Neoplasma 2023; 70(6): 811–818

doi:10.4149/neo_2023_230806N413

Sintilimab, bevacizumab biosimilar, and HAIC for unresectable hepatocellular carcinoma conversion therapy: a prospective, single-arm phase II trial

Dongming LIU#, Han MU#, Changfu LIU#, Weihao ZHANG, Yunlong CUI, Qiang WU, Xiaolin ZHU, Feng FANG, Wei ZHANG, Wenge XING, Qiang LI, Tianqiang SONG*, Wei LU*, Huikai LI*

Liver Cancer Research Center for Prevention and Therapy, Tianjin Cancer Hospital Airport Hospital, Tianjin Medical University Cancer Institute and Hospital, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, National Clinical Research Center for Cancer, Tianjin, China

**Correspondence: tjchi@hotmail.com; LUWEI1966@126.com; lihuikai@tjmuch.com*
#Contributed equally to this work.

Received August 6, 2023 / Accepted December 12, 2023

We assessed the efficacy and safety of sintilimab [an anti-programmed death (PD-1)] plus bevacizumab biosimilar (IBI305), and hepatic arterial infusion chemotherapy (HAIC) in patients with unresectable hepatocellular carcinoma (HCC). The patients received sintilimab (200 mg) plus IBI305 (7.5 mg/kg) and HAIC (FOLFOX for 23 h) and were treated every 3 weeks. The primary endpoint was the objective response rate (ORR) assessed by an independent review committee (IRC) per mRECIST v1.1. Twenty-nine patients were enrolled in our clinical trial (1 patient voluntarily withdrew due to adverse events after the initial treatment). Objective response was reached in 17/29 (58.6%) patients per mRECIST. A total of 19/29 (65.5%) patients became eligible for further treatment; 14 of them completed surgical resection; 1 (5.3%) achieved pathological complete response (pCR); and 5 (26.3%) reached major partial response (mPR). The 1-year OS rate was better in the PR or pCR+mPR+PR group than in the PD+SD group by either mRECIST or pathological assessment (p=0.039 and 0.006). The 1-year EFS rate was better in the PR group than in the PD+SD group by pathological assessment (p=0.007). The most common treatment-related adverse events (TEAEs) in 30 HCC patients included thrombocytopenia (40.0%), hypertension (23.3%), and leukopenia (23.3%). The grade 3-5 TEAEs that were observed were hypertension (10%), diarrhea (6.7%), asthenia (3.3%), and ascites (3.3%). Sintilimab plus IBI305 and HAIC showed promising efficacy and manageable safety in patients with unresectable HCC. It might represent a novel treatment option for these patients.

Key words: sintilimab, bevacizumab biosimilar, hepatic arterial infusion chemotherapy, efficacy, safety

Approximately half of all new liver cancer cases worldwide come from China [1]. It has the second-highest mortality rate of all malignant tumors in China, with approximately 300,000–400,000 deaths from HCC each year [2]. More than 70% of liver cancer patients are diagnosed at an intermediate to advanced stage [3]. The treatment options that are recommended according to the Barcelona Staging Criteria (BCLC stage) of the European Society for the Study of the Liver (EASL) guidelines have been lost in favor to surgery, and the main treatment options are interventional or systemic therapy [4]. The reasons for unresectable HCC can be divided into two levels; one level is unresectable in the surgical sense (BCLC stage B or CNLC stage IIb in our data), including the poor patient's systemic condition, inadequate liver function, and insufficient future liver remnant (FLR). The other level is oncological or biological unresectability (BCLC stage C or CNLC stage III in our data).

The combination of ICIs and anti-vascular endothelial growth factor (anti-VEGF) inhibitors is a key strategy for the treatment of unresectable HCC, normalizing tumor vascularization, shrinking the immunosuppressive tumor microenvironment and reprogramming immune checkpoints to enhance tumor stimulation and infiltration by immune cells [5, 6]. In the IMbrave150 study, the combination strategy of atezolizumab combined with bevacizumab was shown to significantly improve ORR, OS, and progression-free survival (PFS) compared to sorafenib, and was approved by the FDA in May 2020 as a first-line treatment for advanced unresectable HCC [7]. Notably, the incidence of upper gastrointestinal bleeding was relatively high in

HCC patients treated with atezolizumab and bevacizumab [8]. Zhang et al. reported that low-dose (7.5 mg/kg) IBI305 in combination with sintilimab reduced the incidence of adverse events (AEs) without compromising the efficacy of advanced unresectable HCC [9]. In recent years, HAIC has also become an important approach in the comprehensive treatment of mid- and advanced-stage HCC [10]. He et al. evaluated the combined treatment with sorafenib and HAIC of oxaliplatin, fluorouracil, and leucovorin (FOLFOX). The results showed a safe toxic effect profile and a 12-month survival rate of 52.7% in HCC patients with major portal vein invasion [11]. However, the use of anti-VEGF inhibitors combining PD-1 and HAIC in unresectable HCC has rarely been reported.

Therefore, we assessed the efficacy and safety of sintilimab plus low-dose IBI305 and HAIC in patients with unresectable HCC. This phase II trial (NCT05029973) was registered in April 2021.

Materials and methods

Study design and participants. The study was a prospective, single-arm phase II trial at Tianjin Medical University Cancer Institute and Hospital. The main inclusion criteria were as follows: aged 18–75, initial unresectable hepatocellular carcinoma diagnosed histologically, cytologically, or clinically, BCLC stage B and C, China Liver Cancer (CNLC) stage IIb–IIIb, received no previous systemic therapy, expected survival time over 6 months, had a measurable lesion according to the HCC-specific modified Response Evaluation Criteria in Solid Tumours (mRECIST) criteria, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, had a Child-Pugh liver function score of A–B, and sufficient organ and bone marrow functions.

Key exclusion criteria included fibrolamellar carcinoma, intrahepatic cholangiocarcinoma (ICC), combined HCC-cholangiocarcinoma (HCC-CC), sarcomatoid HCC, comorbidities with other active malignancies, active autoimmune disease, previous solid organ or hematological transplantation, clinically diagnosed hepatic encephalopathy, symptomatic ascites or pericardial effusion, known severe varicose veins assessed by endoscopy, evidence of portal hypertension with a high risk of bleeding, acute or chronic active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, diagnosis of immunodeficiency, previous systemic steroid therapy or other immunosuppressive therapy four weeks before the first study dose, and other conditions affecting the safety or study completion determined by the investigator.

The trial was performed in accordance with Good Clinical Practice and the Declaration of Helsinki. The protocol and any amendments were approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (E20210296). All patients provided written, informed consent before enrolment.

Procedures. The patients received triple combination therapy for three cycles, comprised of sintilimab (200 mg every 3 weeks), IBI305 (7.5 mg/kg every 3 weeks), and hepatic arterial infusion chemotherapy (HAIC, FOLFOX every 3 weeks). Tumors were assessed by contrast-enhanced CT or MRI at baseline and after the third/sixth cycle of treatment to evaluate resection probability. As the optimal discontinuation time for IBI305 is generally 6 weeks, the patients who reached conversion surgery criteria were administered an additional cycle of sintilimab and HAIC. After a further three-week interval, radical surgical treatment was performed. The criteria for successful conversion include a Child-Pugh score <7, an ECOG performance status of 0 or 1, no extrahepatic lesion, and R0 resection can be performed with FLR >40% in patients with cirrhosis or FLR >30% in patients without cirrhosis. Adverse events (AEs) were assessed by the investigators throughout the treatment period and up to 90 days after the last cycle of treatment, according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE, version 5.0), including treatment-related adverse events (TRAEs) or serious adverse events (sAEs). Perioperative surgical complications were assessed according to the Clavien-Dindo classification system. A survival follow-up was performed every 60 days (± 7 days) after treatment.

Outcomes. The primary endpoints were ORR and TRAEs. The ORR is mainly based on the pathologic results of patients after surgical treatment with the drug. The secondary endpoints were the surgical conversion rate (the percentage of patients who achieved successful conversion criteria), the pathological complete response (pCR) rate (the percentage of patients who achieved pCR in the patients who completed pathological confirmation), event-free survival (EFS), and OS.

Statistical analysis. The primary endpoint was ORR. Sintilimab combined with bevacizumab biosimilar (IBI305) showed an ORR of 24% per mRECIST in the Orient-32 study, which led to its CFDA approval in unresectable hepatocellular carcinoma. We assumed that the ORR would rise to 50% when it was combined with HAIC. A sample size of 26 patients was estimated to provide at least 84% power to reject a null hypothesis of having an objective response in 24% of the patients at a two-sided significance level of 5%, and 15% more patients were added to compensate for any dropout. Finally, 30 patients were included.

R version 3.4.1 was used for data analyses. Continuous variables are presented as medians with ranges, while categorical variables are described as frequencies and percentages. The ORR, surgical conversion rate, R0 resection rate, pCR rate, and 95% CIs were calculated using the Clopper-Pearson method. The Mann-Whitney U test was used to assess the difference in AFP levels between the before and after conversion treatment groups. SPSS 25.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to evaluate the data. The univariate Kaplan-Meier method was used to analyze the survival

curve of the HCC patients. All tests were two-tailed with a level of significance set at $\alpha<0.05$.

This study is registered with ClinicalTrials.gov, NCT05029973.

Results

Between May 2021 and October 2021, we screened 42 patients, and 30 patients were enrolled and received sintilimab combined with IBI305 and HAIC (Figure 1). Antitumor efficacy outcomes were analyzed in all 29 patients, and safety outcomes were evaluated in 30 patients. All 29 patients completed conversion therapy and tumor assessments at the time of analysis.

The baseline characteristics of the 29 unresectable HCC patients are shown in Table 1. The median age was 55.5 [interquartile range (IQR), 37–73 years]. There were 26 (72.2%) males among the 29 HCC patients in this study. The median duration of treatment was 3 cycles (IQR 3–3.5). Furthermore, 79.3% of the patients had hepatitis B and 13.8% of them had hepatitis C. The median sums of the measurable tumor diameters pretreatment and post-treatment were 9.2 and 6.0 cm (IQR 7.9–10.8, 3.1–9.0). The ratios of BCLC stages B and C were 13.8% and 86.2%, respectively. Vascular invasion (51.7%) or extrahepatic metastasis (48.3%) was observed in most of the patients. The median pretreatment and post-treatment AFP levels were 169.0 and 7.5 ng/ml (IQR 11.7–2270.0, 4.0–137.0), respectively. Initially, the change in tumor size and α-fetoprotein (AFP) levels suggested that there was certain efficacy of conversion therapy.

The study met the primary endpoint, with 17 (58.6%) of the 29 unresectable HCC patients assessed by IRC per mRECIST v1.1 achieving an overall response. Disease control was observed in 23 (79.3%) of the 29 patients, with partial response (PR) in 17 (58.6%) patients and stable disease (SD) in 6 (20.7%) patients (Table 2, Figure 2). The AFP levels decreased significantly (p=0.0302) after conversion treatment (Figure 3). The specific changes in the values have been described above.

A total of 20 patients (69.0%) successfully converted to further treatment (Table 2). However, 1 patient refused further treatment, and 19 patients were included in the final

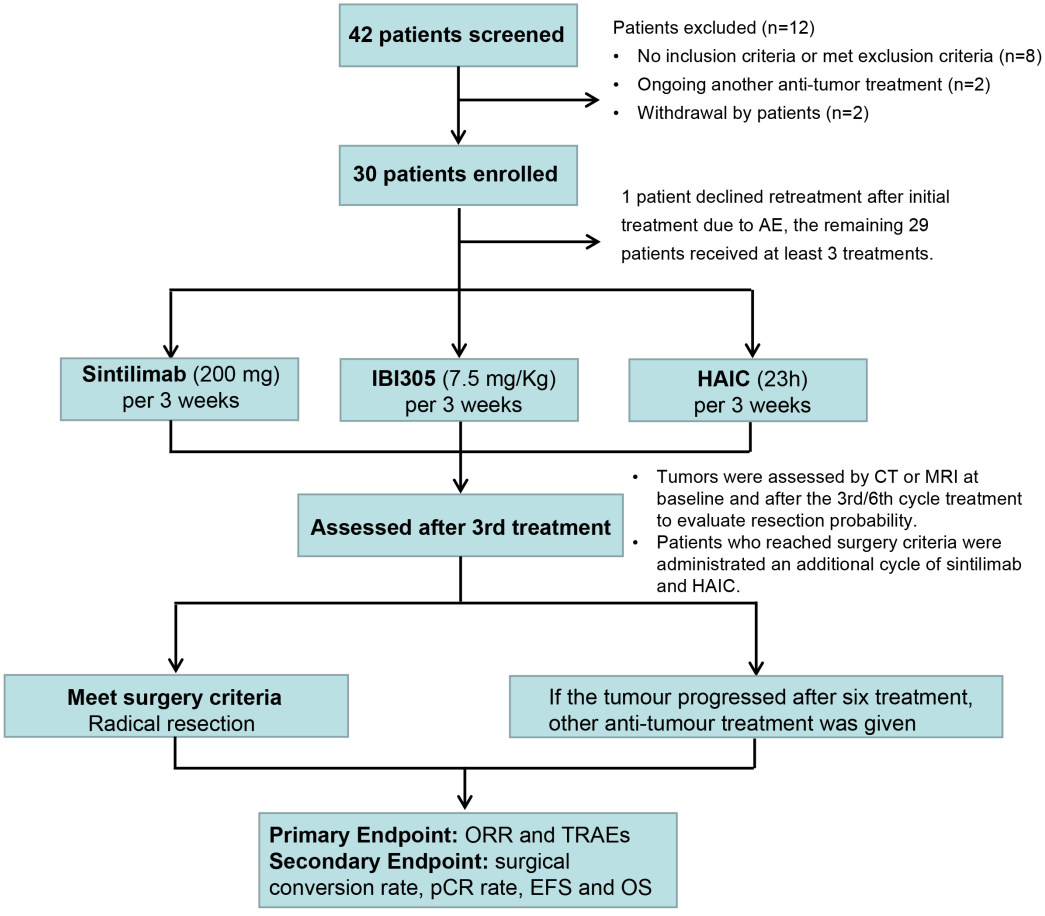

Figure 1. Flow chart of clinical trials NCT05029973.

Table 1. Baseline characteristics of 29 unresectable HCC patients.

Characteristics	Total (n=29)
Sex, n (%)	
male	26 (72.2)
female	3 (8.3)
Age	
median (IQR)	55.0 (47.5–64.0)
ECOG performance status, n (%)	
0	28 (96.6)
1	1 (3.4)
Child-Pugh class, n (%)	
A	28 (96.6)
B	1 (3.4)
Etiology, n (%)	
HBV	23 (79.3)
HCV	4 (13.8)
Nonviral	4 (13.8)
Both	2 (6.9)
Pre-treatment AFP level (ng/ml)	
median (IQR)	169.0 (11.7–2270.0)
Pre-treatment ALT level (U/l)	
median (IQR)	34.0 (22.5–48.5)
Pre-treatment AST level (U/l)	
median (IQR)	40.0 (34.0–61.0)
Pre-treatment tumor size (cm)	
median (IQR)	9.2 (7.9–10.8)
Tumor number, n (%)	
1	16 (55.2)
2	1 (3.4)
3	1 (3.4)
>3	11 (37.9)
Tumor biological behavior, n (%)	
Extrahepatic metastasis	14 (48.3)
Vascular invasion	15 (51.7)
None	4 (13.8)
Both	4 (13.8)
BCLC stage, n (%)	
B	4 (13.8)
C	25 (86.2)
CNLC stage, n (%)	
IIB	4 (13.8)
IIIA	11 (37.9)
IIIB	14 (48.3)
Treatment cycle	
median (IQR)	3 (3–3.5)
Post-treatment AFP level (ng/ml)	
median (IQR)	7.5 (4.0–137.0)
Post-treatment ALT level (U/l)	
median (IQR)	32.0 (19.5–47.0)
Post-treatment AST level (U/l)	
median (IQR)	39.0 (29.5–60.5)
Post-treatment tumor size (cm)	
median (IQR)	6.0 (3.1–9.0)

Table 2. Tumor responses as per mRECIST of 29 unresectable HCC patients.

Tumor remission status	Assessed by mRECIST, n (%)
ORR	17 (58.6)
CR	0 (0.0)
PR	17 (58.6)
SD	6 (20.7)
PD	6 (20.7)
DCR	23 (79.3)
Further treatment	
Surgery	14 (48.3)
RFA	3 (10.3)
Biopsy	2 (6.9)
Refused surgery	1 (3.4)

Table 3. Tumor responses based on pathology of surgery, RFA, and biopsy (n=19).

Tumor remission status	Assessed by pathology, n (%)
pCR	1 (5.3)
mPR	5 (26.3)
PR	12 (63.1)
SD	1 (5.3)

count (Table 3). Of them, 14 patients underwent resection, and all achieved R0 resection, 3 patients underwent radiofrequency ablation (RFA), and 2 patients underwent biopsies to compare the effects of treatment. Of the 19 patients who underwent pathological examination using surgical specimens or biopsy specimens, 1 (5.3%) achieved pCR, and 5 (26.3%) reached mPR.

The median follow-up time was 19.3 months (IQR, 17.7–20.4). The 3/6/9/12 months OS rate of the 29 patients was 93.1%/86.2%/72.4%/65.5%, and the 3/6/9/12 months EFS rate of the 29 patients was 89.7%/62.1%/44.8%/41.4%, respectively (Figure 4). Based on the mRECIST criteria or pathological findings, we divided the 29 patients into two groups: one group of patients who had achieved clinical remission (PR based on mRECIST, pCR+mPR+PR based on pathology) and another group of patients with stable or progressive disease (SD+PD). The differences between these two groups were further compared in terms of the 1-year OS and EFS rates. Based on the mRECIST criteria, the 1-year OS rates of the PR group (n=17) and PD+SD group (n=12) were 82.4% and 41.7%, respectively (p=0.039). The 1-year EFS rates of the PR group and PD+SD group were 52.9% and 25.0%, respectively (p=0.122). According to the pathological findings from samples obtained via surgery, RFA, and biopsy, the 1-year OS rates of the pCR+mPR+PR group (n=19) and PD+SD group (n=10) were 82.4% and 30.0%, respectively (p=0.006). The 1-year EFS rates of the pCR+mPR+PR group and PD+SD group were 57.9% and 10.0%, respectively (p=0.007).

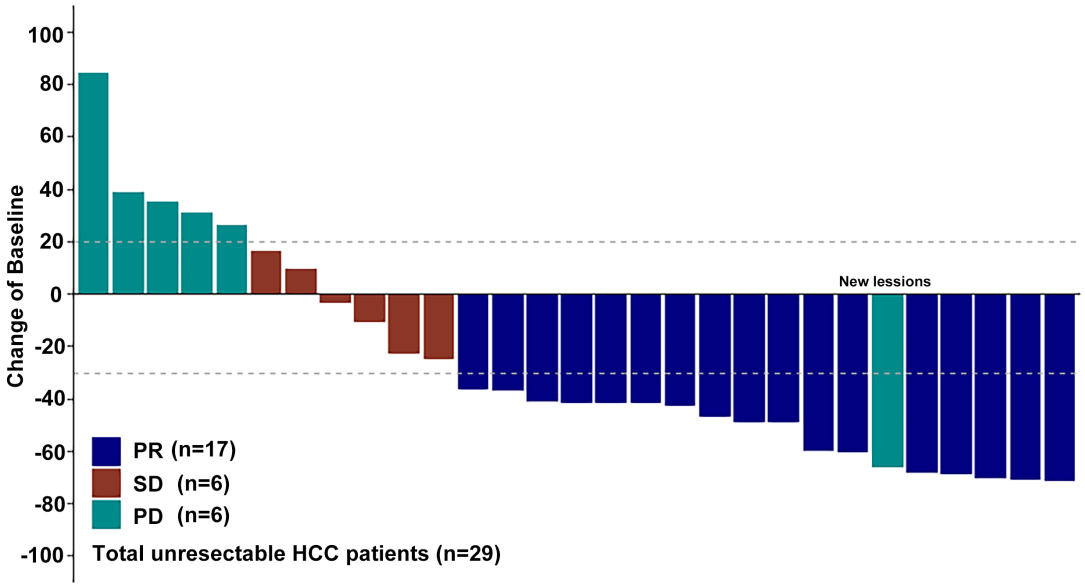

Figure 2. The best change from baseline in the sum of the target lesion diameter per mRECIST in patients who underwent sintilimab combined with IBI305 and HAIC treatment.

The treatment-related adverse events of 30 HCC patients are shown in Table 4. The most common TEAEs in the 30 HCC patients included thrombocytopenia (40.0%), hypertension (23.3%), and leukopenia (23.3%). The grade 3–5 TEAEs that were observed in this cohort included hypertension (10%), diarrhea (6.7%), asthenia (3.3%), and ascites (3.3%). There were no sAEs. Postoperative death occurred in 1 patient because of hepatic failure.

Discussion

Surgical procedures are mainly suitable for patients with early or mid-stage tumors, and the earlier the treatment, the better the outcome. For early-stage liver cancer patients (BCLC stage A), radical hepatectomy is the mainstay of treatment, while radiofrequency ablation of some small hepatocellular carcinomas is feasible [3, 12]. Some patients who meet the criteria for UCSF awaiting liver transplantation can be treated with adjuvant treatments such as selective hepatic artery chemoembolization (TACE) or radiotherapy to delay the progression of liver cancer, which may improve the outcome of liver transplantation [13].

Unresectable HCC is complex and difficult to treat. Once HCC has progressed to an unresectable stage, it is essentially a whole liver lesion or even a systemic lesion, which is not amenable to radical surgery, and the only options are systemic and regional downstage conversion therapy [14]. Therefore, progress in downstaging conversion therapy is crucial to improving the overall outcome of patients with liver cancer [15–17]. Converting a noncurative resection to a potentially curative resection or a potentially curative resec-

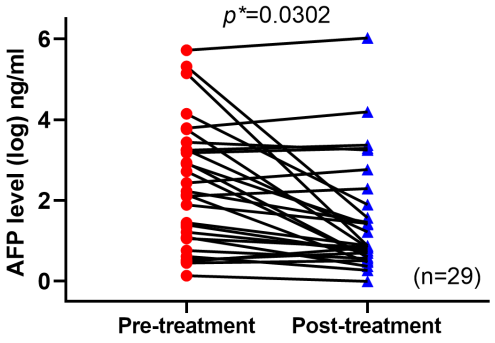

Figure 3. The AFP levels in pre-treatment and post-treatment.

Table 4. Treatment-related adverse events of 30 HCC patients.

TRAE	any Grade, n (%)	Grade 3–5, n (%)
Hypertension	7 (23.3)	3 (10.0)
Hyperbilirubinemia	2 (6.7)	0 (0.0)
Thrombocytopenia	12 (40.0)	0 (0.0)
Alanine aminotransferase increased	4 (13.3)	0 (0.0)
Leukopenia	7 (23.3)	0 (0.0)
Asthenia	2 (6.7)	1 (3.3)
Diarrhea	3 (10.0)	2 (6.7)
Rash	3 (10.0)	0 (0.0)
Hypoalbuminemia	1 (3.3)	0 (0.0)
Anemia	2 (6.7)	0 (0.0)
Hypokalemia	1 (3.3)	0 (0.0)
Ascites	3 (10.0)	1 (3.3)
Edema extremities	3 (10.0)	0

Note: *Although 1 patient voluntarily withdrew from the clinical trial due to an adverse reaction after initial treatment, we still counted the occurrence of adverse reactions in the statistics of TRAE

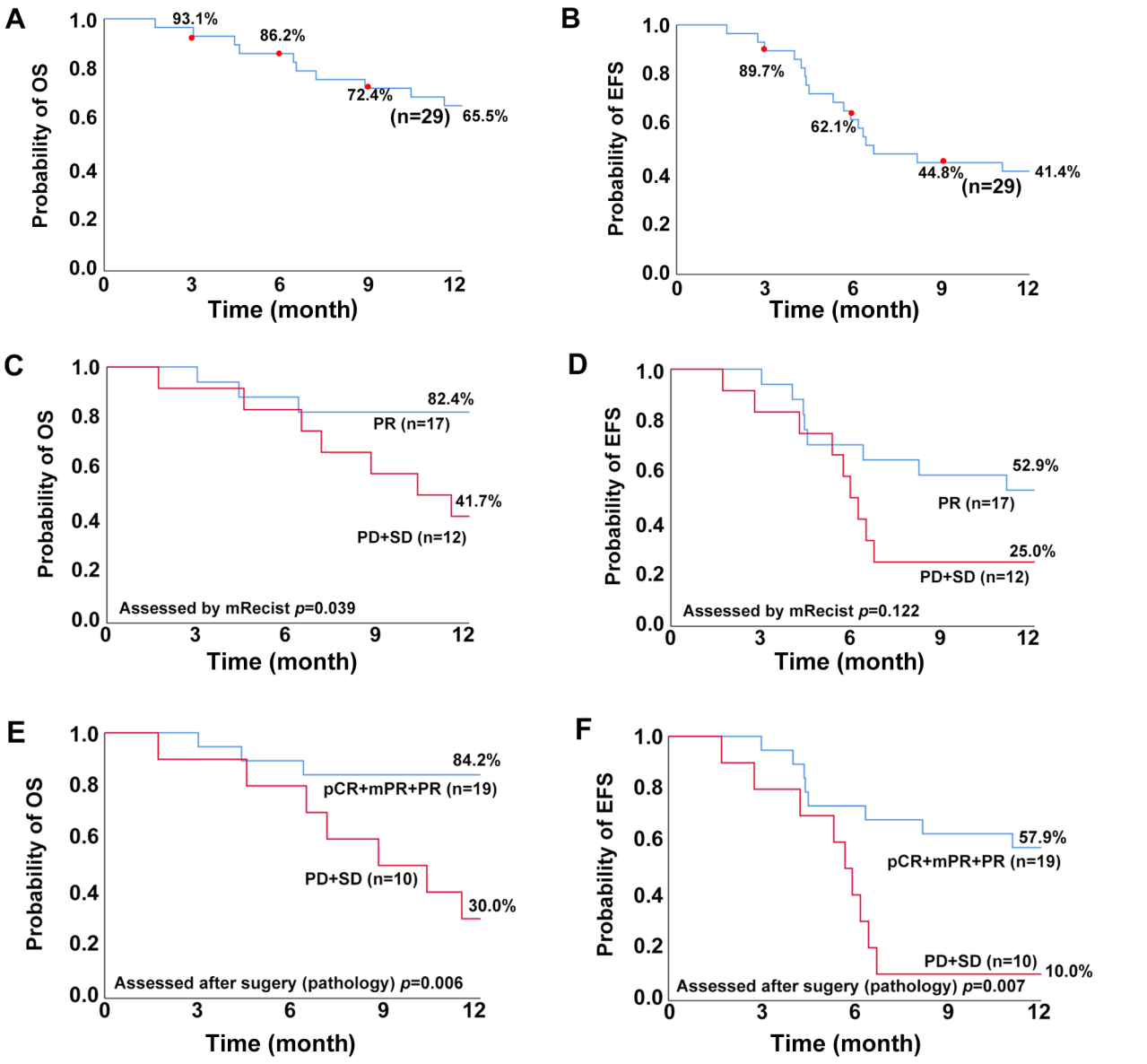

Figure 4. Kaplan-Meier plots of PFS and OS. A, B) OS and EFS in all 29 HCC patients; C, D) 1-year OS and EFS rate of the PR group (n=17) and PD+SD group (n=12) assessed by mRECIST; E, F) 1-year OS and EFS rate of the pCR+mPR+PR group (n=19) and PD+SD group (n=10) assessed by surgery (pathology).

tion to a curative resection through downstaging conversion therapy can help to further OS and PFS in patients with intermediate to advanced liver cancer [18, 19]. An effective downstaging conversion therapy program requires the following factors: first, an effective conversion rate and a high ORR rate, which ensures the magnitude of tumor shrinkage and the degree of pathological necrosis, providing the opportunity for subsequent R0 surgical resection. Second, conversion therapy is less damaging to liver function, as most HCC patients in China have a history of hepatitis or underlying diseases such as cirrhosis, so conversion therapy programs should be carried out without affecting liver function, thus ensuring safety in the perioperative period after conversion therapy. Third, there should be a low rate of AEs, with the occurrence of sAEs being manageable and not affecting the smooth progress of subsequent surgery [20–24].

In our data, there were fewer (13.8%) BCLC stage B HCC patients, who mostly had vascular invasion or extrahepatic metastasis, while the sum of measurable tumor diameters suggested that most patients suffered from large tumor loading. This study presented more objective baseline data on Chinese patients with advanced HCC and was more in

line with real-world study standards. Taking patients with advanced HCC with portal vein trunk thrombosis as an example and from the perspective of surgical techniques, surgical resection can be performed. Due to the biological behavior of malignant tumors, the survival prognosis of these patients is still poor even after hepatectomy, and no curative effect can be achieved [24, 25]. In our study, 8/15 patients with portal vein thrombosis underwent radical surgery after treatment, and 6 patients were still alive one year later. Five of these six patients showed no signs of recurrence. This series of results suggested that there was a correlation between necrosis of portal vein thrombosis and survival prognosis and that conversion therapy could help prolong the survival of these patients by allowing the thrombosis to regress from the main trunk into secondary branches.

The median duration of treatment was 3 cycles (IQR 3–3.5). For advanced HCC, it is important to rapidly reduce the size of the tumor and necrosis of the active tumor components [26]. Therefore, after 3–4 cycles of conversion therapy, if PR or non-enlarging SD could be achieved, surgery might be considered with adequate liver function reserves. In our study, the majority of the patients with PD progressed after 3–4 cycles of treatment, and the prognosis for these patients was poor. Therefore, if PD or enlarged SD is reached after 3–4 cycles of combination therapy, this might be indicative of poor prognosis, and other treatments could be tried. The ORR after sorafenib monotherapy was found to be only 3.3% [27], cabozantinib monotherapy had an ORR of 4.0% [28], regorafenib had an ORR of 6.5%, and lenvatinib monotherapy had an ORR of approximately 18.8% [29]. Pembrolizumab had an ORR of 18.3%, nivolumab had an ORR of 15.0%, and patients with camrelizumab had an ORR of only 14.7% [28]. Combination therapy brings higher ORR benefit compared with single agent, and combination may open a new era of conversion therapy for HCC. A study by Xu et al. demonstrated an ORR of 26.5% after the combination of camrelizumab with the FOLFOX4 regimen [30]. And the ESMO Congress 2019 in the most recent data from the phase Ib study on the combination of pembrolizumab plus lenvatinib for the treatment of advanced HCC showed an ORR of 40.3%. Qin et al. [31] reported an ORR of 44.4% after the combination of camrelizumab with apatinib. A phase Ib clinical study of lenvatinib combined with nivolumab in patients with unresectable HCC in ASCO-GI 2020 showed an ORR of 54.2% after treatment with this combination.

For the dose selection of IBI305, we chose 7.5 mg/kg as the dosing basis. Fewer AEs may have occurred with this dosing. In our trials, the grade 3–5 TEAEs that were observed included hypertension (10%), diarrhea (6.7%), asthenia (3.3%), and ascites (3.3%). Hypertension can be controlled by antihypertensive drugs and usually does not lead to hospitalization or become life-threatening. The aforementioned patients who voluntarily withdrew from the clinical trials experienced symptoms such as grade 3 diarrhea and grade 3 asthenia. This led to poor compliance with treatment, and the patient withdrew from the clinical trial. The rest of the most common TEAEs included thrombocytopenia (40.0%) and leukopenia (23.3%). These TRAEs might be the result of multiple factors, including the hepatitis background, the hypersplenic state, and the treatments and medications of these patients. In conclusion, this phase II study demonstrated that sintilimab combined with IBI305 and HAIC displayed a high ORR, durable response, long survival, and a manageable safety profile in advanced HCC patients within a cohort with a high proportion of patients with HBV infection.

For unresectable HCC patients, downstaging conversion therapy based on regional, systemic therapy is of great significance. Obtaining positive findings in the use of immune-combined targeted therapy in the conversion of initially unresectable HCC has increased the possibility of radical resection, offering hope for longer OS and PFS but future RCTs with larger populations are needed for in-depth exploration.

Acknowledgments: This work was supported by the National Natural Science Foundation of China (82173317), The Science & Technology Development Fund of Tianjin Education Commission for Higher Education (2021KJ192), and Tianjin Health Research Project (TJWJ2022QN015). We are also grateful to Mr. Xiaolei Li of Innovent Biologics (Suzhou) Co., Ltd. Medical Affairs for his help with the content of this article.

References

[1] CHEN W, ZHENG R, BAADE PD, ZHANG S, ZENG H et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66: 115–132. https://doi.org/10.3322/caac.21338

[2] SPERBER AD, BANGDIWALA SI, DROSSMAN DA, GHOSHAL UC, SIMREN M et al. Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. Gastroenterology 2021; 160: 99–114.e3. https://doi.org/10.1053/j.gastro.2020.04.014

[3] EL-SERAG HB, RUDOLPH KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007; 132: 2557–2576. https://doi.org/10.1053/j.gastro.2007.04.061

[4] OLIVERI RS, WETTERSLEV J, GLUUD C. Hepatocellular carcinoma. Lancet 2012; 380: 470; author reply 470–471. https://doi.org/10.1016/S0140-6736(12)61285-9

[5] KUDO M. A New Era in Systemic Therapy for Hepatocellular Carcinoma: Atezolizumab plus Bevacizumab Combination Therapy. Liver Cancer 2020; 9: 119–137. https://doi.org/10.1159/000505189

[6] LAPEYRE-PROST A, TERME M, PERNOT S, POINTET AL, VORON T et al. Immunomodulatory Activity of VEGF in Cancer. Int Rev Cell Mol Biol 2017; 330: 295–342. https://doi.org/10.1016/bs.ircmb.2016.09.007

[7] CHENG AL, QIN S, IKEDA M, GALLE PR, DUCREUX M et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol 2022; 76: 862–873. https://doi.org/10.1016/j.jhep.2021.11.030

[8] FINN RS, QIN S, IKEDA M, GALLE PR, DUCREUX M et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020; 382: 1894–1905. https://doi.org/10.1056/NEJMoa1915745

[9] ZHANG W, GONG C, PENG X, BI X, SUN Y et al. Serum Concentration of CD137 and Tumor Infiltration by M1 Macrophages Predict the Response to Sintilimab plus Bevacizumab Biosimilar in Advanced Hepatocellular Carcinoma Patients. Clin Cancer Res 2022; 28: 3499–3508. https://doi.org/10.1158/1078-0432.CCR-21-3972

[10] SONG DS, SONG MJ, BAE SH, CHUNG WJ, JANG JY et al. A comparative study between sorafenib and hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. J Gastroenterol 2015; 50: 445–454. https://doi.org/10.1007/s00535-014-0978-3

[11] HE M, LI Q, ZOU R, SHEN J, FANG W et al. Sorafenib Plus Hepatic Arterial Infusion of Oxaliplatin, Fluorouracil, and Leucovorin vs Sorafenib Alone for Hepatocellular Carcinoma With Portal Vein Invasion: A Randomized Clinical Trial. JAMA Oncol 2019; 5: 953–960. https://doi.org/10.1001/jamaoncol.2019.0250

[12] LIANG L, CHEN TH, LI C, XING H, HAN J et al. A systematic review comparing outcomes of surgical resection and non-surgical treatments for patients with hepatocellular carcinoma and portal vein tumor thrombus. HPB (Oxford) 2018; 20: 1119–1129. https://doi.org/10.1016/j.hpb.2018.06.1804

[13] PIñERO F, ANDERS M, BOIN IF, CHAGAS A, QUIñONEZ E et al. Liver transplantation for hepatocellular carcinoma: impact of expansion criteria in a multicenter cohort study from a high waitlist mortality region. Transpl Int 2021; 34: 97–109. https://doi.org/10.1111/tri.13767

[14] ZHANG T, ZHANG L, XU Y, LU X, ZHAO H et al. Neoadjuvant therapy and immunotherapy strategies for hepatocellular carcinoma. Am J Cancer Res 2020; 10: 1658–1667.

[15] SCHREIBER RD, OLD LJ, SMYTH MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science 2011; 331: 1565–1570. https://doi.org/10.1126/science.1203486

[16] SUN HC, ZHU XD. Downstaging Conversion Therapy in Patients With Initially Unresectable Advanced Hepatocellular Carcinoma: An Overview. Front Oncol 2021; 11: 772195. https://doi.org/10.3389/fonc.2021.772195

[17] SHEMESH CS, CHAN P, SHAO H, XU DZ, COMBS D et al. Atezolizumab and Bevacizumab in Patients with Unresectable Hepatocellular Carcinoma: Pharmacokinetic and Safety Assessments Based on Hepatic Impairment Status and Geographic Region. Liver Cancer 2021; 10: 485–499. https://doi.org/10.1159/000515817

[18] SUN HC, ZHOU J, WANG Z, LIU X, XIE Q et al. Chinese expert consensus on conversion therapy for hepatocellular carcinoma (2021 edition). Hepatobiliary Surg Nutr 2022; 11: 227–252. https://doi.org/10.21037/hbsn-21-328

[19] LIU D, SONG T. Changes in and challenges regarding the surgical treatment of hepatocellular carcinoma in China. Biosci Trends 2021; 15: 142–147. https://doi.org/10.5582/bst.2021.01083

[20] HE MK, LIANG RB, ZHAO Y, XU YJ, CHEN HW et al. Lenvatinib, toripalimab, plus hepatic arterial infusion chemotherapy versus lenvatinib alone for advanced hepatocellular carcinoma. Ther Adv Med Oncol 2021; 13: 17588359211002720. https://doi.org/10.1177/17588359211002720

[21] QIN S, BI F, GU S, BAI Y, CHEN Z et al. Donafenib Versus Sorafenib in First-Line Treatment of Unresectable or Metastatic Hepatocellular Carcinoma: A Randomized, Open-Label, Parallel-Controlled Phase II-III Trial. J Clin Oncol 2021; 39: 3002–3011. https://doi.org/10.1200/JCO.21.00163

[22] XU J, SHEN J, GU S, ZHANG Y, WU L et al. Camrelizumab in Combination with Apatinib in Patients with Advanced Hepatocellular Carcinoma (RESCUE): A Nonrandomized, Open-label, Phase II Trial. Clin Cancer Res 2021; 27: 1003–1011. https://doi.org/10.1158/1078-0432.CCR-20-2571

[23] ZHOU J, SUN H, WANG Z, CONG W, WANG J et al. Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2019 Edition). Liver Cancer 2020; 9: 682–720. https://doi.org/10.1159/000509424

[24] FINN RS, IKEDA M, ZHU AX, SUNG MW, BARON AD et al. Phase Ib Study of Lenvatinib Plus Pembrolizumab in Patients With Unresectable Hepatocellular Carcinoma. J Clin Oncol 2020; 38: 2960–2970. https://doi.org/10.1200/JCO.20.00808

[25] YANG JD, HAINAUT P, GORES GJ, AMADOU A, PLYMOTH A et al. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol 2019; 16: 589–604. https://doi.org/10.1038/s41575-019-0186-y

[26] ZHAO HT, CAI JQ. Chinese expert consensus on neoadjuvant and conversion therapies for hepatocellular carcinoma. World J Gastroenterol 2021; 27: 8069–8080. https://doi.org/10.3748/wjg.v27.i47.8069

[27] CHENG AL, KANG YK, CHEN Z, TSAO CJ, QIN S et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10: 25–34. https://doi.org/10.1016/S1470-2045(08)70285-7

[28] ABOU-ALFA GK, MEYER T, CHENG AL, EL-KHOUEIRY AB, RIMASSA L et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med 2018; 379: 54–63. https://doi.org/10.1056/NEJMoa1717002

[29] KUDO M, FINN RS, QIN S, HAN KH, IKEDA K et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018; 391: 1163–1173. https://doi.org/10.1016/S0140-6736(18)30207-1

[30] XU J, FAN J, QIN X, CAI J, GU J et al. Chinese guidelines for the diagnosis and comprehensive treatment of colorectal liver metastases (version 2018). J Cancer Res Clin Oncol 2019; 145: 725–736. https://doi.org/10.1007/s00432-018-2795-1

[31] QIN S, REN Z, MENG Z, CHEN Z, CHAI X et al. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial. Lancet Oncol 2020; 21: 571–580. https://doi.org/10.1016/S1470-2045(20)30011-5