDT discussion to confirm surgical eligibility.

7.2 Safety Assessment

Safety evaluation adheres to NCI CTCAE Version 6.0, including:

Incidence, nature, and severity of AEs and SAEs;

Abnormal laboratory parameters (hematology, serum biochemistry, coagulation, thyroid function);

Changes in vital signs, physical examination, ECG, echocardiogram;

Immune-related Adverse Events (irAEs);

Perioperative surgical complications.

8 Adverse Event Reporting

8.1 Definition of Adverse Event (AE)

Any unexpected clinically significant medical event occurring after the first administration of study treatment, regardless of presumed causal relationship to study intervention.

8.2 Classification of AEs

Treatment-Related Adverse Events (TRAEs): AEs judged by investigators to have a reasonable causal association with study treatment.

Immune-Related Adverse Events (irAEs): AEs attributed to the

immunotherapeutic mechanism of AK112.

8.4 Definition of Serious Adverse Event (SAE)

An AE meeting any of the following criteria: resulting in death, life-threatening, requiring hospitalization or prolonged hospital stay, permanent or substantial disability/functional impairment, congenital anomaly/birth defect, or other medically significant critical events. All SAEs must be reported to the Institutional Review Board (IRB) and the principal investigator within 24 hours of detection.

8.5 Severity Grading

All AEs graded 1–5 per NCI CTCAE v6.0.

8.6 Causality Assessment

Investigators classify AE-treatment causality based on temporal sequence, pharmacological characteristics, known toxicity profiles, dechallenge/ rechallenge response, concomitant medications, and underlying comorbidities: Definitely Related, Probably Related, Possibly Related, Possibly Unrelated, and Definitely Unrelated.

9 Data Storage and Management

All study data are entered by authorized research staff into an Electronic Data Capture (EDC) system. Source documents (informed consent, original medical records, and laboratory reports) shall be retained as primary trial records. Study data shall be preserved for a minimum of 5 years after trial completion.

10 Quality Assurance

A comprehensive quality management system will be implemented, including standardized operating procedures (SOPs), investigator training and qualification certification, periodic data monitoring and query resolution, and an independent Data Monitoring Committee (IDMC) to periodically review safety and efficacy interim data.

11 Statistical Analysis

11.1 Sample Size Calculation

Sample size estimated via Simon two-stage design with the following statistical assumptions: one-sided $\alpha = 0.05$; null hypothesis conversion rate $p_0 = 10\%$; alternative hypothesis conversion rate $p_1 = 35\%$; statistical power = 80%. Planned total enrollment of 29 eligible subjects with ~20% buffer accounting for screen failure/discontinuation. Stage I enrolls 11 patients; terminate early if ≤1 R0 resection; proceed to Stage II if ≥2 R0 resections, accumulating a total of 18 evaluable patients. The trial meets primary efficacy criteria if total R0 resections ≥5 in 18 evaluable patients.

11.2 Statistical Methods for Efficacy Analysis

Statistical analyses were performed using SPSS 28.0 software. All statistical tests are two-sided with $\alpha = 0.05$. Categorical endpoints (resection rate, ORR, DCR) are summarized using descriptive statistics, with 95% confidence intervals calculated by the Clopper-Pearson method. Time-to-event endpoints (PFS, Duration of Response, RFS) are analyzed via Kaplan-Meier survival curves to estimate the median survival

and cumulative survival rates. Safety endpoints (AE/SAE incidence) are compared using Chi-square or t-tests based on variable type.

11.3 Interim Analysis

Interim analysis is conducted upon completion of Stage I (11 enrolled patients with full conversion therapy and surgical evaluation). If ≤1 R0 resection is observed, the IDMC and principal investigator jointly decide whether to terminate the trial early. The IDMC reserves authority to recommend trial modification or immediate termination based on emerging safety data at any time.

12 Data Collection and Administration

12.1 Case Report Forms / EDC System

All trial data are captured via electronic data capture with dual-data entry, built-in logical validation, and range checks to guarantee data integrity.

12.2 Data Management

Data management includes standardized coding, data cleaning, and database lock procedures. All data modifications retain full audit trails. The database will be locked upon trial completion prior to statistical analysis.

13 Ethical Standards and Informed Consent

This clinical trial will be conducted in full compliance with the Declaration of Helsinki (2024 Version), *Measures for the Administration of Investigator-Initiated Clinical Research in Medical and Health Institutions (2024 Edition)*, and all national domestic clinical trial regulatory guidelines and laws of the People's Republic of China. The full protocol shall be reviewed and formally approved by the Institutional Review Board (IRB) prior to trial initiation, with signature confirmation by the principal investigator and study lead. All subsequent protocol amendments require re-submission and re-approval by the IRB prior to implementation. If critical new safety information regarding study investigational products is identified mid-trial, the written informed consent document shall be revised, re-approved by the IRB, and re-signed by all actively enrolled subjects.

Prior to enrollment, investigators shall provide a full detailed explanation of all trial-related information to prospective subjects/legal representatives, including trial nature, research objectives, potential clinical benefits and foreseeable risks, alternative standard therapeutic options, and all subject rights and obligations stipulated in the trial protocol. Subjects may only initiate any study-related procedures after full comprehension and voluntary signature of the written informed consent form.

14 Confidentiality and Data Security

All subject personal identifiable information (PII) will be fully de-identified via unique trial subject identification numbers replacing all legal names. All trial data will be stored in encrypted electronic databases with role-based access control limited exclusively to authorized trial staff. All personnel participating in trial execution shall sign a formal confidentiality agreement. No individually identifiable subject information will be disclosed in any trial academic publication or conference

presentation.

15 Clinical Trial Insurance and Compensation

All enrolled subjects will be covered by dedicated clinical trial liability insurance. Subjects who sustain study-related adverse health injuries will receive timely standardized medical treatment and eligible financial compensation in accordance with relevant national laws, regulations, and insurance policy clauses.

16 Publication and Intellectual Property

Trial results will be submitted for publication in domestic and international peer-reviewed journals and presented at relevant academic conferences. Intellectual property rights shall be governed by institutional and sponsor agreements.

17 References

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