Safety and Efficacy of HepaticArterial Infusion Chemotherapy (GP Regimen) and Intra-arterial Infusion of Envafolimab Combined with Lenvatinib for Unresectable Advanced First-line Biliary Tract Cancer: AMulticenter, Phase Ib/II, Single-arm Clinical Study

Unique Protocol ID:2026121

Date:May 18th, 2026

Safety and Efficacy of Hepatic Arterial Infusion Chemotherapy (GP Regimen) and Intra-arterial Infusion of Envafolimab Combined with Lenvatinib for Unresectable Advanced First-line Biliary Tract Cancer: A Multicenter, Phase Ib/II, Single-arm Clinical Study

Ruihong Dai[1] Facheng Lu[1] Weibing Leng[1] Qing He[1] Wenhao Guo[1] Tao Hai[1] Chang Liu[1]⋆

1: Interventional Diagnosis and Treatment Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China.

⋆Corresponding author: Chang Liu, Interventional Diagnosis and Treatment Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China. Email: drliuchang@wchscu.cn; Tel: 18980606382.

Abstract

Background : Biliary tract cancer (BTC) often presents at an advanced stage with poor prognosis. While combining chemotherapy with immunotherapy has become standard, outcomes remain suboptimal. This study aims to investigate the safety and efficacy of hepatic arterial infusion (HAI) chemotherapy (gemcitabine and cisplatin, GP) combined with intraoperative arterial Envafolimab Injection and oral Lenvatinib as first-line treatment for unresectable BTC.

Methods:This open-label, multicenter, single-arm phase Ib/II trial enrolls patients with unresectable BTC. Phase Ib (n=9) explores dose-limiting toxicities (DLTs) over 28 days across three dose cohorts of HAI-GP plus arterial Envafolimab Injection and lenvatinib to determine the recommended phase II dose (RP2D). Phase II (n=20) will evaluate the RP2D regimen for two initial cycles. Patients with response or stable disease receive up to six cycles of the combination, followed by maintenance lenvatinib (8 mg daily) and subcutaneous Envafolimab Injection (RP2D dose, day 1, q3w) until progression, unacceptable toxicity, or completion of two years. The primary endpoint for phase II is objective response rate (ORR). Secondary endpoints include disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety (NCI-CTCAE v5.0).

Discussion:This trial explores a novel synergistic strategy combining regional chemotherapy, intra-arterial immunotherapy, and oral targeted therapy to enhance local tumor control and systemic antitumor immunity while potentially minimizing systemic toxicity. The phase Ib/II design allows for dose optimization and preliminary

Funding: This work was supported by the Chengdu Medical Research Project (Grant No. 2024069) from the Chengdu Municipal Health Commission.

efficacy assessment, providing a foundation for future larger-scale investigations. Findings may offer a new treatment paradigm for this challenging malignancy.

Trial registration: This study has been approved by the Ethics.Committee of West China Hospital of Sichuan University (IRB No. 2026121).The trial was prospectively registered at ClinicalTrial Registry ().

Keywords:Biliary tract cancer, Hepatic arterial infusion, Envafolimab Injection, Lenvatinib, Immunotherapy, Phase I/II

Background

Biliary tract carcinoma (BTC) encompasses gallbladder cancer (GBC) and intrahepatic/extrahepatic cholangiocarcinoma (CC), representing approximately 3% of all gastrointestinal malignancies[1-3]. According to the latest data from the National Cancer Center, there are an estimated 55,700[4] new cases of gallbladder cancer annually in China. Globally, the incidence of BTC is increasing, with the highest prevalence observed in Asian countries[5].

For advanced biliary tract malignancies, systemic therapies including chemotherapy, immunotherapy, and targeted therapy remain the mainstay of treatment. The ABC-02 [6]trial established the gemcitabine plus cisplatin (GP) regimen as the standard first-line therapy for advanced BTC. In 2022, the ASCO GI interim analysis of the TOPAZ-1[7] trial confirmed the combination of GP chemotherapy with durvalumab as a standard treatment for advanced first-line BTC. In recent years, studies investigating chemotherapy and PD-1/PD-L1 monoclonal antibodies in combination with targeted agents have shown promising progress. At the 2021 ESMO Congress, results from a single-arm, single-center clinical trial of toripalimab plus lenvatinib with GEMOX chemotherapy [8]for advanced intrahepatic cholangiocarcinoma demonstrated an objective response rate (ORR) of 80%, a disease control rate (DCR) of 93.3%, a 6-month overall survival (OS) rate of 90.0%, with median OS not yet reached. Data from several prospective studies indicate that PD-1/PD-L1 antibodies combined with lenvatinib can yield favorable outcomes in advanced BTC. Andrea Cercek et al. [9]conducted a Phase II single-center trial demonstrating that hepatic arterial infusion chemotherapy (HAIC) with GEMOX provided clinical benefit for unresectable intrahepatic cholangiocarcinoma (ICC). Cai et al. [10]performed a retrospective study showing significantly longer OIPFS in the HAIC group compared with the TACE group; HAIC offered superior intrahepatic

tumor control relative to TACE. For patients with unresectable BTC, HAIC represents an effective and safe therapeutic option that may prolong survival, pending confirmation from large-scale clinical trials.

At present, therapeutic choices for advanced BTC are limited, underscoring the need to explore novel, effective treatment strategies. The efficacy of doublet chemotherapy or PD-1/PD-L1 immunotherapy combined with targeted therapy in the first-line setting remains inadequate. Clinically, unmet needs persist for BTC patients, with new regimens required to achieve control over both intrahepatic and extrahepatic lesions, delivering both high short-term objective response rates and sustained long-term disease control. The Double-IA-001[11] study confirmed the efficacy and safety of the triple therapy consisting of hepatic arterial infusion chemotherapy (HAIC) plus intra-arterial immunotherapy infusion and oral targeted therapy in patients with BCLC stage C hepatocellular carcinoma (HCC). A prospective Phase II clinical trial (T-double, NCT04796025) led by Professor Gao Fei's team [12]at Sun Yat-sen University Cancer Center, published in the high-impact oncology journal 《Cancer Letters》(Q1), further validated that transarterial chemoembolization combined with intra-arterial infusion of targeted and immunotherapeutic agents can enhance efficacy while reducing toxicity. In patients with Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma, transarterial chemoembolization (TACE) combined with intra-arterial infusion of sintilimab and bevacizumab achieved an ORR of 66.7%, a complete response (CR) rate of 9.5%, a median progression-free survival (PFS) of 6.0 months, and a median overall survival (OS) of 12.2 months, with safety remaining manageable.

In summary, this study aims to evaluate the safety and efficacy of hepatic arterial infusion chemotherapy (GP regimen) combined with intra-arterial infusion of envafolimab and lenvatinib for the treatment of unresectable biliary tract cancer.

Research Methods:

Experimental Overview / Research Treatment Regimen

This is an open-label, multicenter, Phase Ib/II, single-arm clinical trial. Patients with unresectable biliary tract cancer will be enrolled to receive hepatic arterial infusion chemotherapy (GP regimen) combined with intra-arterial infusion of envafolimab and lenvatinib as first-line therapy. In Phase Ib, nine patients will be enrolled and allocated to three dose cohorts to receive the combination regimen of HAIC (GP) + intra-arterial infusion of envafolimab + lenvatinib. Dose-limiting toxicities (DLTs) will be monitored for 28 days following administration. If no DLTs occur, the regimen will be considered tolerable, and patients will continue follow-up until 60 days post-administration. Upon

completion of Phase Ib, the principal investigator will determine, based on safety and tolerability, whether to proceed to Phase II and will define the Phase II dosing regimen.

The Phase II portion plans to enroll 20 patients, who will receive two cycles of HAIC (GP) + intra-arterial infusion of envafolimab + lenvatinib at the optimal dose established in Phase Ib. Efficacy will be assessed upon re-examination. Patients demonstrating clinical benefit will complete a total of six cycles of the combination regimen, followed by maintenance therapy (lenvatinib 8 mg orally once daily + envafolimab at the optimal Phase Ib dose, administered subcutaneously on Day 1 every three weeks) until completion of two years of therapy, disease progression, intolerable toxicity, death, withdrawal of informed consent, or investigator-determined treatment discontinuation. This study will provide a preliminary evaluation of the safety and efficacy of HAIC (GP) + intra-arterial infusion of envafolimab + lenvatinib in unresectable biliary tract cancer.

Details are shown in Figure 1.

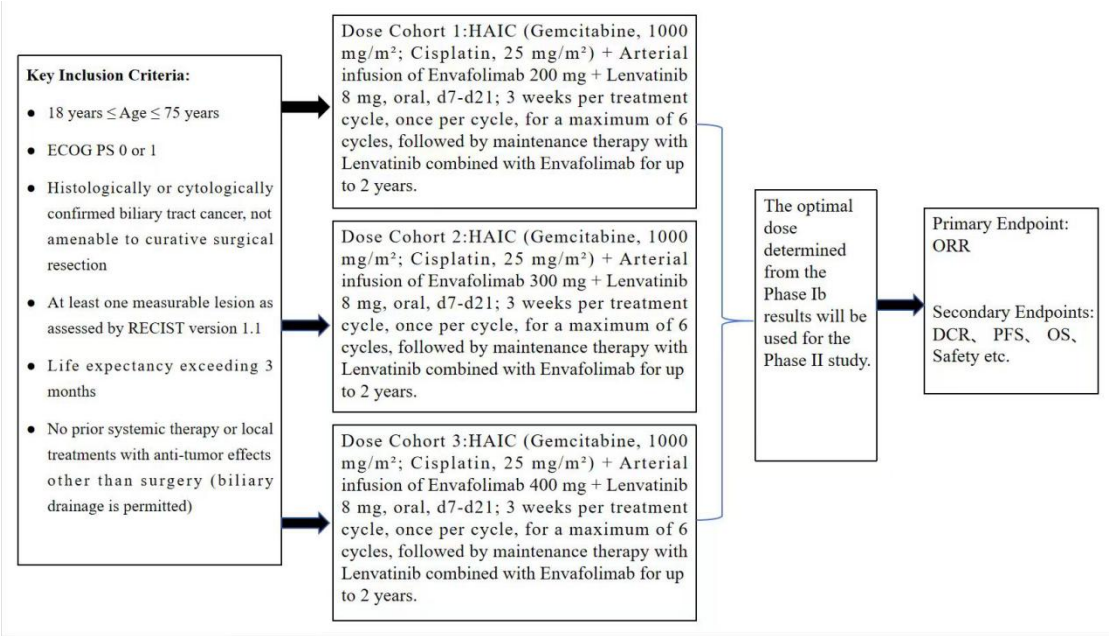

Figure 1. Research Protocol Flowchart

Enrolled patients will receive hepatic arterial infusion chemotherapy with gemcitabine and cisplatin on Day 1 of each cycle, with envafolimab administered via catheter. From Day 7 onward, patients will initiate oral lenvatinib therapy, with each treatment cycle lasting three weeks. Efficacy evaluations, including tumor imaging and laboratory tests, will be performed every two treatment cycles to assess disease control and determine

eligibility for surgical intervention or continued therapy. Patients exhibiting disease progression will withdraw from the study and may receive alternative treatments. Patients continuing therapy will undergo clinical reassessment after completing six cycles, including tumor imaging and laboratory evaluations, to determine treatment efficacy and eligibility for surgery or maintenance therapy.

Patients receiving maintenance therapy will continue oral lenvatinib in combination with subcutaneous envafolimab until disease progression, death, intolerable toxicity, withdrawal of informed consent, initiation of new anti-cancer therapy, or other protocol-specified termination criteria. Safety assessments will be conducted according to NCI CTCAE v5.0 from the first dose through 30 days after the final dose. Following safety follow-up, subjects will enter a survival follow-up phase, with assessments conducted every 90±7days until death or study completion.

Imaging assessment requirements: Contrast-enhanced CT of the chest and whole abdomen (or, if contraindicated, MRI of the whole abdomen plus non-contrast chest CT) will be performed every six weeks. After disease progression, at least one follow-up imaging assessment should be performed if feasible.

The investigator will evaluate the patient's disease response according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and the modified RECIST (mRECIST) version 1.1. Following drug discontinuation, patients will be followed for a period of 2 years, with assessments conducted once every 3 months, calculated from the date of the first administration.

Main Inclusion Criteria:

Patients must meet all of the following inclusion criteria:

1) Age between 18 years and [missing value] years, inclusive.

2) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

3) Histologically or cytologically confirmed biliary tract carcinoma, deemed unsuitable for radical surgical resection.

4) At least one measurable lesion as determined by the investigator in accordance with mRECIST or RECIST version 1.1.

5) Estimated life expectancy greater than 3 months.

6) No prior systemic therapy or local anti-tumor treatment, except for surgery (biliary drainage is permitted).

7) Patients who experience relapse more than 6 months after completion of postoperative adjuvant therapy may be enrolled.

8) Child–Pugh score of [missing value] points.

9) Adequate organ function to meet the criteria for chemotherapy:

a) Bone marrow function: absolute neutrophil count ⩾ [missing value]/L; platelet count ⩾ [missing value]; hemoglobin ⩾ [missing value];

b) Hepatic function: total bilirubin ⩽ [missing value] × upper limit of normal (ULN); for patients without liver metastases, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ⩽ [missing value] × ULN; for patients with confirmed liver metastases, AST and ALT ⩽ [missing value] × ULN;

c) Renal function: serum creatinine ⩽ [missing value] × ULN; routine urinalysis showing urinary protein < [missing value]; if baseline urinary protein is [missing value], a 24-hour urine collection must confirm total protein ⩽ 1 g/24 h;

d) Coagulation function: international normalized ratio (INR) or prothrombin time (PT) ⩽ 1.5 × ULN; for patients receiving anticoagulant therapy, PT must be within the therapeutic range intended for the anticoagulant used.

10) Female patients must be postmenopausal or, if premenopausal, have a negative urine or serum pregnancy test; male patients must agree to use effective contraception or have undergone surgical sterilization during the trial and for 8 weeks following the final dose of the study drug.

Main Exclusion Criteria:

Patients meeting any of the following criteria will be excluded:

1) Known hypersensitivity to the investigational drug(s).

2) Current participation in another interventional clinical trial, or receipt of any investigational drug or use of investigational device within 4 weeks prior to first dosing.

3) History of malignancy outside the biliary tract within 5 years prior to first dosing, except for adequately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and/or carcinoma in situ that has been completely resected.

4) Previous treatment with immune checkpoint inhibitors including anti–PD-1, anti–PD-

L1, or anti–PD-L2 agents, or drugs targeting other stimulatory or co-inhibitory T-cell receptors (e.g., CTLA-4, OX-40, CD137).

5) History of solid organ or hematopoietic stem cell transplantation.

6) Any condition requiring systemic corticosteroids (equivalent to prednisone or above) or other immunosuppressive therapy within 14 days prior to randomization.

7) Active autoimmune disease or history of autoimmune disease with potential for recurrence.

8) Radiographic evidence of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), or prior noninfectious pneumonitis identified on screening chest computed tomography (CT).

9) Severe infection within 4 weeks prior to randomization, including but not limited to hospitalization due to infectious complications, bacteremia, or severe pneumonia.

10) Severe chronic or active infection (including tuberculosis) requiring systemic (oral or intravenous) antibiotic therapy within 14 days prior to randomization.

11) Known history of Human Immunodeficiency Virus (HIV) infection (i.e., HIV-1/2 antibody positive); untreated active Hepatitis B. *Note: Subjects with Hepatitis B meeting the following criteria are eligible: HBV viral load < 2000 copies/mL (200 IU/mL) prior to the first dose, with anti-HBV therapy administered throughout the chemotherapy period to prevent viral reactivation. For subjects who are anti-HBc (+), HBsAg (-), anti-HBs (-), and HBV viral load (-), prophylactic anti-HBV therapy is not required, but close monitoring for viral reactivation is necessary.* Patients with active Hepatitis C infection (HCV antibody positive and HCV-RNA above the lower limit of detection) are excluded.

12) Concurrent participation in another therapeutic clinical trial.

13) Presence of obstructive jaundice (enrollment permitted following active intervention such as biliary drainage or stenting and subsequent normalization of liver function).

14) Meeting any of the following cardiovascular criteria:

a) New York Heart Association (NYHA) Class II or higher heart failure within 3 months prior to initiation of study treatment;

b) Major cardiovascular events including myocarditis, myocardial infarction, cerebrovascular events, unstable arrhythmia, or unstable angina within 6 months prior to initiation of study treatment;

c) Symptomatic pulmonary embolism within [missing value] months prior to randomization;

d) Known artery disease or left ventricular ejection fraction (LVEF) < 40%.

15) Lactating women.

16) Women of childbearing potential unwilling to use contraception.

17) Vulnerable populations other than elderly or illiterate individuals, including those with mental illness, cognitive impairment, or critical illness.

18) Any other reason deemed by the investigator to render the subject unsuitable for study participation.

Withdrawal Criteria

1) Voluntary withdrawal by the subject.

2) Investigator determines the subject is unsuitable to continue participation.

3) Development of distant metastases during treatment or inability to tolerate continued therapy due to severe adverse events.

Study Endpoints

Primary endpoint for Phase Ib: Dose-Limiting Toxicity (DLT). The DLT observation period extends from the first dose to 28 days post-administration. If, among 9 patients enrolled in Phase Ib, the number experiencing DLT is $\leqslant 1$ ， the dose level will be considered well tolerated; if the number is $\geqslant 2$, dose reduction and re-evaluation will be required until a well-tolerated dose is established as the Recommended Phase II Dose (RP2D).

Secondary endpoint for Phase Ib:Tolerability.

Primary endpoint for Phase II:Objective Response Rate (ORR), defined as the proportion of patients achieving a predefined reduction in tumor volume maintained for the minimum required duration, including Complete Response (CR) and Partial Response (PR).

Secondary endpoints for Phase II:

1. Disease Control Rate (DCR): Defined as the proportion of patients achieving predefined tumor volume control (reduction or stabilization) maintained for the

minimum required duration. Based on RECIST v1.1 or mRECIST criteria, DCR is the sum of percentages for CR, PR, and Stable Disease (SD) during treatment or within 30 days after discontinuation of study drug .

- Complete Response (CR): Disappearance of all target lesions, absence of new lesions, and normalization of tumor markers, maintained for at least 4 weeks.
- Partial Response (PR): Reduction in the sum of diameters of target lesions by [missing value], maintained for at least 4 weeks.
- Stable Disease (SD): The change in the sum of the maximum diameters of target lesions ranges between a reduction of no more than 30% and an increase of no more than 20% and sustained for a minimum duration of 4 weeks.

2. Progression-Free Survival (PFS): The interval from the subject's first dose to the earliest occurrence of disease progression or death from any cause. Progression events are defined as an increase in the sum of the maximum diameters of target lesions by $\geqslant 30\%$, the emergence of new lesions or metastases, or death from any cause.

3. Overall Survival (OS): The interval from the subject's first dose to death from any

4. 3-month and 6-month Progression-Free Survival Rate: The proportion of patients evaluable for efficacy who remain free of disease progression or death from any cause after 3 months and 6 months of treatment.

5. 6-month and 12-month Mortality Rate: The proportion of patients among the total enrolled who have died from any cause at 6 months and 12 months following initiation of treatment.

6. Safety Indicators: Vital signs, laboratory parameters, adverse events (AE), serious adverse events (SAE), and drug-related AE/SAE. Laboratory evaluations will be performed every 2 treatment cycles to monitor safety.

Data Collection and Follow-up

Study drug administration schedule: Gemcitabine, Cisplatin, and Envafolimab are administered on Day 1 (± 3 days) of each cycle; Lenvatinib is administered on Day 7 (± 3 days) of each cycle. Each cycle lasts 21 days. The first cycle must commence within 3 days after patient enrollment.

All procedures during the treatment period must be completed within 3 days prior to

dosing, except for baseline imaging assessments, which must be performed within 21 days before initiation of study treatment. Imaging assessments are scheduled for Week 6 (± 1 week) and Week 12 (± 1 week). The end-of-treatment visit must be conducted within 30 days after the final dose.

After treatment discontinuation, follow-up will be conducted for 2 years from the date of first dose, with evaluations performed every 3 months (± 14 days).

Statistical Analysis and Sample Size

Timing of efficacy and safety analyses: When $\geqslant 75\%$ patients have died, data will be extracted from the clinical database for statistical evaluation of efficacy and safety endpoints.

All analyses will be performed using SAS statistical software. All statistical tests will be two-sided; a P-value of <0.05 will denote statistical significance, and confidence intervals will be calculated at a 95% confidence level.

Baseline data will be analyzed using the Full Analysis Set (FAS). All efficacy endpoints will be analyzed using both the Full Analysis Set and the Per-Protocol Set (PPS). For primary efficacy endpoints including ORR, DCR, and PFS, the primary analysis population will be the ITT set, with PPS analysis conducted as confirmatory during final evaluation. Safety analyses will be performed using the Safety Set (SS).

Quantitative variables at each visit will be summarized as mean ± standard deviation or median (minimum, maximum). Comparisons with baseline screening values will use paired t-tests for within-group changes. Between-group differences before and after treatment will be evaluated using Analysis of Variance (ANOVA) or rank-sum tests.

Phase Ib planned enrollment: 3 patients per group for safety assessment. Phase II planned enrollment: 20 patients initially, with a total enrollment of 29 patients. Safety and efficacy of the treatment regimen were preliminarily assessed to provide supporting data for subsequent investigations.

Study Discussion:

Most biliary tract cancers (BTC) are diagnosed at a middle-to-late stage or with distant metastases. The 5-year survival rate is lower than 5%, and the overall prognosis is poor[13,14] . For advanced biliary tract malignancies, systemic therapies such as

chemotherapy, immunotherapy, and targeted therapy constitute the primary treatment strategies. In 2022, the ASCO GI meeting officially reported interim results from the Phase III clinical trial in the BTC field (TOPAZ-1)[7]. This study enrolled 685 patients with unresectable advanced or metastatic BTC. The median overall survival (OS) was 12.8 months in the Durvalumab plus GC group versus 11.5 months in the GC group （HR=0.80；95% CI，0.66-0.97；P=0.021）. The median progression-free survival (PFS) was 7.2 months in the Durvalumab plus GC group versus 5.7 months in the GC group(HR=0.75；95%CI，0.64-0.89；P =0.001).In 2023, it was announced at the AACR conference that the KEYNOTE-966[15]trial achieved its primary endpoint. This randomized, placebo-controlled, global multicenter Phase III study enrolled 1,069 patients with unresectable, previously untreated locally advanced or metastatic BTC. Compared with GC plus placebo, GC plus Pembrolizumab yielded a median OS of 12.7 months versus 10.9 months （HR=0.83；95% CI，0.72-0.95；P=0.0034）; however, median PFS did not reach the pre-specified threshold for statistical significance, at 6.5 months versus 5.6 months（HR=0.86；95% CI，0.75-1；P=0.0225）. In the final analysis, the overall response rate (ORR) for both groups was 29%. BTC exhibits an immunosuppressive tumor microenvironment; combining anti–vascular endothelial growth factor agents with chemotherapy may enhance anti-tumor immunity and improve responsiveness to immune checkpoint inhibitors. In 2024, the IMbrave151[16]Phase II randomized, double-blind clinical trial presented updated results at the ASCO GI conference. This trial enrolled 162 patients with first-line advanced BTC. Results showed that Atezolizumab + Bevacizumab + chemotherapy versus Atezolizumab + placebo + chemotherapy achieved a median OS of 14.9 months versus 14.6 months （HR=0.97；95% CI，0.64-1.47） and a median PFS of 8.35 months versus 7.9 months（HR=0.67；95% CI，0.46-0.95）. The response rates for both groups were 26.6%、26.5%, and the incidence of grade 3/4 adverse events was 73%. The findings indicate that the addition of Bevacizumab to first-line immunotherapy plus chemotherapy yields a modest improvement in PFS without OS benefit. Although the aforementioned regimens may be considered first-line options for unresectable BTC, it is notable that combining immunotherapy and targeted therapy has increased median OS by only approximately 2 months, with median OS still around 1 year. Moreover, the incidence of adverse events has risen substantially, reducing treatment tolerability. These outcomes remain far from satisfactory, underscoring the need to investigate novel and more effective therapeutic approaches.

HAIC is a therapeutic approach in which drugs are delivered directly into the tumor-feeding artery via hepatic artery catheterization. Its primary advantage lies in the capacity to administer high doses of chemotherapeutic agents directly to the hepatic

artery branches supplying the tumor through repeated infusions. The procedure is relatively straightforward and can increase local drug concentrations while minimizing systemic adverse effects, offering the potential to “downstage” patients with unresectable advanced intrahepatic cholangiocarcinoma from an “incurable disease.” The Double-IA-001 [11]study has confirmed the efficacy and safety of the triple regimen comprising “Hepatic Arterial Infusion Chemotherapy (HAIC) + Arterial Infusion of Immunotherapy + Oral Targeted Agents” in patients with BCLC stage C HCC. A prospective Phase II clinical trial (T-double, NCT04796025) conducted by Professor Gao Fei’s team[12] at the Sun Yat-sen University Cancer Center was published in the internationally renowned oncology journa《I Cancer Letters 》(Q1, IF=9.1). The findings further demonstrated that transarterial chemoembolization combined with arterial infusion of targeted and immune agents can enhance therapeutic efficacy and reduce toxicity: in patients with Barcelona Clinic Liver Cancer (BCLC) stage C HCC, Transarterial Chemoembolization (TACE) combined with arterial infusion of Sintilimab and Bevacizumab achieved an ORR of [missing value], a Complete Response (CR) rate of [missing value], a median Progression-Free Survival (PFS) of 6.0 months, and a median Overall Survival (OS) of 12.2 months, with safety deemed controllable.

Envafolimab is a subcutaneously administered PD-L1 monoclonal antibody independently developed in China, approved for marketing in November 2021. Its Phase II clinical trial (CN006)[17] was led and conducted by the Department of Gastrointestinal Oncology at Peking University Cancer Hospital. This study suggests that Envafolimab possesses good tolerability and safety. Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor. In the biliary tract cancer cohort of the LEAP-005 study[18], 31 patients with metastatic BTC received Lenvatinib plus Pembrolizumab. Among these, 3 patients achieved PR, and 18 patients were assessed as stable disease (SD), with a disease control rate (DCR) reaching 68%; the median duration of response (DOR) was 5.3 months; the median PFS was 6.1 months; and the median overall survival (OS) was 8.6 months. A single-arm, single-center clinical trial of Toripalimab plus Lenvatinib and GEMOX chemotherapy[19] for advanced intrahepatic cholangiocarcinoma demonstrated that, among 30 enrolled patients, the objective response rate (ORR) reached 80%, the DCR reached 93.3%, and the 6-month OS rate was 90%, with good tolerability. The findings from these small-sample studies preliminarily support the efficacy and safety of Lenvatinib combined with immunotherapy in advanced biliary tract cancer.

Based on these clinical research data, we designed a multicenter, Phase Ib/II, single-arm clinical study to evaluate the safety and efficacy of hepatic arterial infusion chemotherapy (GP regimen) with intraoperative arterial infusion of Envafolimab

combined with Lenvatinib for first-line treatment of unresectable advanced biliary tract cancer. The objective is to explore a novel first-line treatment model for patients with unresectable BTC, achieve high response rates and improved survival outcomes, and further enhance prognosis in advanced cases. BTC is characterized by strong local invasiveness and the limited effectiveness of systemic chemotherapy, immunotherapy, and targeted therapy. Hepatic arterial infusion of the GP regimen delivers high local drug concentrations precisely to tumor sites, thereby reducing treatment-related adverse effects. Intraoperative arterial infusion of Envafolimab addresses the limited efficacy of systemic immune drug administration in BTC and reduces toxicities associated with systemic delivery. Coupled with the convenience of oral Lenvatinib, this strategy augments therapeutic efficacy while supporting patient adherence, making it more suitable for clinical adoption. Chemotherapy eradicates tumor cells and releases tumor antigens; Lenvatinib remodels the tumor microenvironment and improves vascular perfusion; and Envafolimab activates anti-tumor immune responses. This combination achieves a synergistic effect integrating chemotherapy, anti-angiogenesis, and immunotherapy, offering a targeted combination strategy for unresectable advanced biliary tract cancer.

This study adopts a Phase Ib/II design, enabling exploration of the maximum tolerated dose, dose-limiting toxicity, and the recommended Phase II dose during the Phase Ib stage to ensure safety in subsequent efficacy evaluation. This design also enhances trial efficiency and reduces patient screening time through a seamless transition, addressing the urgent clinical need of biliary tract cancer patients for effective treatment strategies. Furthermore, the multicenter enrollment approach expands the sample pool and minimizes the heterogeneity inherent in single-center populations, thereby increasing the representativeness and generalizability of the study results. As a multicenter clinical investigation, the study adheres strictly to standardized experimental procedures and data management protocols, with efficacy and safety evaluations conducted by specialized teams, ensuring scientific rigor and reliability of the findings. On the other hand, this study employs a single-arm, non-controlled design; thus, results may be influenced by selection bias, observational bias, and similar factors, making it difficult to determine the therapeutic contribution of each individual drug within the regimen. Second, the relatively small sample size limits accurate evaluation of the efficacy differences of the combination regimen across biliary tract cancer at different anatomical sites. Third, patients with biliary tract cancer often present with comorbidities such as impaired liver function and biliary obstruction; although inclusion criteria accounted for baseline patient status, it is not possible to completely eliminate the impact of baseline liver function variations and interventions for comorbidities on treatment efficacy and safety assessments. Despite these limitations related to study

design, sample size, and potential enrollment bias, the findings nonetheless provide valuable reference for clinical strategies addressing the treatment challenges of unresectable advanced biliary tract cancer.

In summary, this multicenter Phase Ib/II single-arm study of hepatic arterial infusion chemotherapy (GP regimen) combined with intra-arterial infusion of Envafolimab and Lenvatinib for first-line treatment of unresectable advanced biliary tract cancer investigates an innovative local-plus-systemic regimen integrating chemotherapy, antiangiogenic therapy, and immunotherapy. The preliminary efficacy and safety signals identified offer a crucial clinical foundation for further optimization and validation of this approach, and yield important insights into combination therapies involving precise local drug delivery for biliary tract cancer. Future directions, based on these results, include conducting large-sample, randomized controlled Phase III trials and incorporating biomarker testing for patient stratification, along with detailed exploration of the pharmacokinetics and synergistic mechanisms of local drug delivery. Such efforts aim to promote the precision, standardization, and clinical translation of this regimen, ultimately providing safer and more effective treatment options for patients with unresectable advanced biliary tract cancer, thereby improving overall prognosis for BTC patients.

Abbreviations

AE Adverse Event

CI Confidence Interval

CR complete response

DoR Duration of response

DCR Disease control rate

EPSCC Extrapulmonary Small Cell Carcinoma

ECOG PS Eastern Cooperative Oncology Group – performance status

HIV Human immunodeficiency virus

HR Hazard Ratio

NCI CTCAE National Cancer Institute Common Terminology Criteria for

Adverse Events

ORR Objective Response Rate

OS Overall survival

PD-L1/PD-1 Programmed death-1/ligand 1

PFS Progression-free survivalDamato et al. BMC Cancer (2025) 25:1763

PR partial response

QoL quality of life

RECIST Response Evaluation Criteria in Solid Tumors

SD stable disease

Acknowledgments:

Not applicable

Author Contributions:

Liu chang and Dai Ruihong designed the study and wrote the original protocol. Rui-Hong Dai and Fa-Cheng Lu drafted the manuscript. All the other authors directly contributed, read, and approved the final manuscript.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This study was found by the Chengdu Medical Research Project in 2026

Data Availability

Not applicable

Ethics statement

The ethics committee on Biomedical Research of West China Hospital of Sichuan University approved this study All participants will sign written informed consent prior to participation in any study activities.

Consent for Publication

Not applicable

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Benavides M AA, Gallego J, et al. Biliary tract cancers: SEOM clinical guidelines. [J].Clinical & Translational Oncology, 2015, 17(12):982-7. DOI:10.1007/s12094-015-1436-2.
2. Hundal Rajveer SEA. Gallbladder cancer: epidemiology and outcome. [J]Clinical epidemiology, 2014, 6:99-109 doi:DOI:10.2147/CLEP.S37357.
3. Bray Freddie FJ, Soerjomataram Isabelle, et al. . Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. [J]CA: a cancer journal for clinicians, 2018, 68(6):394-424, doi:DOI:10.3322/caac.21492.
4. Han Bingfeng ZR, Zeng Hongmei, et al. Cancer incidence and mortality in China, 2022. [J].Journal of the National Cancer Center, 2024, 4(1):47-53. DOI:10.1016/j.jncc.2024.01.006.
5. Shahid A Khan HCT, Brian R Davidson, et al. Cholangiocarcinoma. Lancet. 2005 Oct 8;366(9493):1303-14.
6. Eberlein TJ. Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer. Yearbook of Surgery 2011;2011(310–312, doi:10.1016/s0090-3671(10)79889-x
7. Oh DY, He AR, Bouattour M, et al. Durvalumab or placebo plus gemcitabine and cisplatin in participants with advanced biliary tract cancer (TOPAZ-1): updated overall survival from a randomised phase 3 study. Lancet Gastroenterol Hepatol 2024;9(8):694–704, doi:10.1016/S2468-1253(24)00095-5
8. Huang XY, Shi GM, Zheng ZT, et al. Anti-PD1 antibody toripalimab combined with lenvatinib, or GEMOX chemotherapy combined with lenvatinib as first-line therapy in patients with advanced intrahepatic cholangiocarcinoma: a randomized, open, two-cohort Phase 2 Study. BMC Med 2025;23(1):573, doi:10.1186/s12916-025-04404-4
9. Cercek A, Boerner T, Tan BR, et al. Assessment of Hepatic Arterial Infusion of Floxuridine in Combination With Systemic Gemcitabine and Oxaliplatin in Patients With Unresectable Intrahepatic Cholangiocarcinoma: A Phase 2 Clinical Trial. JAMA Oncol 2020;6(1):60–67, doi:10.1001/jamaoncol.2019.3718
10. Cai Z, He C, Zhao C, et al. Survival Comparisons of Hepatic Arterial Infusion Chemotherapy With mFOLFOX and Transarterial Chemoembolization in Patients With Unresectable Intrahepatic Cholangiocarcinoma. Front Oncol 2021;11(611118, doi:10.3389/fonc.2021.611118
11. Shen L, Cao F, Liu Y, et al. Hepatic artery infusion of FOLFOX chemotherapy plus

camrelizumab combined with sorafenib for advanced hepatocellular carcinoma in Barcelona Clinic Liver Cancer stage C (Double-IA-001): a phase II trial. BMC Med 2025;23(1):275, doi:10.1186/s12916-025-04110-1
12. Mu MY, Chen ZX, Cao YZ, et al. Transarterial chemoembolization combined with intra-arterial infusion of sintilimab and bevacizumab for advanced hepatocellular carcinoma: a phase 2 study. Cancer Lett 2025;628(217851, doi:10.1016/j.canlet.2025.217851
13. Chai Y. Immunotherapy of biliary tract cancer. Tumour Biol 2016;37(3):2817–21, doi:10.1007/s13277-015-4743-x
14. Valle JW, Lamarca A, Goyal L, et al. New Horizons for Precision Medicine in Biliary Tract Cancers. Cancer Discov 2017;7(9):943–962, doi:10.1158/2159-8290.CD-17-0245
15. Kelley RK, Ueno M, Yoo C, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023;401(10391):1853–1865, doi:10.1016/S0140-6736(23)00727-4
16. Macarulla T, Ren Z, Chon HJ, et al. Atezolizumab Plus Chemotherapy With or Without Bevacizumab in Advanced Biliary Tract Cancer: Clinical and Biomarker Data From the Randomized Phase II IMbrave151 Trial. J Clin Oncol 2025;43(5):545–557, doi:10.1200/JCO.24.00337
17. Li J, Deng Y, Zhang W, et al. Subcutaneous envafolimab monotherapy in patients with advanced defective mismatch repair/microsatellite instability high solid tumors. J Hematol Oncol 2021;14(1):95, doi:10.1186/s13045-021-01095-1
18. Victoria Ruiz Iván UNV, Jamal Rahima, et al. . Lenvatinib Plus Pembrolizumab for Patients With Previously Treated Advanced Colorectal Cancer: Results From the Phase II LEAP-005 Study. Clinical colorectal cancer 2026, doi:10.1016/j.clcc.2026.01.003.
19. Jian Zhou FJ, Shi Guo-Ming, et al. . Gemox chemotherapy in combination with anti-PD1 antibody toripalimab and lenvatinib as first-line treatment for advanced intrahepatic cholangiocarcinoma: A phase 2 clinical trial. JOURNAL OF CLINICAL ONCOLOGY, 2021, 39(15_suppl):4094-4094 doi:10.1200/JCO.2021.39.15