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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

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Abstract

Background This research aimed to assess the efficacy and safety of a regimen combining lenvatinib with an anti-PD-1 antibody or chemotherapy in patients with advanced intrahepatic cholangiocarcinoma (ICC).

Methods A two-arm, open-label, phase II trial was carried out. Participants in Arm A received 240 mg of toripalimab intravenously on day 1 of each 3-week cycle, plus daily oral lenvatinib at 8 mg (< 60 kg) or 12 mg (≥60 kg). Participants in Arm B were administered the same daily lenvatinib in combination with GEMOX chemotherapy: 85 mg/m^2 oxaliplatin on day 1, and 1 g/m^2 gemcitabine on days 1 and 8 every 3 weeks for 6-8 cycles. The primary endpoint was the objective response rate (ORR) per RECIST 1.1, with secondary endpoints included treatment-related adverse events (AEs), overall survival (OS), and progression-free survival (PFS).

Results Sixty one patients were recruited, with 31 in Arm A and 30 in Arm B. The ORR of Arm A was 32.3% (10/31; 95% CI: 16.7%–51.4%), and three patients underwent surgery after tumor downstaging. The median OS was 20.3 months (95% CI: 9.3–27.1), and median PFS was 8.9 months (95% CI: 4.2–13.9). Arm B showed an ORR of 40.0% (12/30; 95% CI: 22.7%–59.4%), and one patient proceeded to surgery after downstaging. Median OS was 15.5 months (95% CI: 9.6–23.8), and median PFS was 8.0 months (95% CI: 5.0–11.4). Adverse events (AEs) related to treatment were observed in most patients, with grade 3–4 AEs in 35.5% of Arm A and 40.0% of Arm B. The most frequent AEs were fatigue (71% vs. 63%), paresthesia (45% vs. 40%), and gingivitis (45% vs. 20%). Grade 4 thrombocytopenia occurred

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in 6.7% of Arm B. No grade 5 AEs were observed. Peripheral blood analysis showed monocyte levels decreased in PR(partial response) patients in Arm A but increased in PR patients in Arm B.

Conclusions The Combination of lenvatinib with either anti-PD-1 antibody or GEMOX chemotherapy is a well-tolerated and effective treatment for advanced ICC.

Trail registration ClinicalTrials.gov, NCT04361331

Keywords Intrahepatic cholangiocarcinoma, Lenvatinib, Anti-PD-1 antibody, GEMOX chemotherapy

Background

Intrahepatic cholangiocarcinoma (ICC), which develops from the bile ducts, represents the second most prevalent form of liver cancer [1]. It has been increasing steadily on a global scale, especially in Southeast Asia, where it overtakes that in western countries [2]. The primary challenge in managing ICC lies in the absence of methods for early detection, since distinct symptoms or diagnostic indicators are not present during the initial stages [2, 3]. This often leads to diagnoses at advanced stages where the cancer has already spread, leaving most patients ineligible for surgical removal and facing a survival time of just 4–6 months [4]. Even with surgery, fewer than 40% of patients with stage II or more advanced tumors survive beyond five years, with a high recurrence rate [5]. Advanced cases are typically treated with systemic chemotherapy plus immunotherapy [3]. The lasted updated data from the TOPAZ-1 trial indicated that the estimated 2-year overall survival rate was 23.6% (95% CI 18.7–28.9) for durvalumab combined with gemcitabine plus cisplatin and 11.5% (95% CI 7.6–16.2) for placebo plus gemcitabine-cisplatin [6]. KEYNOTE-966 trial demonstrated that median OS was 12.7 months (95% CI 11.5–13.6) in the pembrolizumab group in combination with gemcitabine and cisplatin compared to 10.9 months (9.9–11.6) in the placebo plus gemcitabine and cisplatin group ($p=0.0200$), with this survival benefit continue in the following 3 year [7, 8].

In a phase 2 trial of advanced biliary tract malignancies, lenvatinib, administered as a second-line therapy, demonstrated a 12% ORR, thereby supporting its efficacy in the treatment of advanced intrahepatic cholangiocarcinoma [9]. PD-1 and PD-L1 antibody have shown encouraging results in treating various cancers. PD-1 antibody treatment demonstrated an overall response rate of 22% and a median OS exceeding 14 months in patients with advanced biliary cancer [10]. The combination of lenvatinib and pembrolizumab as a second-line treatment in the LEAP-005 study further supports their efficacy against biliary tract cancers [11]. These findings suggest that combining lenvatinib with PD-1 antibody may be an effective strategy for ICC, but more clinical research is needed to confirm this approach.

In the field of oncology, gemcitabine and platinum compounds, including oxaliplatin, are commonly used in treating various cancers [12]. The combination of gemcitabine and cisplatin has been regarded a first-line chemotherapy regimen for ICC for the past ten years [1]. However, in recent years, the GEMOX regimen has been used as the experimental control arm in several clinical trials of advanced biliary tract cancer and has shown good anti-tumor activity [13–15]. Findings from the GERCOR study highlight the effectiveness of the GEMOX protocol, which combines gemcitabine with oxaliplatin, with an ORR 36%, stable disease 26%, progressive disease 39%, and median PFS of 5.7 months [16].

Chemotherapy, including the GEMOX regimen, is a cornerstone in the treatment of ICC, with new investigations exploring the potential of targeted and immune therapies [17]. A phase 2 trial conducted at our center combined toripalimab(an anti-PD1 antibody), lenvatinib, and GEMOX for a first-line treatment for advanced ICC, demonstrating encouraging outcomes with an 80% ORR, a median OS of 22.5 months, and a median PFS of 10.2 months, without any grade 5 adverse reactions [18]. This study aims to investigate the combination of lenvatinib with anti-PD-1 antibodies, as well as lenvatinib combination with GEMOX as an initial treatment for advanced stages of ICC. To date, no studies have reported on the use of lenvatinib in combination with anti-PD-1 antibodies or GEMOX in the first-line therapy of advanced ICC. By addressing this gap in the current literature, our study seeks to investigate whether reducing one of the agents could still maintain comparable effectiveness, thereby providing new perspectives for optimizing cancer treatment regimens.

Methods

Study design and participants

Comparison of the two cohorts with standard of care historical data. The previous study showed an ORR of 14% for routine receipt of the GEMOX regimen, with a prespecified objective remission rate of 40% for the combination therapy, alpha = 0.05, power = 0.9, and 25 patients to be enrolled in each cohort; if the calculation is based

on 20% of the shedding cases, 30 patients in each cohort would need to be enrolled for a total of 60 patients. A single cohort study can be discontinued if 10 patients are enrolled with an ORR of less than 20% (2 patients) as assessed by efficacy.

This phase 2 clinical trial, conducted at Zhongshan Hospital of Fudan University was a single-center, randomized, open-label study with two separate groups. The study aimed to evaluate the efficacy and safety of two treatment regimens for patients with advanced or unresectable intrahepatic cholangiocarcinoma. One regimen consisted of the anti-PD1 antibody toripalimab with lenvatinib (Arm A), and the other combined GEMOX, which is a mix of gemcitabine and oxaliplatin, with lenvatinib (Arm B). The study, which enrolled participants from March 6 to October 26, 2020, included 61 participants, with 31 patients in the toripalimab-lenvatinib combination and 30 patients in GEMOX-lenvatinib. The data cutoff for the analysis is September 1, 2023.

The trial included individuals aged 18 and 75 years, who had been histopathologically diagnosed with intrahepatic cholangiocarcinoma with at least one lesion measurable according to RECIST 1.1 standards. Patients with unresectable intrahepatic cholangiocarcinoma (ICC) or those diagnosed with ICC recurrence and metastasis after surgery, who have not received systemic treatment within 6 months. Patients were required to have an ECOG performance status of 0 or 1 and fall within the Child–Pugh classification A. Additionally, they needed to meet certain laboratory criteria, including sufficient levels of neutrophils ($\geq 1.5*10^9$/L), platelets ($\geq 100*10^9$/L), hemoglobin (≥ 9 g/dl), and serum albumin (≥ 3 g/dl), thyroid—stimulating hormone (TSH) $\leq 1\times$ the upper limit of normal (ULN) with triiodothyronine (T3) and thyroxine (T4) within the normal range; total bilirubin $\leq 1.5\times$ULN, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 3\times$ULN; serum creatinine $\leq 1.5\times$ULN and creatinine clearance ≥ 60 ml/min (calculated using the Cockcroft—Gault formula).

Patients with hepatocellular carcinoma, mixed hepatocellular-cholangiocarcinoma, or non-cholangiocarcinoma-containing malignancies are excluded from participation. Additionally, patients with a history of other malignancies, except for adequately treated non-melanoma skin cancer, cervical carcinoma in situ, or papillary thyroid carcinoma are excluded. Patients with severe cardiopulmonary or renal dysfunction, uncontrolled hypertension (BP $\geq$ 140/90 mmHg), or PT > 14 s and bleeding tendency or on anticoagulation/thrombolysis are excluded. Patients with HBV DNA > 2000 copies/mL or HCV RNA > 1000 IU/mL despite treatment, esophagogastric varices history, significant bleeding within 3 months or bleeding tendency, active infection needing systemic treatment, active pulmonary tuberculosis within 1 year (or inactive but untreated/active after 1 year), positive HIV1 and HIV2 antibodies, or a history of substance abuse, drug hypersensitivity to study drugs, or any condition affecting safety/compliance as judged by the investigator are also excluded.

The study followed the principles of Good Clinical Practice Guidelines and the Declaration of Helsinki, with approval from the institutional review boards of Zhongshan Hospital (B2020-038). Written informed consent was obtained from all participants prior to their involvement. This trial is registered at Clinicaltrials.gov. ID: NCT04361331.

Randomization and masking

Patients who fulfilled all eligibility criteria and had provided written informed consent were randomly assigned in a 1:1 proportion to either Arm A (toripalimab in combination with lenvatinib) or Arm B (lenvatinib paired with GEMOX). The random allocation sequence was created using a computer-generarted random number table prepared by an independent statistician who was not involved in patient recruitment or treatment. Allocation was caried out through sequentially numbered, sealed, opaque envelopes to ensure allocation concealment until the time of assignment. As an open-label trial, no blinding masking was performed. The treatment allocation was known to all investigators, participants, and the study sponsor.

Procedures

Arm A patients were given an intravenous toripalimab at 240 mg every three weeks, paired with orally lenvatinib that varied based on weight: 8 mg daily for those under 60 kg and 12 mg for those 60 kg or above. Arm B used a similar lenvatinib dosing schedule, combined with GEMOX chemotherapy administered intravenously every three weeks, consisting of 85 mg/m^2 of oxaliplatin on day 1 and 1 g/m^2 of gemcitabine on days 1 and 8, across 6 to 8 cycles.

Treatment was discontinued if patients experienced intolerable side effects, or disease progression, as assessed by the study's investigators, if they sought cancer treatment outside the study's protocol, or if they decided to withdraw consent. To assess disease progression, enhanced MRI or CT scans were performed every

9 ± 2 weeks, in accordance with RECIST 1.1 guidelines. Chemotherapy could last up to 6 cycles for responsive cases and all the patients received no more than 8 cycles of chemotherapy, while toripalimab and lenvatinib might continue for a maximum of a year. After one year, if the disease has not progressed, patients can choose to continue with the current treatment. The research team planned to follow up with the participants for two years following the protocol.

Outcomes and assessments

The primary outcome measure for the two groups was the ORR, defined as the proportion of patients experiencing either complete or partial reduction in tumor. Secondary endpoints included monitoring any adverse effects from the treatment, overall survival time from date of first dose of drug to death from any cause (or until the last check-in if no death occurred), and progression-free survival time from date of first dose of drug to either the first sign of the disease worsening or death from any cause, whichever happened first. Each of these outcomes adhered to the standards set by RECIST 1.1. Safety evaluations included tracking all adverse effects, using the terminology and grading of the CTCAE Version 5.0, and recording any serious adverse events.

Peripheral blood collection and laboratory tests

All patients received standardized peripheral blood sample collection prior to treatment and after each treatment cycle. The baseline samples before treatment were

Table 1 Patient baseline characteristics for each cohort

Characteristics	Arm A ($n=31$)	Arm B ($n=30$)
Age, years		
mean (range)	58.4 (25–73)	59.2 (33–74)
Sex		
Male	13 (41.9)	16 (53.3)
Female	18 (58.1)	14 (46.7)
TNM stage at baseline		
II	3(9.7)	1 (3.3)
IIIA	0 (0)	1(3.3)
IIIB	3 (9.7)	5 (16.7)
IV	25 (80.6)	23 (76.7)
History of hepatolithiasis		
Yes	3 (9.7)	3 (10)
No	28 (90.3)	27 (90)
HBsAg/HbcAb		
Positive	24 (77.4)	23 (76.7)
Negative	7 (22.6)	7 (23.3)
Prior systemic therapy		
Yes	0 (0)	0 (0)
No	31 (100)	30 (100)
CA19-9 (U/mL)		
≥ 37	15 (48.4)	17 (56.7)
< 37	16 (51.6)	13 (43.3)

Appreciation: *HBsAg* hepatitis B surface antigen, *HBcAb* Hepatitis B core antibody, *CA19-9* Carbohydrate antigen 19–9

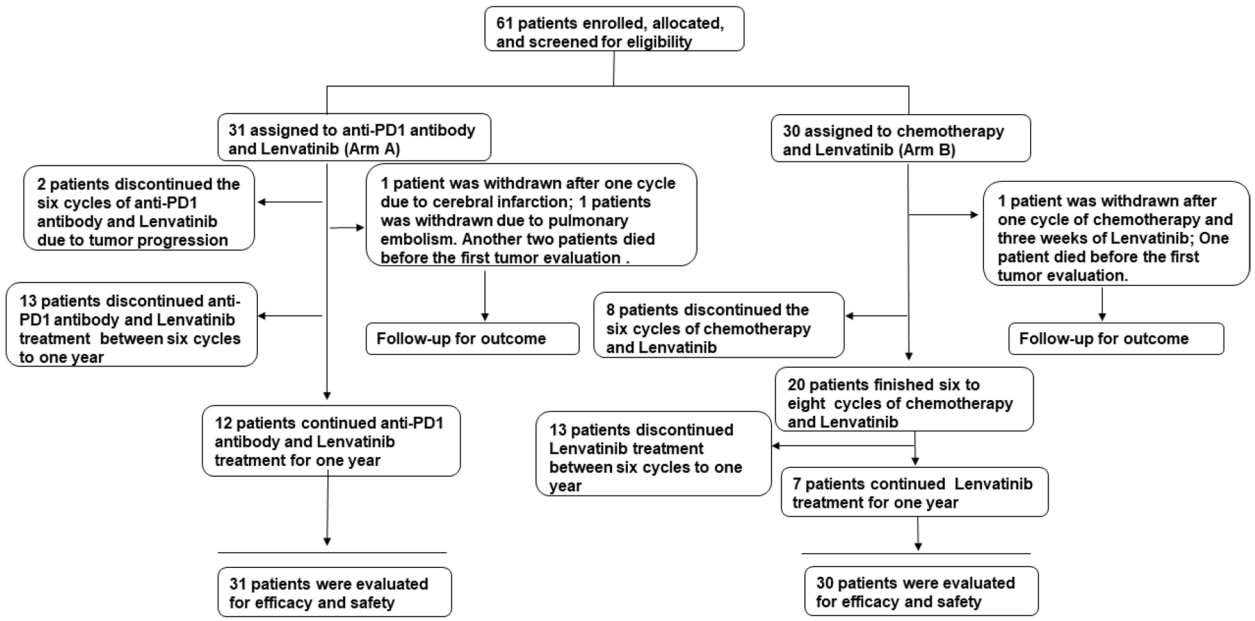


Fig. 1 Flowchart for patient selection

used to document the patients' initial conditions, while the post -treatment samples were analyzed to assess the treatment efficacy, including neutrophil percentage, lymphocyte percentage, monocyte percentage, eosinophil percentage, basophil percentage, neutrophil count, lymphocyte count, and so on. The detection of cytokines,

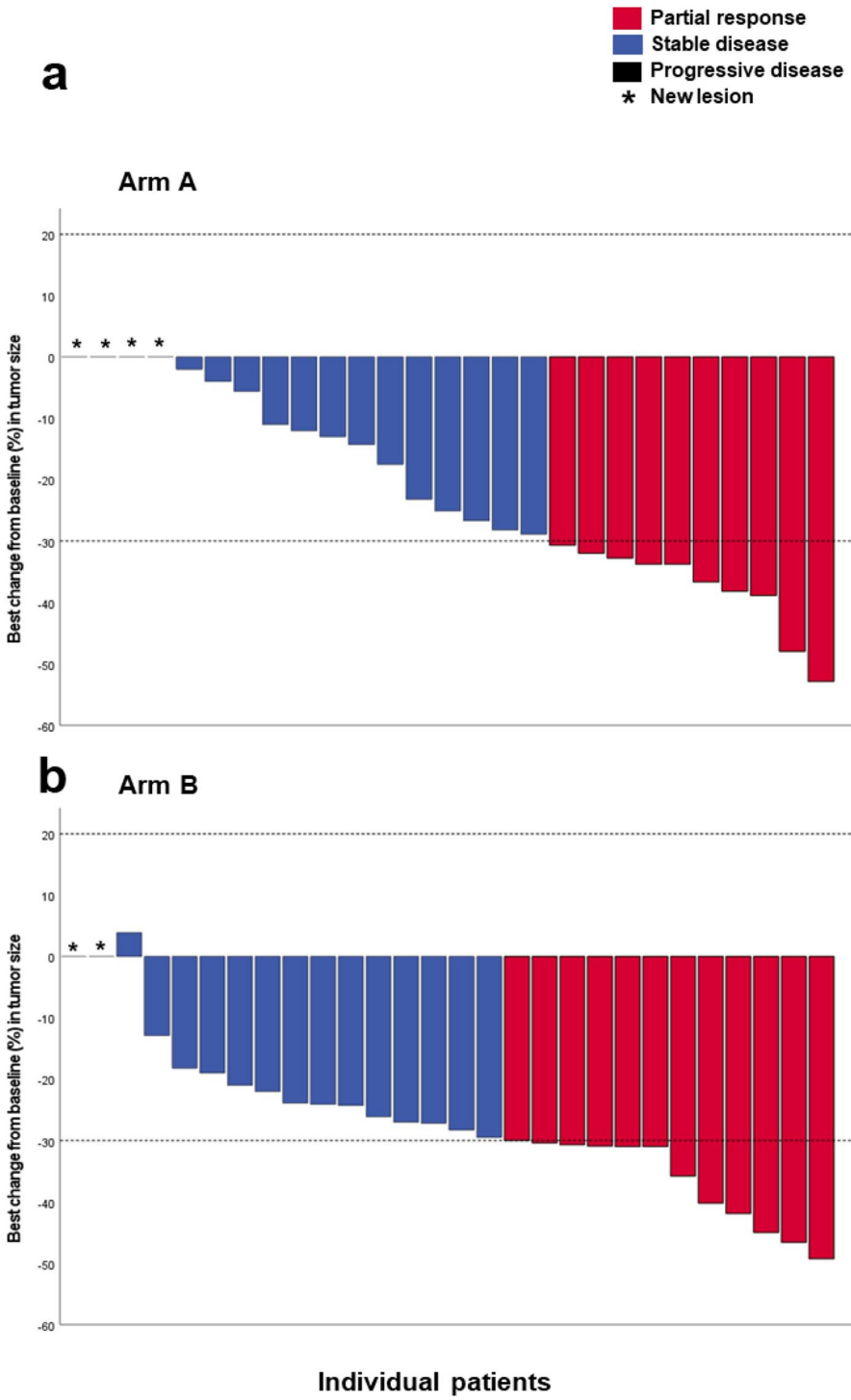


Fig. 2 Tumor response to combined therapy of toripalimab combined with lenvatinib, or lenvatinib combined with GEMOX (**a**) Arm A: toripalimab combined with lenvatinib (4 patients were not evaluated); (**b**) Arm B: lenvatinib combined with GEMOX (2 patients were not evaluated for tumor response)

including tumor necrosis factor (TNF), interleukin-1β (IL-1β), interleukin-2 receptor (IL-2R), interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-10 (IL-10), was also examined.

Statistical analysis

The proportion of patients with the best overall response (ORR) (defined as CR and PR) assessed by the investigators per RECIST1.1. The ORRs and 95% confidence intervals (CIs) were derived using the Clopper-Pearson method. Median overall survival, progression-free survival, and duration of response were determined using the Kaplan–Meier method, and their 95% CIs were calculated with the Brookmeyer-Crowley method.

The baseline peripheral blood levels of immune cells and cytokines in patients in Arm A and Arm B were analyzed between responders and non-responders using univariate logistic regression analysis. The association between baseline peripheral blood markers and tumor treatment response were analysed by odds ratios (OR) with 95% CI. Unpaired t-tests were performed to assess the significant differences in the levels of these markers between the groups. Paired t-tests were used to analyze the changes in peripheral blood markers from baseline to post-treatment among responders. Statistical significance was determined as a P-value < 0.05. All statistical analyses were conducted using SPSS version 27.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 10 (GraphPad Software, San Diego, CA, USA).

Results

Baseline characteristics (Lenvatnib and Toripalimab (Arm A); Lenvatnib and GEMOX (Arm B))

The investigation comprised two Arms: Arm A with 31 participants and the Arm B with 30 participants. Participant ages spanned from 25 to 74, averaging 58.4 years in the Arm A and 59.2 years in the Arm B. The Arm A was 41.9% male (13/31) compared to 53.3% in the Arm B (16/30). 9.7% (3 participants) in Arm A and 3.3% (1 participant) in Arm B were in TNM Stage II were enrolled in this clinical trial because they had multiple lesions that precluded surgery. A majority of patients, 77.4% of Arm A (24/31) and 76.7% of Arm B (23/30), were found to carry hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Increased levels of carbohydrate antigen 19–9 levels (CA19-9, ≥ 37 U/mL) were observed in 48.4% of the Arm A (15/31) and 56.7% of the Arm B (17/30). (Table 1).

Delivery and efficacy in Arm A and Arm B

At the time of the data cutoff, the median duration of follow-up for all patients was 18.2 months (range, 0.5–41.0 months). Regarding Arm A (Lenvatnib and Toripalimab), as of the final follow-up on September 1, 2023, 25.8% (8 patients) were still alive. 12 patients completed one-year therapy. The lenvatinib dosage was modified in 8 patients owing to AEs,with the relative dose intensity (RDI) was 50%, including 2 patients due to rash, 1 patient due to hypertension, 3 patients due to fatigue and 2 patients due to alanine/aspartate aminotransferase increased or blood bilirubin increased. Treatments of toripalimab were delayed in 3 patients due to AEs, including rash, hyperthyroidism, or alanine/aspartate aminotransferase increased. None patients discontinued the treatment of lenvatinib and PD-1 therapy due to AEs (Fig. 1).

The ORR in Arm A was 32.3% (10/31; 95% CI: 16.7%−51.4%), consisting of 10 partial responses (PR); the disease control rate (DCR) was 74.2% (23/31; 95% CI: 55.4%−88.1%)(Fig. 2a). Each patient's best response is detailed in Additional file 1: Table 1. Three patients underwent surgical resection after down-staging. The median OS was 20.3 months (95% CI: 9.3–27.1 months), with survival rates of 58.1% (95% CI: 39.0–73.1) at one year and 38.7% (95% CI: 22.0–55.1) at two years, respectively. The median progression-free survival (PFS) stood at 8.9 months (95% CI, 4.2–13.9 months), with a one-year

Table 2 Summary of treatment efficacy by arm

Responses	Arm A (*n* = 31)	Arm B (*n* = 30)
CR, *n* (%)	0 (0)	0 (0)
PR, *n* (%)	10 (32.3)	12 (40.0)
SD, *n* (%)	13 (41.9)	14 (46.7)
PD, *n* (%)	4 (12.9)	2 (6.7)
NE, *n* (%)	4 (12.9)	2 (6.7)
ORR, *n* (%)	10 (32.3) (95% CI, 16.7–51.4)	12 (40.0) (95% CI, 22.7–59.4)
DCR, *n* (%)	23 (74.2) (95% CI, 55.4–88.1)	26 (86.7) (95% CI, 69.3–96.2)
Median DoR	11.6 months (95% CI, 6.8–16.0 months)	10.5 months (95% CI, 4.8–12.6 months)
Median TTR	2.2 months (95% CI, 1.9–4.2 months)	2.4 months (95% CI, 2.1–4.8 months)
Median PFS	8.9 months (95% CI, 4.2–13.9 months)	8.0 months (95% CI, 5.0–11.4 months)
Median OS	20.3 months (95% CI, 9.3 months-27.1 months)	15.5 months (95% CI, 9.6 months-23.8 months)
1-year OS (%)	58.1 (95% CI, 39.0–73.1)	62.3 (95% CI, 42.3–77.1)
1-year PFS (%)	44.7 (95% CI, 26.8–61.1)	28.0 (95% CI, 12.9–45.4)
2-year OS (%)	38.7 (95% CI, 22.0–55.1)	33.4 (95% CI, 17.0–50.6)

Appreciation: *CR* Complete response, *PR* Partial response, *SD* Stable disease, *PD* Progression disease, *NE* Not evaluable, *ORR* Objective response rate, *DCR* Disease control rate, *DoR* Duration of response, *TTR* Time to response, *PFS* Progression-free survival, *OS* Overall survival, *CI* Confidence interval

PFS rate of 44.7% (95% CI: 26.8–61.1). The median time to response (TTR) was 2.2 months (95% CI: 1.9–4.2 months), with the median duration of response (DoR) was 11.6 months (95% CI, 6.8–16.0 months) (Table 2, Fig. 3a,c). Detailed TTR and DoR for each participant can be found in Additional file 1: Table 1.

As of the final observation date on September 1, 2023, a survival rate of 20% was noted with 6 patients still alive in Arm B (Lenvatnib and GEMOX). 20 patients completed 6 cycles of GEMOX chemotherapy (Fig. 1). The dosage of GEMOX was modified in 2 patients due to AEs, including vomiting and nausea. Treatments of GEMOX were delayed in 9 patients due to AEs, including nausea, fatigue, platelet count decreased, white blood cell decreased, and alanine/aspartate aminotransferase increaseds. Three patients discontinued GEMOX due to AEs. The dose of lenvatinib was modified in 9 patients due to adverse events (AEs) and the RDI was 50%, including nausea, hypertension, fatigue, and platelet count decreased. None discontinued the lenvatinib treatment due to AEs.

The ORR in Arm B was 40.0% (12 out of 30 patients), with CI ranging from 22.7% to 59.4% (Table 2). The rate of disease control was 86.7% for the cohort (26 out of 30 patients), with a CI between 69.3% and 96.2%, as indicated in Table 2. The median OS spanned 15.5 months, with a CI of 9.6 to 23.8 months, and the survival probabilities at one and two years were 62.3% (CI: 42.3–77.1) and 33.4% (CI: 17.0–50.6), respectively. The median PFS was 8 months (CI: 5.0–11.4 months), with a 12-month PFS of 28.0% (CI: 12.9–45.4)(Fig. 3b, d). The median duration of response (DoR) was 10.5 months (CI: 4.8–12.6 months), and the median time to response (TTR) was 2.4 months (CI: 2.1–4.8 months), both detailed per

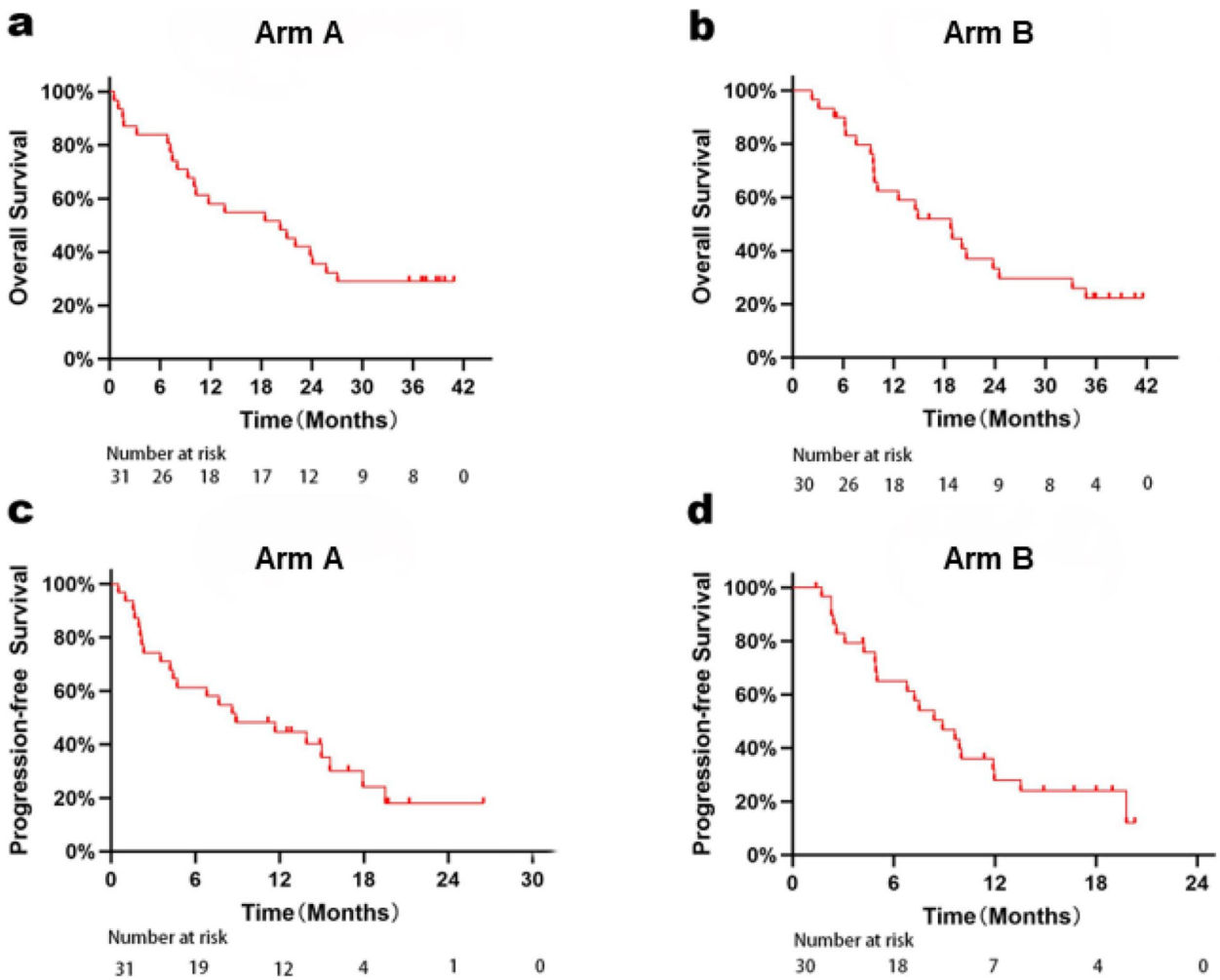


Fig. 3 Patient prognosis to combined therapy of toripalimab combined with lenvatinib, or lenvatinib combined with GEMOX (**a**, **b**) Kaplan–Meier Survival Curves for estimating the probability of overall survival of each arm; (**c**, **d**) Kaplan–Meier Survival Curves for estimating each arm's progression-free survival probability

patient in Additional file 1: Table 1. Subgroup examination, considering factors such as age, gender, TNM stage, history of hepatolithiasis, and HBsAg/HBcAb status, revealed comparable ORRs within each category, which are shown in Table 3.

Adverse events

No cases of grade 5 adverse events were observed. The most frequently reported AEs included fatigue (71% in Arm A, 63% in Arm B), paresthesia (45% in Arm A, 40% in Arm B), gingivitis (45% in Arm A, 20% in Arm B), and insomnia (35% in Arm A, 20% in Arm B) (Table 4).

The Arm A also frequently reported AEs such as rash (41.9%), voice alteration (25.8%), hypertension (29.0%), palmar-plantar erythrodysesthesia syndrome (61.3%), and abdominal pain (29.0%). Immune-related adverse events occurred in Arm A, including hypothyroidism (71.0%), hyperthyroidism (6.5%) and troponin increased (3.2%), as noted in Table 4. In contrast, Arm B frequently experienced AE such as vomiting (46.7%), nausea (50.0%), leg soreness (23.3%), and blood-related toxicities including platelet count decreased (16.7%), neutrophil count decreased (16.7%), and white blood cell decreased (16.7%). Only two individuals in the Arm B cohort suffered from grade 4 AEs related to platelet count decreased.

Table 3 ORR of patients in the subgroup according to baseline characteristics

Subgroup	Arm A ORR, % (95% CI)	Arm B ORR, % (95% CI)
ALL	32 (17–51)	40 (23–59)
Age		
< 65 years	25 (9–49)	44 (22–69)
≥ 65 years	45 (17–77)	33 (10–65)
Sex		
Male	38 (14–68)	38 (15–65)
Female	28 (10–53)	43 (18–71)
TNM stage at baseline		
II	0 (0–71)	67 (3–100)
IIIA		67 (3–100)
IIIB	67 (9–99)	40 (5–85)
IV	32 (15–54)	35 (16–57)
History of hepatolithiasis		
Yes	33 (1–91)	33 (1–91)
No	32 (16–52)	41 (22–61)
HBsAg/HBcAb		
Positive	38 (19–59)	39 (20–61)
Negative	14 (0–58)	43 (10–82)

Appreciation: *HBsAg*, hepatitis B surface antigen, *HBcAb* hepatitis B core antibody

Correlation between Peripheral Blood analyze and Treatment Efficacy in Arm A and Arm B

Peripheral blood parameters at baseline and each tumor evaluation were collected from patients in both groups (Arm A and Arm B), including the following peripheral blood markers: neutrophil percentage, lymphocyte percentage, monocyte percentage, eosinophil percentage, basophil percentage, neutrophil count, lymphocyte count, monocyte count, eosinophil count, basophil count, NLR (neutrophil-to-lymphocyte ratio), TNF, IL-1β, IL-2R, IL-6, IL-8, and IL-10. A comparison was analyzed between the baseline peripheral blood markers of responders and non-responders, along with a comparison of the baseline peripheral blood markers to those measured at the time of tumor assessment in patients achieving partial remission (PR).

The results indicated that in Arm A, significant differences were observed in the baseline proportion (OR = 1.117, 95% CI: 1.002–1.244, P = 0.045) and count of neutrophils (OR = 1.453, 95% CI: 1.015–2.080, P = 0.041) between patients who achieved PR and those who did not (Table 5).Additionally, baseline neutrophil levels were elevated in responders compared to non-responders (Fig. 4a-b), indicating that neutrophil levels could potentially function as an indicator of improved therapeutic response to lenvatinib and toripalimab therapy. Baseline characteristics between responders and non-responders in Arm B did not exhibit statistically significant differences. Detailed data are provided in the Additional file 1: Figure S1-2.

Discussion

Previous studies examining the clinical effectiveness and safety of lenvatinib in combination with anti-PD-1/PD-L1 antibodies as a first-line treatment for ICC are limited [19, 20]. In a phase 2 multicenter study, the GEMOX regimen was adopted as the primary treatment for advanced and metastatic biliary tract carcinoma, demonstrating an OS of 12 months and no grade 4 or higher AEs [21]. The BINGO trial, a phase 2 study, aimed to evaluate the effectiveness and safety of GEMOX with or without cetuximabin advanced biliary tract carcinoma [22]. The GEMOX and EGFR inhibitor resulted in a longer median PFS of 6.1 months compared to 5.5 months for GEMOX alone, with the median OS 11.0 months for the combination group and 12.4 months for the GEMOX group. The ABC-03 trial evaluated the efficacy of cisplatin and gemcitabine with or without cediranib in advanced biliary tract cancer. While no statistically significant improvement in PFS was observed, overall survival in the cediranib plus cisplatin and gemcitabine group was slightly higher (14.1 months, 95% CI 10.2–16.4)

Table 4 Summary of adverse events by Arm

	Arm A ($n=31$)			Arm B ($n=30$)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Non-hematological toxicity						
Alanine/aspartate aminotransferase increased	5	2	0	4	0	0
Electrocardiogram abnormal	2	0	0	3	0	0
Vomiting	0	0	0	14	0	0
Nausea	3	0	0	15	0	0
Fatigue	19	3	0	15	4	0
Paresthesia	14	0	0	12	0	0
Gingivitis	14	0	0	6	0	0
Hypoproteinemia	4	0	0	1	0	0
Rash	13	0	0	3	0	0
Anorexia	4	1	0	4	0	0
Fever	3	0	0	0	0	0
Voice alteration	8	0	0	1	0	0
Constipation	6	0	0	3	0	0
Epistaxis	2	0	0	2	0	0
Hypothyroidism	22*	0	0	4	0	0
Hypertension	6	3	0	3	2	0
Leg soreness	3	0	0	7	0	0
Weight loss	3	0	0	3	0	0
Headache	3	0	0	0	0	0
Palmar-plantar erythrodysesthesia syndrome	17	2	0	2	0	0
Hyperthyroidism	2*	0	0	0	0	0
Diarrhea	3	0	0	1	0	0
Cough	4	0	0	2	0	0
Tinnitus	1	0	0	1	0	0
Proteinuria	5	0	0	4	0	0
Upper gastrointestinal hemorrhage	0	0	0	3	0	0
Abdominal pain	6	3	0	4	0	0
Blood bilirubin increased	1	4	0	1	1	0
Dyspepsia	2	0	0	1	0	0
Insomnia	11	0	0	6	0	0
Hematuria	3	0	0	0	0	0
Sore throat	6	0	0	5	0	0
Alopecia	1	0	0	3	0	0
Troponin increased	1*	0	0	0	0	0
Hyperuricemia	3	0	0	0	0	0
Hematological toxicity						
Platelet count decreased	4	1	0	2	1	2
Neutrophil count decreased	3	0	0	2	3	0
White blood cell decreased	3	0	0	3	2	0

Data are reported as no. Only AEs occurring during treatment or within 30 days of the last study medication are reported. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. A patient with multiple AEs is counted only once in the total row

Appreciation: *AEs* Adverse events

* Immune-related adverse events

compared to the regimen of cisplatin and gemcitabine group alone (11.9 months, 95% CI 9.2–14.3). The hazard ratio was 0.86 (95% CI 0.58–1.27, $p=0.44$), indicating no significant difference, but suggesting a potential clinical benefit of cediranib [23]. In our study, we adopted the lenvatinib and GEMOX combination for treating ICC as

Table 5 Univariate Logistic regression analysis between response to treatment and baseline peripheral factors by arm

Variables	Arm A		Arm B	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Neutrophil percentage	1.117(1.002–1.244)	**0.045**	1.020(0.941–1.106)	0.623
Lymphocyte percentage	0.914(0.821–1.017)	0.098	0.976(0.884–1.077)	0.624
Monocyte percentage	1.078(0.726–1.6)	0.710	0.947(0.721–1.244)	0.696
Eosinophil percentage	0.355(0.114–1.11)	0.075	1.013(0.703–1.462)	0.943
Basophil percentage	0.053(0.001–4.167)	0.188	2.072(0.068–63.292)	0.676
Neutrophil count	1.453(1.015–2.08)	**0.041**	1.022(0.69–1.514)	0.914
Lymphocyte count	0.646(0.156–2.676)	0.546	0.876(0.162–4.725)	0.878
NLR	1.265(0.963–1.661)	0.092	0.961(0.595–1.552)	0.870
Monocyte count	11.117(0.461–268.283)	0.138	0.349(0.011–11.466)	0.554
Eosinophil count	0.000(0–8.742)	0.121	1.673(0.021–133.771)	0.818
Basophil count	0.001(0–2.041 × 10^17)	0.754	3.443(0–4.965 × 10^21)	0.960
TNF	1.08(0.986–1.183)	0.096	1.01(0.982–1.039)	0.477
IL-1β	1.057(0.969–1.153)	0.213	1.063(0.934–1.209)	0.357
IL-2R	1.000(0.998–1.002)	0.785	0.998(0.994–1.002)	0.336
IL-6	0.976(0.897–1.061)	0.566	1.016(0.941–1.097)	0.684
IL-8	0.999(0.997–1.001)	0.497	1.001(0.997–1.005)	0.564
IL-10	1.856(0.787–4.379)	0.158	1.32(0.846–2.059)	0.222

Appreciation: *NLR* Neutrophil-to-lymphocyte ratio, *TNF* Tumor necrosis factor, *IL-1β* Interleukin-1 beta, *IL-2R* Interleukin-2 receptor, *IL-6* Interleukin-6, *IL-8* Interleukin-8, *IL-10* Interleukin-10

a first-line option, achieving positive outcomes without causing severe adverse events.

In our investigation, both participant groups encountered AE from the treatments that were controllable and endurable. The lenvatinib plus toripalimab arm did not experience any severe (grade 4) AE, whereas the lenvatinib plus GEMOX arm had two instances of significant platelet count decreased linked to blood toxicity. Common side effects observed in Arm A such as fatigue, hypothyroidism, palmar-plantar erythrodysesthesia syndrome, paresthesia, gingivitis, rash, and insomnia. Commonly reported in The Arm B was tiredness, queasiness, retching, and paresthesia, which is consistent with previously documented side effects for lenvatinib treatments [24]. More serious AE, particularly blood toxicity, were more prevalent in the Arm B cohort, pointing to chemotherapy as the cause. The observed adverse effects suggest that the treatments used in our research cohorts could be safe and acceptable for potential future use as frontline treatments for ICC, while further research is warranted to verify these observations.

In Arm A, individuals who responded to treatment exhibited notably greater initial percentages and numbers of neutrophils. This difference may reflect the activation of the immune response. Lenvatinib enhances the tumor's sensitivity to immunotherapy by inhibiting tumor angiogenesis, while the anti-PD-1 antibody enhances specific anti-tumor immune responses by relieving T cell suppression. An elevated neutrophil count is recognized as a component of the immune reaction in various immunotherapeutic approaches; this cells play an important role in immune surveillance and can, in certain caes, contribute to tumor immune evasion. Responders with higher baseline neutrophil levels may have a stronger immune response foundation, which allows them to better exploit the therapeutic effects of immune checkpoint inhibitors, such as anti-PD-1 antibodies. This finding provides a good direction for research, and will be followed up with related mechanistic studies in the future. No statistically significant difference was found in the baseline NLR between responders and non-responders (Table 5). A significant reduction in the proportion of monocytes and IL-8 level was observed after treatment in responsers, indicating that immunotherapy might have attenuated the pro-inflammatory activity in the immune microenvironment. IL-8, recognized as a pro-inflammatory factor, has been shown to promote tumor growth and metastasis in the tumor microenvironment [25]. The decline in IL-8 level at post-treatment time suggests a decrease in immune suppression, potentially facilitating a stronger anti-tumor immune response and reinforcing the efficacy of immunotherapy.

In Arm B, the reduction in the proportions of neutrophils and basophils, along with a rise in the proportion

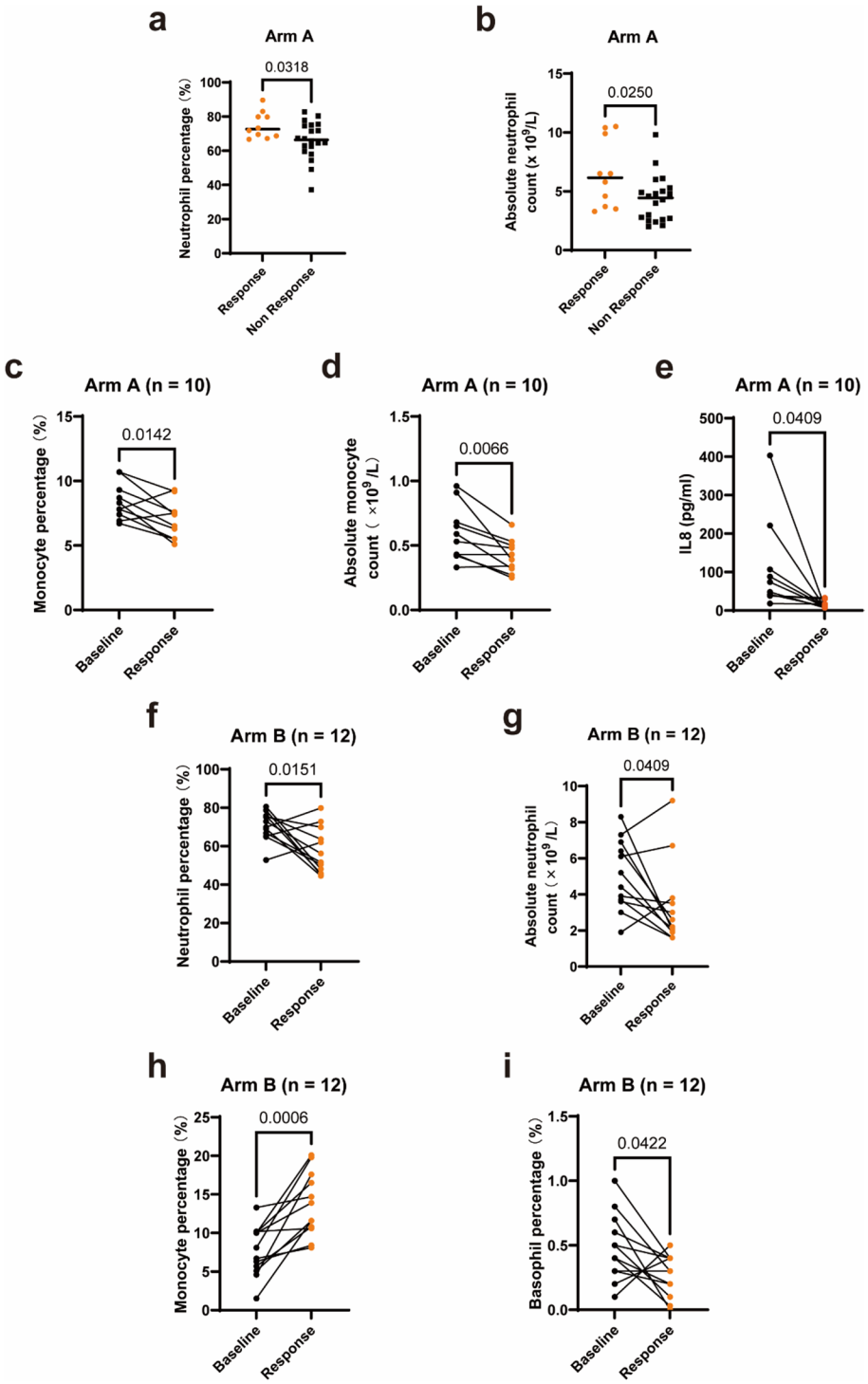


Fig. 4 Indicators with statistically significant differences in peripheral blood tests in Arm A and Arm B (**a**, **b**) Comparison of baseline peripheral blood indicators between responders and non-responders in Arm A. **a** Baseline levels of neutrophil proportion (%) and (**b**) neutrophil counts ($\times 10^9$/L). Statistically significant differences between the two groups were assessed by independent t-tests ($p < 0.05$). **c**-**e** Changes in peripheral blood indicators from baseline to response time in responders in Arm A. **c** Changes in monocyte percentage (%), (**d**) monocyte counts ($\times 10^9$/L), and (**e**) IL-8 (pg/ml). **f**-**i** Changes in peripheral blood indicators from baseline to response time in responders in Arm B. **f** Changes in neutrophil percentage (%),g neutrophil counts ($\times 10^9$/L), (**h**) monocyte percentage (%), and (**i**) basophil percentage (%). Statistically significant differences were assessed by paired t-tests ($p < 0.05$)

of monocytes, suggests that the combination of chemotherapy and lenvatinib might have altered the immune microenvironment, possibly enhancing the immune response. These changes in immune cell composition indicate that, although chemotherapy might induce some degree of immune suppression, the activated immune response could provide support for subsequent immune therapies or contribute to long-term treatment efficacy. It is noteworthy that the changes in monocyte levels after treatment in responders from the two treatment groups exhibited opposite trends. In the lenvatinib plus toripalimab group, monocyte levels significantly decreased after treatment, whereas in the lenvatinib plus GEMOX group, they increased. This observed difference indicates that monocytes might play a crucial role in the combined therapy, warranting further investigation through mechanistic studies.

Our study has certain limitations, such as potential selection bias due to patient recruitment from a single center, which may impact the generalizability of these results. The participants were relatively younger and healthier, which may skew the selection process. Furthermore, design as a non-comparative, single-center phase 2 trial could weaken the reliability of our findings and increase the likelihood of comparison errors. The limited sample size may also lead to selection bias and influence the accuracy of estimation of treatment effectiveness, disease progression, and survival.

Conclusions

In summary, based on a prior study at our center and showing the safety and efficacy of combination therapy toripalimab, lenvatinib plus GEMOX, as the first-line treatment of ICC, we sought to identify which components of the combination therapy are chiefly associated with the response to the treatment and whether the omission of certain components could preserve efficacy while minimizing toxicity. However, the outcomes did not match the success of the full three-drug regimen, suggesting that the triple therapy combination plays an irreplaceable role in the best treatment, prompting further investigation into its underlying mechanisms. Our findings indicate that the combination of lenvatinib with either toripalimab or GEMOX may provide benefits, offering a potential alternative with fewer side effects for ICC patients fail in using triple therapy. However, these results from this small phase 2 study require validation in a larger phase 3 trial. Both of the two combinations therapies studied in our trial can be considered as potential first-line treatment choices of advanced intrahepatic cholangiocarcinoma.

Despite these drawbacks, our study is the first to prospectively evaluate lenvatinib with an anti-PD-1 antibody or with GEMOX as the first-line therapy in advanced ICC patients. It shows encouraging effectiveness, manageable side effects, and practicality, warranting more in-depth trials. Additionally, it proposes other combination treatments for patients who may not be suitable for existing therapies. The trial is registered on Clinicaltrials.gov under the identifier NCT04361331.

Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CA19-9	Carbohydrate antigen 19–9
CI	Confidence interval
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
GEMOX	Gemcitabine plus oxaliplatin
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICC	Intrahepatic cholangiocarcinoma
IL	Interleukin
MRI	Magnetic resonance imaging
NLR	Neutrophil-to-lymphocyte ratio
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PR	Partial response
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RDI	Relative dose intensity
T3	Triiodothyronine
T4	Thyroxine
TNF	Tumor necrosis factor
TTR	Time to response
ULN	Upper limit of normal

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04404-4.

Additional file 1. Figures S1-S2. Figure S1- [Changes in other peripheral blood indicators from baseline to response time in responders in Arm A]. Figure S2–[Changes in other peripheral blood indicators from baseline to response time in responders in Arm B]. Tables S1-S2. Table S1- [Best Response of Each Patient to Treatment in two cohort]. Table S2–[Representativeness of Study Participants].

Additional file 2. CONSORT 2025 checklist item description.

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Authors' contributions

Concept and design: XH, GS, and JZ. Acquisition, analysis, or interpretation of data: XH, GS, ZZ, HS, FL, YJ, YC, GY, ZH, JL, XM, XG, CZ, JF, and JZ. Drafting of

the manuscript: XH, GS, ZZ. Critical revision of the manuscript for important intellectual content: HS, FL, YJ, YC, GY, ZH, JL, XM, XG, CZ. Statistical analysis: FL. Administrative, technical, or material support: XH, GS, ZZ, and JZ. Supervision: XH, GS, and JZ. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol and all amendments were reviewed and approved by the Ethics Committee of each participating site, including the Ethics Committee of Zhongshan Hospital, Fudan University (approval number: B2020-038). The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from all participants prior to enrollment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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