A Phase 2 Study of Camrelizumab for Advanced Hepatocellular Carcinoma: Two-Year Outcomes and Continued Treatment beyond First RECIST-Defined Progression

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Keywords

Camrelizumab · Hepatocellular carcinoma · Long-term follow-up

Abstract

Introduction: In a multicenter, open-label, parallel-group, randomized, phase 2 study for pretreated advanced hepatocellular carcinoma (HCC), camrelizumab showed potent antitumor activity and acceptable safety profile. The aim of this report was to provide long-term data and evaluate potential benefit of treatment with camrelizumab beyond progression. **Methods:** From November 15, 2016, to November 16,

2017, 217 patients received camrelizumab 3 mg/kg intravenously every 2 or 3 weeks. Treatment beyond first Response Evaluation Criteria in Solid Tumors (RECIST)-defined progression (TBP) with camrelizumab was allowed. **Results:** At data cutoff of December 16, 2019 (>2 years after the last patient enrollment; median duration of follow-up, 13.2 months [IQR 5.7–25.8]), 14 (43.8%) of the 32 responses per blinded independent central review were ongoing. The median duration of response was not reached (range 2.5–30.5 + months). The ongoing response rates at 12, 18, and 24 months were 68.3% (95% confidence interval [CI] 47.7–82.2),

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59.8% (95% CI 38.8–75.6), and 53.1% (95% CI 31.0–71.0), respectively. The median overall survival (OS) was 14.2 months (95% CI 11.5–16.3). The 18- and 24-month OS rates were 41.3% (95% CI 34.6–47.9) and 33.7% (95% CI 27.3–40.2), respectively. Of the 172 patients who experienced RECIST-defined progression per investigator, 102 received TBP, while 70 did not (non-TBP). The median OS was 16.9 months (95% CI 13.3–22.6) in the TBP group versus 9.4 months (95% CI 5.8–14.8) in the non-TBP group, and the 18- and 24-month OS rates were 47.5% (95% CI 37.3–56.9) versus 33.1% (95% CI 22.3–44.3) and 38.8% (95% CI 29.2–48.4) versus 23.2% (95% CI 13.8–34.1), respectively. No new safety signals of camrelizumab were observed. **Conclusions:** With prolonged follow-up, camrelizumab continues to demonstrate the durable response and long survival in pretreated advanced HCC patients with manageable toxicities, especially in those who continued the treatment beyond first RECIST-defined progression.

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Introduction

The development of immunotherapy has provided more treatment options for patients with advanced hepatocellular carcinoma (HCC). Based on the results of the phase 2 CheckMate-040 and KEYNOTE-224 trials, nivolumab and pembrolizumab were approved in the USA for the treatment of patients with advanced HCC previously treated with sorafenib [1, 2]. In the phase 3 CheckMate-459 trial, nivolumab was compared with sorafenib as a first-line therapy for the advanced HCC. While the overall survival (OS) did not reach statistical significance, clinically meaningful benefits in OS, objective response rate (ORR) and complete response rate were observed for nivolumab [3, 4]. Consequently, nivolumab was approved in the USA and recommended by the National Comprehensive Cancer Network guideline as a first-line therapy for patients with advanced HCC and ineligible for tyrosine kinase inhibitors or other antiangiogenic agents [5]. In the phase 3 KEYNOTE-240 trial, which compared pembrolizumab to placebo as a second-line treatment for advanced HCC, OS and progression-free survival (PFS) did not reach statistical significance. Nevertheless, a strong trend of improvement in OS and PFS was observed for pembrolizumab and post hoc sensitivity analysis showed that OS was significantly longer with pembrolizumab when post-study anticancer therapies were accounted for [6].

Camrelizumab is another humanized monoclonal antibody against programmed cell death protein 1 (PD-1) which can efficiently block the interaction between PD-1 on T cells and programmed death-ligand 1 (PD-L1) on the tumor cells [7]. We have conducted a multicenter phase 2 trial to evaluate the efficacy and safety of camrelizumab in pretreated patients with advanced HCC in China [8]. This is so far the largest study of single-agent immunotherapy in a predominantly hepatitis B virus (HBV)-related HCC population. At a median follow-up of 12.5 months, the ORR for patients treated with camrelizumab was 14.7% (95% confidence interval [CI] 10.3–20.2) and the median duration of response (DoR) was not reached; the 6-month OS rate was 74.4% (95% CI 68.0–79.7) and the median OS was not reached. The common treatment-related adverse events (TRAEs) included low-grade reactive cutaneous capillary endothelial proliferation (RCCEP), increased aspartate aminotransferase, increased alanine aminotransferase, and proteinuria [9]. Based on these findings, camrelizumab was approved in patients with advanced HCC previously treated with sorafenib and/or oxaliplatin-based chemotherapy in China.

During treatment with immunotherapy, increased tumor immune infiltration and delayed response may occur, manifesting as a clinical response following the initial radiographic disease progression (PD) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [10, 11]. In the phase 2 trial of camrelizumab in pretreated patients with advanced HCC, patients were allowed to receive camrelizumab beyond progression if the clinical benefits and tolerance to the drug were perceived by the investigator [8]. This study reports the long-term (>2 years after the last patient enrollment) data for the overall population, including DoR and OS, and explored for the first time the clinical benefits of continued treatment with camrelizumab beyond first PD.

Materials and Methods

Patients and Study Design

The complete protocol for this multicenter, open-label, parallel-group (dose regimen, every 2 or 3 weeks), randomized phase 2 trial (ClinicalTrials.gov, NCT02989922) has been published [8]. Briefly, adult patients (aged ≥18 years) with advanced HCC who had progressed on or were intolerant to the previous systemic treatment for HCC were enrolled. Using block randomization (block size of 4) via a centralized interactive Web-response system, we randomly assigned patients (1:1) to receive intravenous camrelizumab 3 mg/kg every 2 or 3 weeks in 6-week cycles until RECIST v1.1-defined PD (per investigator's assessment), intolerable

Table 1. Duration of response in overall population

	Blinded independent central review (<i>n</i> = 217)	Investigator review (<i>n</i> = 217)
Duration of response		
Median, months (range)	NR (2.5–30.5+)	NR (2.6–31.8+)
Ongoing responses		
At data cutoff* (<i>n</i> / <i>N</i> (%))	14/32 (43.8)	13/31 (41.9)
6 months (95% CI), %	75.9 (55.9–87.7)	77.2 (58.0–88.4)
9 months (95% CI), %	72.1 (51.7–85.0)	73.7 (54.1–85.9)
12 months (95% CI), %	68.3 (47.7–82.2)	70.1 (50.4–83.2)
18 months (95% CI), %	59.8 (38.8–75.6)	51.8 (32.4–68.2)
24 months (95% CI), %	53.1 (31.0–71.0)	44.4 (25.9–61.4)

Tumor response was assessed based on the RECIST, v1.1 guideline. NR, not reached; RECIST, Response Evaluation Criteria in Solid Tumors. * Data cutoff was December 16, 2019, over 2 years after last patient enrolled.

toxicity, withdrawal of consent, investigator decision, or end of the study. The primary end points of the study were ORR per blinded independent central review (BICR) according to RECIST v1.1 and 6-month OS.

The first on-study radiographic assessment was performed at week 8 after treatment initiation, every 6 weeks thereafter within the first 12 months of treatment, and then every 12 weeks until PD or end of treatment. Any AE occurring from the time of informed consent until 90 days after the last dose of study drug was tightly monitored and documented. All AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03, except for RCCEP. RCCEP was graded as follows: Grade 1, nodule(s) with a maximum diameter of ≤10 mm, with or without rupture and hemorrhage; Grade 2, nodule(s) with a maximum diameter of >10 mm, with or without rupture and hemorrhage; Grade 3, generalized nodules over the body, may be complicated by skin infection; Grade 4, multiple and generalized nodules, life-threatening condition; Grade 5, death.

Continued Treatment beyond First RECIST-Defined Progression

Per protocol, treatment beyond first RECIST-defined progression (TBP) was allowed in the study. Patients who had investigator-assessed radiographic PD were permitted to continue camrelizumab treatment if meeting the following criteria: investigator-assessed clinical benefits and tolerance of the study treatment, no clear decline in the performance status or deterioration in cancer-related symptoms, signed informed consent form detailing the possible risks and discomfort, and other therapeutic options. For assessment of clinical benefit, the investigators were required to take into consideration if the patient was clinically deteriorating and if the patient could benefit from continued treatment. TBP patients were required to receive tumor assessment according to the protocol until treatment discontinuation.

Statistical Methods

All randomized patients who received at least 1 dose of camrelizumab were included in the full analysis set. All patients who received at least 1 dose of camrelizumab were included in the safety set. All summaries were conducted with the 2 dosing regimen groups combined together. Patients who experienced RECIST-defined PD per investigator were included in the TBP or non-TBP group based on whether they continued camrelizumab treatment beyond progression.

Descriptive statistics were used to summarize the baseline characteristics. Median DoR and OS, and ongoing response and OS rates at 6, 12, 18, and 24 months were estimated using the Kaplan-Meier method. The 95% CIs for the median DoR and OS were calculated according to the Brookmeyer and Crowley method. The CIs for the ongoing response rates and OS rates at the time points defined previously were derived using the log-log transformation with back transformation to a CI on the untransformed scale. All statistical analyses were done with SAS (v9.4).

Results

Two-Year Efficacy Outcomes of Overall Population

Between November 15, 2016, and November 16, 2017, a total of 217 patients were enrolled and received at least 1 dose of camrelizumab: 109 in every 2 weeks group and 108 in every 3 weeks group. As of data cutoff on December 16, 2019, the median follow-up was 13.2 months (IQR 5.7–25.8). Treatment was continuing in 20 patients who did not experience disease progression (online suppl. Table S1; see www.karger.com/doi/10.1159/000516470 for all online suppl. material).

Among the 32 patients with an objective response per BICR, 14 (43.8%) responses were still ongoing. The median DoR was not reached (range 2.5–30.5 + months). The ongoing response rates at 6, 12, 18, and 24 months were 75.9% (95% CI 55.9–87.7), 68.3% (95% CI 47.7–82.2), 59.8% (95% CI 38.8–75.6), and 53.1% (95% CI 31.0–71.0), respectively. DoR analysis per investigator was consistent with BICR results (Table 1).

At the data cutoff, 146 (67.3%) of 217 patients died and the median OS was 14.2 months (95% CI 11.5–16.3). The 12-, 18-, and 24-month OS rates were 55.9% (95% CI 49.0–62.3), 41.3% (95% CI 34.6–47.9), and 33.7% (95% CI 27.3–40.2), respectively (Fig. 1).

Treatment beyond Progression

Of the 172 (79.3%) patients who experienced RECIST-defined PD per investigator, 102 (59.3%) continued camrelizumab treatment (TBP group) while 70 (40.7%) did not (non-TBP group). The baseline characteristics for the 2 groups are presented in Table 2. Compared with the non-TBP group, the TBP group had a slightly higher pro-

Table 2. Baseline characteristics of patients with RECIST-defined progression

	Non-TBP (n = 70)	TBP (n = 102)	TBP >30%* (n = 24)
Age, years	48.5 (42.0–60.0)	49.0 (41.0–56.0)	46.5 (40.0–51.5)
Male	62 (88.6)	96 (94.1)	23 (95.8)
Eastern Cooperative Oncology Group performance status			
0	21 (30.0)	23 (22.5)	6 (25.0)
1	49 (70.0)	79 (77.5)	18 (75.0)
AFP ≥400 ng/mL	36 (51.4)	50 (49.0)	10 (41.7)
BCLC stage			
B	5 (7.1)	6 (5.9)	0
C	65 (92.9)	96 (94.1)	24 (100)
Extrahepatic metastasis	54 (77.1)	83 (81.4)	22 (91.7)
HBV infection	57 (81.4)	89 (87.3)	21 (87.5)
Child-Pugh class			
A (5–6)	68 (97.1)	101 (99.0)	24 (100)
B (7)	2 (2.9)	1 (1.0)	0
Prior systemic therapy			
Targeted therapy	63 (90.0)	91 (89.2)	21 (87.5)
Chemotherapy	25 (35.7)	28 (27.5)	6 (25.0)
Lines of prior systemic therapy			
1	47 (67.1)	82 (80.4)	21 (87.5)
2	13 (18.6)	14 (13.7)	3 (12.5)
≥3	6 (8.6)	5 (4.9)	0
Others**	4 (5.7)	1 (1.0)	0
Time from initial diagnosis to start of study treatment, years	1.3 (0.5–2.4)	1.4 (0.8–2.9)	1.3 (0.7–3.3)

Data are *n* (%) or median (interquartile range). TBP, treatment beyond first RECIST-defined progression; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; RECIST, Response Evaluation Criteria in Solid Tumors. * Patients in the TBP >30% group had at least 30% reduction in target lesion from baseline with continued camrelizumab treatment beyond first RECIST-defined progression. ** The 5 patients had received prior systemic therapy, but the treatment lines were not clearly recorded.

Fig. 1. Overall survival of all patients. CI, confidence interval.

Fig. 2. Overall survival of patients with RECIST-defined progression. **a** Overall survival in patients treated beyond first RECIST-defined progression with camrelizumab versus those did not. **b** Overall survival in patients who had a change from baseline in target lesion sizes that exceeded the 30% reduction with continued camrelizumab treatment beyond first RECIST-defined progression. NR, not reached; TBP, treatment beyond first RECIST-defined progression; RECIST, Response Evaluation Criteria in Solid Tumors; CI, confidence interval.

portion of the patients with an Eastern Cooperative Oncology Group performance score of 1 (77.5 vs. 70.0%) and extrahepatic metastases (81.4 vs. 77.1%), and a slightly lower proportion of patients with prior treatment with chemotherapy (27.5 vs. 35.7%) and ≥ 2 prior lines of systemic therapy (18.6 vs. 27.1%). In the TBP group, the median duration of exposure with camrelizumab after first PD was 2.7 months (range 1.4–4.8) and the duration of total exposure was 6.2 months (range 2.0–32.2). Subsequent anticancer therapy after PD for the TBP and non-TBP groups is presented in online suppl. Table S2.

At the data cutoff, 66 (64.7%) patients in the TBP group and 53 (75.7%) patients in the non-TBP group had died. The median OS was 16.9 months (95% CI 13.3–22.6) in the TBP group versus 9.4 months (95% CI 5.8–14.8) in the non-TBP group. The respective OS rates at 6, 12, 18, and

24 months were 91.1% (95% CI 83.6–95.3) versus 61.4% (95% CI 49.0–71.7), 67.1% (95% CI 56.9–75.3) versus 43.7% (95% CI 31.8–54.9), 47.5% (95% CI 37.3–56.9) versus 33.1% (95% CI 22.3–44.3), and 38.8% (95% CI 29.2–48.4) versus 23.2% (95% CI 13.8–34.1) (Fig. 2a).

In the TBP group, 24 (23.5%) of 102 patients had a target lesion reduction from baseline of $>30\%$ after first RECIST-defined progression; among them, the first PD in the majority of patients was due to the progression of nontarget lesions and appearance of new lesions, with only 2 (8.3%) having progression in the target lesions (Fig. 3). In these 24 patients, the median OS was not reached (95% CI 19.4–not reached), and the 6-, 12-, 18-, and 24-month OS rates were 100% (95% CI not reached), 87.5% (95% CI 66.1–95.8), 75.0% (95% CI 52.6–87.9) and 62.5% (95% CI 40.3–78.4), respectively (Fig. 2b).

Fig. 3. Change in target lesion sizes over time in patients who had at least 30% reduction from baseline with continued camrelizumab treatment beyond first RECIST-defined progression. RECIST, Response Evaluation Criteria in Solid Tumors.

Two-Year Safety Outcomes of Overall Population

At least 1 TRAE occurred in 198 (91.2%) of 217 patients and the incidence rate of Grade 3 or worse TRAE was 24.0% (52 patients) (Table 3). The most common TRAE was RCCEP (66.8%), but all were of Grade 1 or 2. Except for abnormal hepatic function (6 patients, 2.8%), all Grade 3 or worse TRAEs occurring in >2% patients were laboratory abnormalities, including increased aspartate aminotransferase (11 patients [5.1%]), decreased neutrophil count (7 patients [3.2%]), decreased white blood cell count (6 patients [2.8%]), increased lipase (6 patients [2.8%]), increased alanine aminotransferase (5 patients [2.3%]), increased γ -glutamyltransferase (5 patients [2.3%]), and increased blood bilirubin (5 patients [2.3%]).

Treatment-related serious AEs occurred in 26 (12.0%) patients. The most frequent was abnormal hepatic function (5 patients [2.3%]), and all were of Grade 3 or 4 severity (online suppl. Table S3). TRAEs resulted in treatment interruption in 38 (17.5%) patients and treatment discontinuation in 8 (3.7%). No deaths occurred due to TRAEs during the extended follow-up.

Discussion

In this updated analysis, we confirmed the efficacy of camrelizumab as a second-line or later therapy for patients with advanced HCC. After a follow-up for at least

2 years, camrelizumab continued to show the durable objective response and survival benefits (median OS, 14.2 months; 24-month OS rate, 33.7%). In patients with advanced HCC who continued camrelizumab after first RECIST-defined PD, 23.5% had a target lesion reduction of >30% relative to baseline after PD; the median OS was 16.9 months and the 24-month OS rate was 38.8%, demonstrating the clinical benefits of treatment beyond progression for camrelizumab. In addition, we noted no new safety signals with prolonged treatment of camrelizumab.

Compared with patients with advanced HCC who failed standard first-line therapy in the CheckMate-040, KEYNOTE-224, and KEYNOTE-240 trials, our study population had poorer baseline characteristics, including a higher proportion of patients with Eastern Cooperative Oncology Group performance score of 1, extrahepatic metastases, high AFP level, BCLC stage C and heavy pre-treatment. In HCC patients who failed standard therapy, camrelizumab as a second-line or later treatment achieved comparable median OS (14.2 vs. 15.1 month), 18-month (41.3 vs. 44.6%) and 24-month OS rates (38.8 vs. 33.7%) versus nivolumab and comparable median OS (14.2 vs. 12.9 months [KEYNOTE-224] and 13.9 months [KEYNOTE-240]) versus pembrolizumab [12, 13]. Notably, a high proportion (83%) of patients in our study had HBV infection, which was identified as a poor prognostic factor for sorafenib-treated HCC patients in a previous meta-analysis [14]. On the other hand, survival of sorafenib-

Table 3. Treatment-related adverse events

	Overall population (<i>n</i> = 217)	
	all grades	grade ≥3
Treatment-related adverse events	198 (91.2)	52 (24.0)
Any grade treatment-related adverse events occurring in at least 5% of patients		
RCCEP	145 (66.8)	0
Aspartate aminotransferase increased	58 (26.7)	11 (5.1)
Alanine aminotransferase increased	56 (25.8)	5 (2.3)
Proteinuria	56 (25.8)	1 (0.5)
Blood bilirubin increased	42 (19.4)	5 (2.3)
Platelet count decreased	35 (16.1)	4 (1.8)
White blood cell count decreased	26 (12.0)	6 (2.8)
Hypothyroidism	24 (11.1)	0
Fatigue	22 (10.1)	0
Neutrophil count decreased	21 (9.7)	7 (3.2)
Blood thyroid stimulating hormone increased	20 (9.2)	0
Rash	19 (8.8)	0
γ-Glutamyltransferase increased	18 (8.3)	5 (2.3)
Conjugated bilirubin increased	18 (8.3)	3 (1.4)
Anemia	15 (6.9)	2 (0.9)
Lipase increased	14 (6.5)	6 (2.8)
Lymphocyte count decreased	13 (6.0)	1 (0.5)
Blood alkaline phosphatase increased	13 (6.0)	4 (1.8)
Appetite decreased	13 (6.0)	0
Fever	13 (6.0)	1 (0.5)
Hepatic function abnormal*	13 (6.0)	6 (2.8)
Diarrhea	12 (5.5)	0
Hyperthyroidism	12 (5.5)	0
Hypertension	12 (5.5)	2 (0.9)
Protein urine	11 (5.1)	0
Hypoalbuminemia	11 (5.1)	1 (0.5)

Data are *n* (%). RCCEP, reactive cutaneous capillary endothelial proliferation.

* Abnormal hepatic function refers to at least 2 laboratory abnormalities caused by impaired liver function, such as abnormalities of liver enzymes, bilirubin, coagulation function, and serum albumin, with or without clinical symptoms.

experienced HCC patients who received nivolumab was not found to be associated with HCC etiology (median OS in HBV-infected vs. uninfected: 14.8 vs. 15.1 months) in the exploratory analysis for the CheckMate-040 trial. The influence of HBV infection on the survival benefits of immunotherapy requires more study. In addition to immunotherapy, other FDA-approved second-line or later treatment for advanced HCC include the multikinase inhibitors regorafenib (second-line) and cabozantinib (second-/third-line). In HCC patients who were refractory to standard therapy, the median OS of 14.2 months for camrelizumab compared favorably with the 10.6 months for regorafenib [15] and the 10.2 months for cabozantinib [16]. While full comparisons across trials were difficult, the survival benefits achieved with camrelizumab appeared consistent with other approved

agents for advanced HCC in a second-line or later setting after sorafenib or chemotherapy, despite poorer patient baseline status. On the other hand, atezolizumab plus bevacizumab has recently been established as a first-line therapy for advanced HCC based on the results of the IMbrave150 trial [17]. The role of camrelizumab in the second-line setting after atezolizumab plus bevacizumab requires further investigation.

In the 32 (14.7%) HCC patients with an objective response per BICR, the median DoR was not reached and the ongoing response rates at 12, 18, and 24 months were 68.3, 59.8, and 53.1%, respectively, showing durable responses to camrelizumab. In comparison, the ORRs for nivolumab and pembrolizumab were 14% and 17–18.3%, respectively in sorafenib-experienced HCC patients, and the median DoR were 19.4 and 13.8

months, respectively [12, 13, 18]. It should be noted that the median DoR for nivolumab in the overall (Asian plus non-Asian) population and Asian population were 19.4 and 9.7 months, respectively, suggesting a possible regional difference in durability of immunotherapy owing to the difference in patient-disease characteristics. In the present study, the median DoR obtained with camrelizumab in Chinese HCC patients was at least comparable to that obtained with nivolumab or pembrolizumab regardless of patient ethnicity. To date, there is no validated predictive biomarker or imaging marker for the immunotherapy in a second-line or later setting for advanced HCC, although markers such as the expression of PD-1/PD-L1 on tumor-infiltrating lymphocytes and tumor stiffness (as assessed by magnetic resonance elastography) showed some promise [12, 19]. Our study clearly demonstrated that there was a subset of patients who could derive significant and durable benefit from camrelizumab treatment, and therefore more effects should be directed at the exploration and identification of predictive biomarkers for the immune response in the future.

Patients treated with immunotherapy may develop atypical response pattern, manifested as pseudoprogression [20]. To prevent premature treatment discontinuation, patients in our study were permitted to continue camrelizumab treatment beyond RECIST-defined PD if there were clinical benefits and no unacceptable toxicity as judged by the investigator. The criteria for TBP were generally consistent with those used in trials of nivolumab, pembrolizumab, and atezolizumab in treatment of other solid tumors [21–24]. In total, 23.5% of TBP patients had reductions in the target lesion of >30% compared with baseline after first RECIST-defined PD, suggesting that TBP could exert antitumor effects and may slow or even inhibit the growth of tumor. Accordingly, the median OS from the first dose of camrelizumab was 16.9 months (95% CI 13.3–22.6) for TBP patients (unreached for the subset with >30% reduction in target lesion after PD) compared with 9.4 months for non-TBP patients. Nevertheless, the better clinical outcome for the TBP group should be interpreted with caution as the patients in the TBP and non-TBP groups were not randomly assigned. The decision of TBP was based on the judgment of the investigator in terms of potential clinical benefits and could be influenced by patient clinical condition at PD. However, these data support the notion that the survival benefits from immunotherapy could not be fully assessed with surrogate radiographic end points based on the RECIST v1.1. Indeed, the discordance between PFS

and OS as an efficacy end point and the clinical benefits of TBP have also been noted in other trials of immune checkpoint inhibitors in the solid tumors [22–26]. Since delayed response may occur with immunotherapy and disease (total tumor burden) stabilization after RECIST-defined PD could also reflect therapeutic effect, a number of specific immune-related response criteria have been subsequently developed, including irRC, irRECIST, iRECIST, and imRECIST [27–30], to complement the classic RECIST v1.1 assessment.

In this updated analysis, the safety data for camrelizumab in treatment of HCC were similar to our previous report, with all AEs being manageable and no new safety signals noted [8]. The spectrum of TRAEs for camrelizumab was generally consistent with other PD-1 inhibitors, except for RCCEP, which is the most common AE associated with camrelizumab monotherapy. RCCEP mainly occurs on the skin of the head, face, and trunk and often spontaneously regresses or resolves after discontinuation of camrelizumab [9]. In this study, no increase in the occurrence rate (66.8%) or severity (all Grade 1–2) of RCCEP was observed with increased treatment exposure, supporting previous reports in solid tumors that RCCEP mainly occurred in early treatment cycles of camrelizumab [31].

The study has some limitations. First, this is a phase 2 trial with no control arm. Second, the efficacy and survival benefits of camrelizumab may be influenced by HCC etiology as well as disease presentation and management. Therefore, the performance of camrelizumab in a second-line or later setting for advanced HCC in other regions/populations remains to be confirmed. Given that the additive or synergic effects of combination therapy may improve the immune response, 2 randomized, confirmative phase 3 trials (NCT03764293 and NCT03605706) are currently underway comparing camrelizumab combination therapy with standard of care for advanced HCC in the first-line setting (including 1 international trial assessing camrelizumab plus apatinib vs. sorafenib). In addition, analysis of treatment efficacy for TBP and non-TBP groups was retrospective in nature, and the between-group comparison might be confounded by patient/disease characteristics at baseline and at first PD. Nevertheless, 23.5% of TBP patients achieved a target lesion reduction of >30% compared with baseline after first PD and a 2-year OS rate of 62.5%, suggesting that continued treatment of camrelizumab after PD provided significant clinical benefits to at least a fraction of the patients.

Conclusions

With prolonged follow-up, camrelizumab continues to demonstrate the durable response and long survival in pretreated advanced HCC patients with manageable toxicities, especially in those who continued treatment beyond first RECIST-defined progression. These findings further confirmed that camrelizumab monotherapy could represent a valuable therapeutic option for advanced HCC in a second-line or later setting.

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Statement of Ethics

The study protocol and all amendments were reviewed and approved by the Ethics Committee of each study site. The study was conducted in accordance with the Declaration of Helsinki, Good

Clinical Practice, and local laws and regulatory requirements. All patients provided written informed consent. The trial is registered with ClinicalTrials.gov, NCT02989922.

Conflict of Interest Statement

L.W., P.Y., and J.Z. are employees of Jiangsu Hengrui Pharmaceuticals. All other co-authors declare no competing interests.

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Author Contributions

S.Q., Z.R., J.Z., and L.W. conceived and designed the study. S.Q., Z.R., Z.M., Z.C., X.Chai, J.X., Y.B., L.Y., H.Z., W.F., X.L., X. Chen, and E.L. enrolled patients and collected the data. P.Y. directed the data analyses. All authors participated in the data interpretation and manuscript development. All authors approved the final version to be submitted.

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