Original Article

Efficacy and safety of regorafenib as a first-line agent alone or in combination with an immune checkpoint inhibitor for advanced hepatocellular carcinoma: a retrospective cohort study

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Background: The RESORCE-III trial demonstrated that advanced hepatocellular carcinoma (HCC) patients who progressed on sorafenib and had second-line therapy with regorafenib improved overall survival compared with placebo. Later, immunotherapy with immune checkpoint inhibitors (ICIs) combined with antiangiogenetic antibodies has evolved as the preferred first-line treatment for fit patients. We aimed to explore the efficacy and safety of regorafenib as a first-line agent alone or in combination with ICIs in patients with advanced HCC.

Methods: We identified 50 patients with advanced HCC treated with regorafenib as a first-line agent. Two patients were lost to follow-up and excluded. Baseline factors, dosing, concomitant use of ICIs, toxicity and outcome of treatment were recorded from electronic medical records.

Results: Twenty-six patients received regorafenib as monotherapy and twenty-two received regorafenib + ICI in combination. In the total cohort, the median progression-free survival (mPFS) was 7.7 months and the median overall survival (mOS) was 16.7 months (P=0.02). Objective response rate (ORR) and disease control rate (DCR) assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were 21% and 73%. In the regorafenib monotherapy group, mPFS was 5.9 months, and mOS was 13.9 months; in the combination group, mPFS was 7.8 months, and mOS was 23.6 months. ORR and DCR were 15% and 65% in the monotherapy group, and 27% and 82% in the combined treatment group, respectively.

Conclusions: Regorafenib used in combination with ICIs had a mild safety profile and resulted in improved response and an almost doubling of mOS compared to monotherapy, warranting further prospective evaluation in a randomized study.

Keywords: Hepatocellular carcinoma (HCC); first-line therapy; regorafenib; immune checkpoint inhibitor (ICI)

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Introduction

Hepatocellular carcinoma (HCC) is the 5th and 7th most common cancer and the 2nd and 6th leading cause of cancer deaths worldwide in adult men and women, respectively (1,2). Hepatitis B virus (HBV) and hepatitis C virus (HCV) cause 60% and 33% of HCCs, respectively, in developing countries, compared to 23% and 20% in developed countries (3,4). Surgical resection remains an essential means of obtaining a cure for patients with early- to mid-stage HCC. However, even with R0 resection, the recurrence rate of the disease is still as high as 50% to 70% at 5 years after surgery (5). Like most tumors, HCC has no obvious symptoms in its early stages, so many patients have developed advanced disease by the time of initial diagnosis (6).

For over a decade, sorafenib was the only first-line agent approved for treating advanced HCC (7). In recent years, the therapeutic field has been rapidly evolving, with the approval of additional first- and second-line systemic therapies, most of which are targeted and immunotherapy (8). Regorafenib achieved notable success as a second-line treatment option for advanced HCC as a result of findings in the phase III RESORCE study, published in 2017. Treatment of patients progressing on sorafenib with regorafenib in second line showed a median overall survival (mOS) of 10.6 months and a mPFS of 3.1 months (9). The mOS from initiation of first-line treatment was 26 months for patients treated with sequential regorafenib after sorafenib (10).

In addition, there are many studies demonstrating good progress with regorafenib as a second-line agent in advanced HCC (11-13). Although regorafenib was initially approved as a second-line therapeutic agent, given the significant survival benefit it has shown in second-line therapy, we hypothesized that regorafenib may be equally effective in first-line therapy. Therefore, this single-institution, retrospective cohort study aimed to investigate the efficacy and safety of regorafenib as a first-line agent alone or in combination with immune checkpoint inhibitors (ICIs) in patients with advanced HCC. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-315/rc).

Highlight box

Key findings

- Regorafenib, alone or combined with immune checkpoint inhibitors (ICIs), demonstrates enhanced efficacy and survival in treating advanced hepatocellular carcinoma (HCC)with a manageable safety profile.

What is known and what is new?

- Regorafenib, a multi-kinase inhibitor, has demonstrated efficacy as a second-line treatment for advanced HCC after sorafenib therapy has failed, and is FDA-approved for this indication.
- This study positions regorafenib as a novel first-line therapy for advanced HCC, offering superior efficacy and survival when paired with ICIs, and underscores the predictive value of the CRAFITY score.

What is the implication, and what should change now?

- Implications suggest regorafenib as a potential first-line therapy for advanced HCC, necessitating validation through RCTs and possible revisions to treatment guidelines.

Methods

Study design and patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) (14). The study was approved by Science and Technology Ethics Committee of Tianjin First Central Hospital (No. 2023DZX08) and informed consent was taken from all the patients.

Our database was retrospectively established and prospectively maintained. We collected demographic, clinical and survival data from December 2018 to February 2022 from the electronic medical records of all patients with advanced HCC treated with regorafenib as first-line therapy alone or combined with ICIs at the Tianjin First Central Hospital, China. Baseline patient characteristics were collected within 1 week prior to initiation of regorafenib therapy.

The inclusion criteria were as follows: pathologically or clinically confirmed HCC (15); adult patients with advanced HCC not suitable for surgical resection; and regorafenib treatment used as first-line therapy for at least one 28-day course of treatment. Exclusion criteria were: participation in other interventional clinical studies during regorafenib dosing; and incomplete follow-up.

Treatment, toxicity and monitoring

Patients received a standard start dose of regorafenib 160 mg orally for the first 3 weeks and discontinued it for 1 week, making for a 5-week dosing cycle. Dose adjustments and interruptions were made at the treating physician's

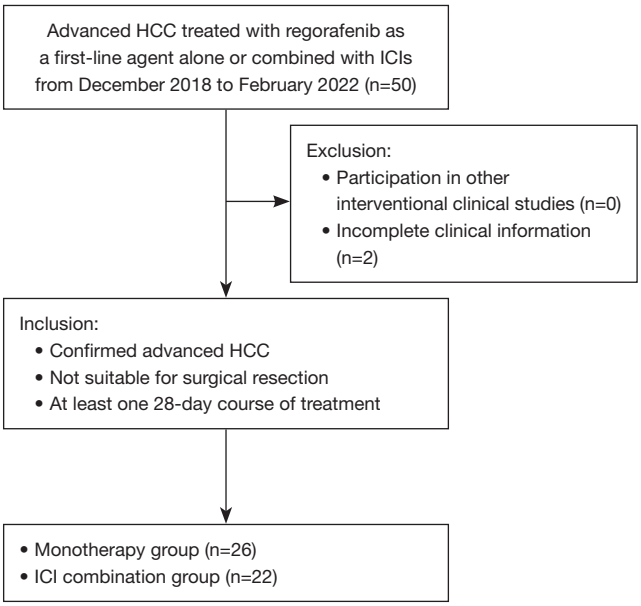

Figure 1 Flow diagram of patient enrolment. HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor.

discretion, depending on the type and severity of the adverse events (AEs). A dose reduction to 80 mg once daily, and to 40 mg in exceptional cases, was allowed, similar to the protocol of the RESORCE trial. Concurrent treatment with ICIs included atezolizumab, palivizumab, carrilizumab, and treprolizumab, but was not counted explicitly because some patients switched ICIs during the treatment. Treatment continued until disease progression, death or intolerable toxicity. The general monitoring strategy included physical examination, serum alpha-fetoprotein (AFP), contrast-enhanced computed tomography (CT) of the chest and abdomen, and contrast-enhanced magnetic resonance imaging (MRI) of the abdomen and pelvis. Laboratory and imaging tests were completed after every 2–4 cycles. Treatment-related AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE V5.0) (16).

Treatment response and survival

According to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (17), the objective response rate (ORR) was defined as the incidence of complete and partial response. The disease control rate (DCR) was the incidence of complete response, partial response, and stable disease. Progression-free survival (PFS) was defined as the time from initiation of regorafenib to confirmation of tumor progression or death or the last follow-up visit, whichever came first. Overall survival (OS) was defined as the time from initiation of regorafenib to death or the last follow-up visit.

CRAFITY score

Using two variables, AFP and C-reactive protein (CRP), to create the CRAFITY score, has shown to provide excellent prognostic stratification of HCC patients treated with tyrosine kinase inhibitors (TKIs) in combination with immunotherapy (18). CRP is a recognized marker of cancer-induced systemic inflammation (19). In the local tumor microenvironment, inflammation has multiple protumor effects, including the promotion of cancer cell proliferation, metastatic dissemination, angiogenesis, and suppression of adaptive immunity (20). AFP is a widely used serum biomarker in the treatment of HCC (21). Both expression of AFP and high absolute values of AFP at baseline are known negative prognostic factors (22).

Statistical analysis

Categorical data are described as number (percentage), and quantitative data are described as median (range). Categorical data were compared between the two groups using the chi-square test or Fisher's exact test. The Mann-Whitney *U* test or Student's *t*-test was used to compare quantitative data between two groups. The Kaplan-Meier method was used for PFS and OS curves, and the log-rank test was used to compare the two groups. All tests were bilateral, and $P<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS Statistics version 22.0.

Results

Study patients and baseline characteristics

We identified, reviewed and collected information on at total of 50 patients. Two patients (4%) were lost to follow-up and excluded from further analyses. Of the 48 patients enrolled, 26 received regorafenib as monotherapy and 22 received regorafenib + ICI (*Figure 1*). Baseline characteristics are shown in *Table 1*. During the study period, 26 patients with advanced HCC receiving regorafenib as first-line therapy were enrolled, with a median age of 54 years (range,

Table 1 The baseline characteristics of all regorafenib-treated patients and distributed according to treatment with monotherapy or in combination with ICIs

Variable	Regorafenib (n=26)	Regorafenib + ICI (n=22)	N	P
Age, years, median [range]	54 [38–74]	53 [42–75]	–	0.65
Gender, n [%]				>0.99
Male	18 [69]	15 [68]	33	
Female	8 [31]	7 [32]	15	
ECOG PS, n [%]				0.64
0	10 [38]	8 [36]	18	
1	14 [54]	12 [55]	26	
2	2 [8]	2 [9]	4	
Child-Pugh, n [%]				0.83
A	15 [58]	12 [55]	27	
B	11 [42]	10 [46]	11	
AFP, μg/L, median [range]	96.8 [1.2–1,210]	65.8 [8.2–1,210]	–	0.36
ALT, U/L, median [range]	41.0 [10.9–160.6]	73.9 [18.5–177.6]	–	0.22
AST, U/L, median [range]	39.0 [13.5–147.6]	42.0 [18.6–188.6]	–	0.35
ALB, g/L, median [range]	37.3 [24.5–48.1]	39.1 [27.1–46.9]	–	0.98
CRP, mg/L, median [range]	29.5 [3.9–113.4]	25.8 [2.6–118.3]	–	0.35
Hepatitis B virus infection, n [%]				0.74
No	6 [23]	6 [27]	12	
Yes	20 [77]	16 [73]	36	
Liver cirrhosis, n [%]				0.48
No	7 [27]	8 [36]	15	
Yes	19 [73]	14 [64]	33	
BCLC stage, n [%]				0.68
B	11 [42]	8 [36]	19	
C	15 [58]	14 [64]	29	
Tumor diameter, n [%]				0.41
<5 cm	10 [39]	6 [27]	16	
≥5 cm	16 [61]	16 [73]	32	
Tumor numbers, n [%]				>0.99
Single	3 [12]	3 [14]	6	
Multiple	23 [88]	19 [86]	42	
Vascular invasion, n [%]				0.44
No	17 [65]	12 [55]	29	
Yes	9 [35]	10 [45]	19	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Regorafenib (n=26)	Regorafenib + ICI (n=22)	N	P
Extrahepatic metastasis, n [%]				0.56
No	21 [81]	20 [91]	41	
Yes	5 [19]	2 [9]	7	

AFP is the undiluted value. ICI, immune checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group Performance Status; AFP, alpha-fetoprotein; ALT, alanine transaminase; AST, aspartate aminotransferase; ALB, albumin; CRP, C-reactive protein; BCLC, Barcelona Clinic Liver Cancer.

Table 2 Treatment responses according to RECIST 1.1

Response	Regorafenib (n=26)	Regorafenib + ICI (n=22)
CR	0	1 (4%)
PR	4 (15%)	5 (23%)
SD	13 (50%)	12 (55%)
PD	9 (35%)	4 (18%)
ORR	4 (15%)	6 (27%)
DCR	17 (65%)	18 (82%)

RECIST, Response Evaluation Criteria In Solid Tumors; ICI, immune checkpoint inhibitor; CR, complete response; PR, partial response; SD, stable disease; PD, progress disease; ORR, objective response rate; DCR, disease control rate.

38–74 years) and a sex ratio of 69% men to 31% women; 22 patients received regorafenib in combination with ICIs, with a median age of 53 years (range, 42–75 years) and 68% men. The two treatment groups were comparable as baseline clinical parameters were not significantly different.

Treatment efficacy

The efficacy evaluation is shown in *Table 2*. The ORR and DCR of the total cohort was 21% and 73%, respectively. The ORRs and DCRs were significantly higher in the combination group compared to monotherapy group (27% *vs.* 15%, P=0.51 and 82% *vs.* 65%, P=0.34, respectively).

With a median follow-up of 20 months (range, 5–38 months), the mPFS in the total cohort of 48 patients was 7.7 months (95% CI: 5.9–10.4), with a 6-month PFS rate of 63% (95% CI: 50–79%) and a 12-month PFS rate of 20% (95% CI: 10–38%). The mOS was 16.7 months (95% CI: 14.3–23.6), the 12-month OS rate was 83% (95% CI: 72–95%), and the 24-month OS rate was 24% (95% CI: 13–45%).

When comparing treatment groups (*Figure 2*), the mPFS in the monotherapy group was significantly shorter, 5.9 months (95% CI: 5.6–10.3) than in the combination group, 7.8 months (95% CI: 7.3–14.5) (P=0.046). The mOS in the monotherapy group was 13.9 months (95% CI: 13.5–22.5), while the mOS in the combination group was almost twice as long, 23.6 months [95% CI: 16.6–not reached (NR)] (P=0.01).

The CRAFITY score significantly stratified the prognosis of patients in both the monotherapy and ICI combination treatment groups (P=0.02; P=0.03 (*Figure 3*).

Regorafenib dose was reduced early in most (87.5%) patients. However, the distribution of initial and final daily stable doses of regorafenib for the monotherapy and ICI combination treatment group were similar (P=0.69; P=0.65, respectively) (*Figure 4*). Analyses of associations between dosing of regorafenib and outcome, indicated improved PFS and OS with higher doses (see Appendix 1).

Adverse events

The incidence of treatment-related AEs was similar (35% *vs.* 36%, P=0.89) in the monotherapy and ICI combination groups, with only one grade III/IV AE in the monotherapy group and no grade III/IV AEs in the combination treatment group (*Table 3*). We found improved OS (P=0.04), but not PFS (P=0.36) in patients with hand/foot skin reactions compared to patients without (*Figure 5*).

Discussion

Given the proven efficacy of regorafenib in second-line therapy and the potential benefit to first-line therapy, we selected regorafenib as first-line therapy. This decision was also influenced by current clinical practice and emerging research trends that support a reassessment of

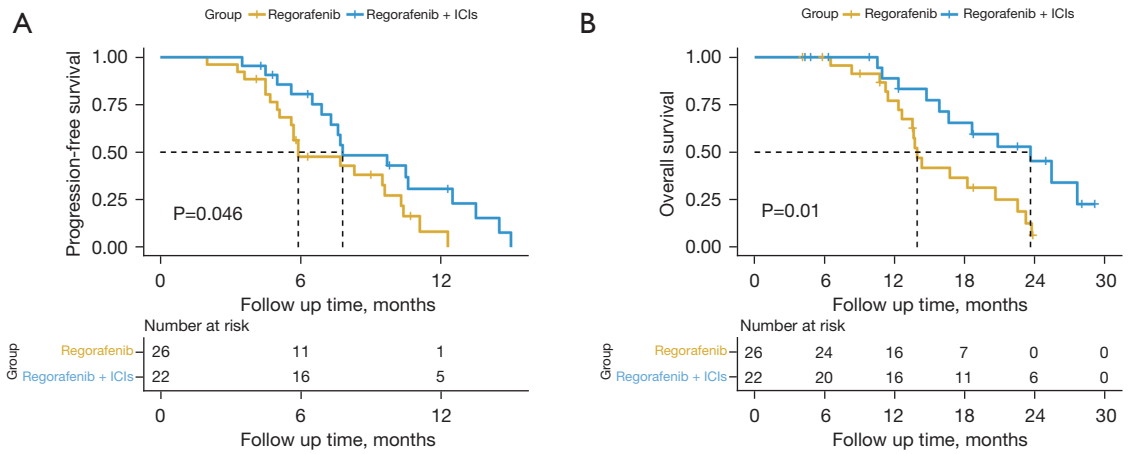

Figure 2 Kaplan-Meier curves of PFS and OS in the regorafenib and regorafenib + ICI groups. (A) The mPFS of regorafenib and regorafenib + ICI was 5.9 and 7.8 months, respectively (P=0.046). (B) The mOS of regorafenib and regorafenib + ICI was 13.9 and 23.6 months, respectively (P=0.01). PFS, progression-free survival; OS, overall survival; ICI, immune checkpoint inhibitor.

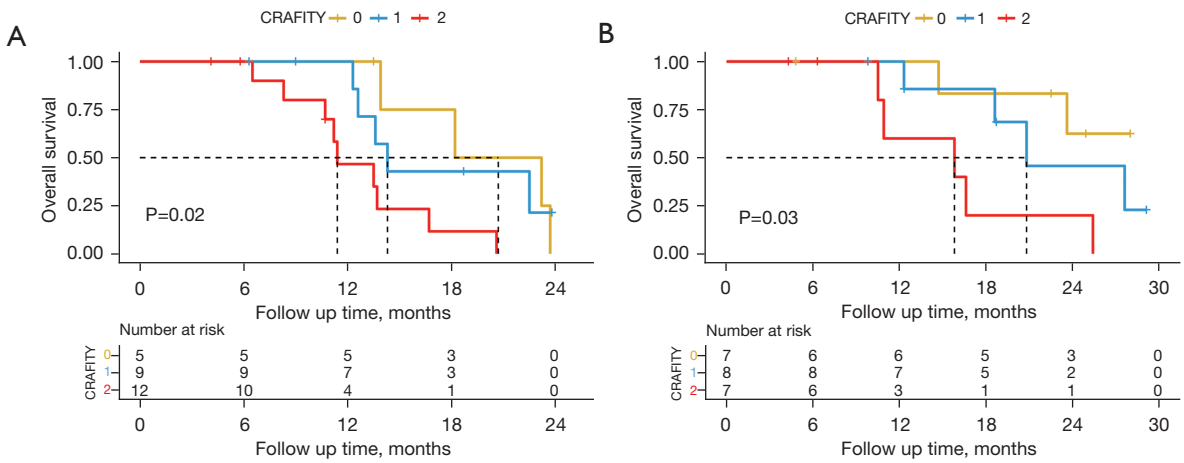

Figure 3 Survival curves for CRAFITY score in the regorafenib and regorafenib + ICI groups. (A) Comparison of survival curves of patients with different CRAFITY scores in the regorafenib group (P=0.02). (B) Comparison of survival curves of patients with different CRAFITY score in the regorafenib + ICI group (P=0.03). CRAFITY, CRP and AFP in Immunotherapy; ICI, immune checkpoint inhibitor; CRP, C-reaction protein; AFP, alpha-fetoprotein.

the existing treatment sequence. Our retrospective study evaluated the safety and efficacy of regorafenib as a first-line agent alone or in combination with ICIs in patients with advanced HCC. Sorafenib, has been shown to inhibit HCC proliferation and invasive ability (23) and is approved for first-line treatment of advanced disease (24). Compared to sorafenib, regorafenib possesses higher biological activity than the former and has more targets of action, inhibiting kinases associated with angiogenesis and tumorigenesis (25), such as vascular endothelial growth factor receptor VEGFR1-3, tyrosine-protein kinase receptors TIE and Ret, platelet-derived growth factor receptor PDGFR-β, basic fibroblast growth factor receptor FGFR-1/2, serine/threonine protein kinase Raf, and mitogen-activated protein kinase p38, thereby exerting antitumor effects (26-28). In addition, regorafenib can improve the tumor microenvironment; for example, regorafenib regulates macrophages and increases the proliferation and activation of $CD8^+$ T cells to enhance antitumor immunity, and it can inhibit signal transduction and the STAT3 signaling

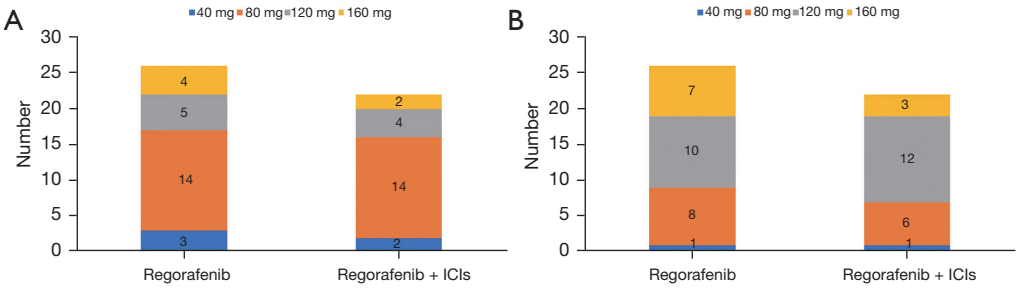

Figure 4 Distribution of the initial daily stable dose* (A) and final daily stable dose (B) of the 26 patients in the regorafenib group and the 22 patients in the regorafenib + ICI group. *, stable daily dosing was defined as maintaining the same dose for at least one whole treatment cycle (28 days), and if the patient's stable daily dose varied between treatment cycles, the initial stable daily dose and the final stable daily dose were both counted. The initial dose of regorafenib was 160 mg in all 48 patients. ICI, immune checkpoint inhibitor.

Table 3 Treatment-related adverse events according to CTC

Adverse event	All grades		Grade III/IV	
	Regorafenib	Regorafenib + ICIs	Regorafenib	Regorafenib + ICIs
Hand-foot skin reaction	6 (23%)	5 (23%)	1(4%)	0
Anorexia	3 (12%)	4 (18%)	0	0
Nausea	2 (8%)	3 (14%)	0	0
Diarrhea	4 (15%)	1 (5%)	0	0
Hypertension	2 (8%)	0	0	0
Fatigue	2 (8%)	5 (23%)	0	0
Neutropenia	1 (4%)	1 (5%)	0	0
Thrombocytopenia	2 (8%)	2 (9%)	0	0
Rash	5 (19%)	4 (18%)	0	0

ICI, immune checkpoint inhibitor; CTC, common terminology criteria.

pathway by increasing the cytolytic activity of NK cells, which eventually leads to apoptosis of HCC cells (29-31). Compared with lenvatinib, also an approved first-line drug for advanced HCC (32), regorafenib improves tumor immune microenvironment-related pathways through its targets TIE2, CSF1R and RAF to achieve immune enhancement and antitumor cell proliferation (33).

In this retrospective cohort study, we found a mPFS of 5.9 months in the monotherapy group and 7.8 months in the combination group, which compare favorably with the 2.8 months reported in patients with advanced HCC treated with first-line sorafenib in Asian patients (34,35). In addition, the mOS was almost twice as long in the combination group as in the monotherapy group (13.9 *vs.* 23.6 months), suggesting that ICI may act synergistically with regorafenib and warranting confirmation in a prospective randomized trial. We could reproduce the strong prognostic value of the CRAFITY score (22) and of hand/foot skin reactions developing during treatment (13).

Dose-response analyses suggested that a stable dose of 160 mg or regorafenib provides optimal efficacy, if tolerated. Hand/foot skin reactions are the most common side effect caused by TKI's targeting vascular endothelial growth factor receptor (VEGFR) (36).

Although our study design did not directly compare regorafenib with standard of care (Lenvatinib or Atezolizumab/bevacizumab), we made indirect comparisons through a literature review and available clinical trial data. We found that while Lenvatinib and Atezolizumab/bevacizumab have been shown to be effective first-line

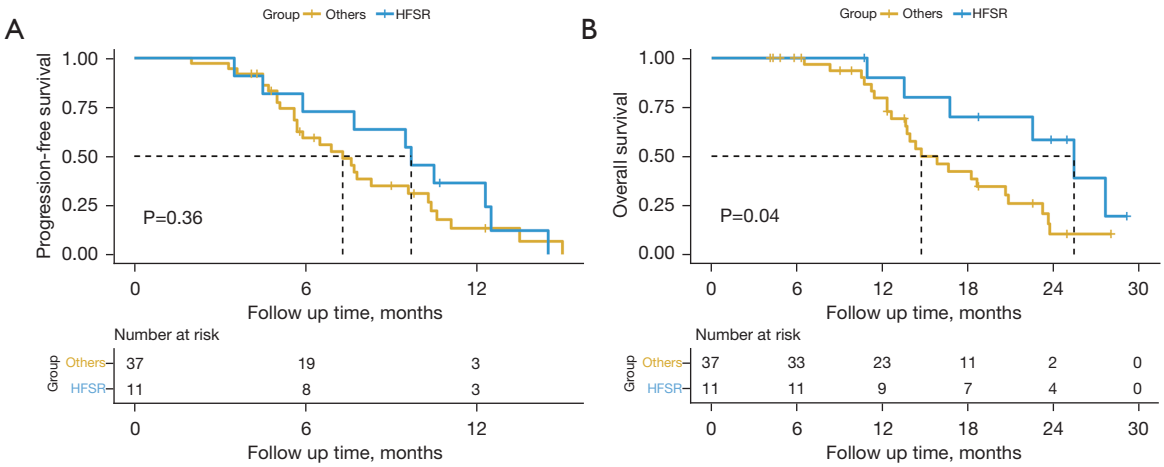

Figure 5 Comparison of survival curves of patients with and without hand/foot skin reactions. (A) Comparison of PFS survival curves (P=0.36). (B) Comparison of OS survival curves (P=0.04). PFS, progression-free survival; OS, overall survival; HFSR, hand/foot skin reactions.

treatment options, regorafenib may offer additional therapeutic advantages in certain patient populations, particularly in those who are resistant or intolerant to standard therapy (37). There are limitations to this study. First, the sample size of this study is relatively small, reducing its statistical power. Second, this was a retrospective study with some confounding factors and biases, including probable underreporting of AEs, and future prospective studies applying fixed protocols are needed to validate the findings. Comparisons of results with those of RCTs should therefore be done with reservations.

Conclusions

In conclusion, this retrospective, real-world study showed that regorafenib as a first-line agent alone or in combination with ICIs is active and seems to have a favorable safety profile. As the mOS of patients treated with regorafenib and ICI in combination was almost two years and approx. twice as long as compared to the monotherapy group, and the registered toxicity mild, further studies of the combination for first-line treatment of advanced HCC seems warranted.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-315/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-315/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-315/coif). M.L. reports research funding by Scandion Oncology A/S, Denmark. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Science and Technology Ethics Committee of Tianjin First Central Hospital (No. 2023DZX08) and informed consent was taken from all the patients.

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