Original Article

A multi-center retrospective study on the efficacy and safety of regorafenib *vs.* regorafenib combined with PD-1 inhibitors as a second-line therapy in patients with advanced hepatocellular carcinoma

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Background: At present, there are no definitive optimal treatment options for patients with hepatocellular carcinoma (HCC) following first-line treatment failure. To maximize the survival benefit of patients, we compared the combination therapy of regorafenib and programmed death-1 (PD-1) inhibitors with regorafenib monotherapy as a second-line treatment for patients with advanced HCC.

Methods: Our multicenter retrospective study evaluated consecutive patients with advanced HCC who received regorafenib plus PD-1 inhibitors or regorafenib alone as a later-line therapy from May 2019 to January 2022. The primary endpoint was progression-free survival (PFS), and the secondary endpoints included the objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety. Efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, and safety was assessed by Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Results: A total of 133 patients were included in the study (regardless of first-line treatment), including 94 who received regorafenib plus PD-1 inhibitors and 39 who received regorafenib. The regorafenib plus PD-1 inhibitors group had a significantly higher ORR (25.53% *vs.* 10.26%, P=0.015), higher DCR (87.23% *vs.* 66.67%, P=0.006), and longer PFS (median 9.0 *vs.* 4.0 months, P<0.0001) than the regorafenib group. Meanwhile, the median OS (mOS) did not differ between the regorafenib plus PD-1 and regorafenib monotherapy groups {mOS, 14.0 months [95% confidence interval (CI), 14.0–16.0 months] *vs.* 12.0 months (95% CI, 10.0–22.0 months)}. There was no notable difference in the total incidence of treatment-related adverse effects (TRAEs) (71.79% *vs.* 78.72%, P=0.39) and the incidence of grade 3/4 serious adverse effects (5.13% *vs.* 18.09%, P=0.19) between the regorafenib monotherapy group and PD-1 inhibitors combination group.

Conclusions: Compared with regorafenib alone, regorafenib combined with PD-1 inhibitors therapy increased PFS, ORR but did not improve OS, and can be used an option in second-line HCC therapy, regardless of first-line treatments. Regorafenib combined with PD-1 inhibitors is recommended as early as a second-line therapy to benefit patients. The combination regimen was as safe as regorafenib monotherapy for treatment of HCC in patients with compensated liver disease [Child-Turcotte-Pugh (CTP) A/B].

Keywords: Efficacy; safety; regorafenib; hepatocellular carcinoma (HCC)

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Introduction

Primary liver cancer is among the most common malignant tumors worldwide, and China accounts for about 50% of all new HCC cases and deaths every year. Among them, hepatocellular carcinoma (HCC) is the main pathological type of primary liver cancer, accounting for about 85–90% (1). Due to its insidious onset, various malignant potential, and ease of distant metastasis, patients often present with advance tumor stage at the time of diagnosis. For these patients, the opportunity for radical surgery has been missed (2), and systemic therapy is required to prolong their overall survival (OS).

In recent years, our understanding of immunotherapy for advanced HCC has grown dramatically and has changed the treatment paradigm (3). Immune checkpoint inhibitors (ICIs) are now well established as active agents for advanced-stage HCC (4). The combinations of atezolizumab and bevacizumab as well as programmed death-1 (PD-1) and tyrosine kinase inhibitors (TKIs) have become the preferred first-line treatment regimens for unresectable HCC (5,6). The IMbrave150 trial shows that combination therapy was superior to sorafenib in terms of the co-primary endpoints, OS and progression-free survival (PFS) [median OS (mOS), 19.2 *vs.* 13.4 months; median PFS (mPFS), 6.8 *vs.* 4.3 months] (7). KEYNOTE-524, a phase I clinical study of pembrolizumab combined with lenvatinib as a first-line treatment for HCC reported an objective response rate (ORR) of 36.0%, a median disease control rate (mDCR) of 12.6 months, a mPFS of 8.6 months, and a mOS as high as 20.4 months (8). Based on these results, considerable changes were made in the 2022 National Comprehensive Cancer Network (NCCN) guidelines for HCC, namely, ICI combination therapy has become the prioritized and preferred regimen for the first-line treatment of HCC. Furthermore, China's 2022 *Guidelines for the diagnosis and treatment of primary liver cancer* have also changed significantly (9). Compared to the NCCN guidelines, the Chinese guidelines have added one Chinese domestic PD-1 antibody and antiangiogenic combination regimen, and one domestically-developed small molecular TKI agent—donafenib—as the first-line HCC treatment. However, the biggest difference between the two guidelines is that the Chinese guidelines present some reference comments for TKIs, chemotherapeutic agents combine with ICIs regimens, as well as cytotoxic T-lymphocyte-associated protein 4 (CTLA4) inhibitor plus PD-1/programmed cell death ligand 1 (PD-L1) inhibitor combination regimens (9), providing additional treatment options for physicians and patients. ICI monotherapy has also been proposed as a first-line treatment option under certain circumstances, emphasizing that systemic HCC therapy has entered the immunotherapy era (10).

Up to now, regorafenib monotherapy has been recommended by many guidelines as a second-line

Highlight box

Key findings

- Regorafenib combined with PD-1 inhibitors is recommended as early as a second-line therapy to benefit patients.

What is known and what is new?

- Targeted therapy combined immunotherapy is an important treatment for advanced HCC.
- Compared with regorafenib alone, regorafenib combined with PD-1 inhibitors therapy increased PFS, ORR. The combination regimen was as safe as regorafenib monotherapy for treatment of HCC in patients with compensated liver disease.

What is the implication, and what should change now?

- Regorafenib plus PD-1 inhibitors could be used as a preferable second-line therapy regimen for HCC following several kinds of first-line treatment failure.

treatment; as far as systemic therapy is concerned, patients with HCC who have progressed in first-line treatment are currently the first choice for sequential treatment with regorafenib. However, its actual effect cannot meet clinical expectations (11) as it can only improve OS inferiority compared to other treatment options (12). In real-world clinical practice, regorafenib combined with PD-1 is increasingly being used in the second-line treatment of advanced HCC, but it remains uncertain if it is more effective and provides improved outcomes compared with regorafenib alone. Moreover, the relative safety of these treatment options has not yet been elucidated. At present, relevant reports have only included a limited number of cases from single centers (13) and, thus, further investigation is needed. Therefore, we conducted this multicenter retrospective study to compare the efficacy and safety of regorafenib monotherapy and regorafenib combined with PD-1 inhibitors as a later-line therapy in patients with advanced HCC to provide a more comprehensive evidence-based reference. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6614/rc).

Methods

Study design and patients

This study retrospectively assessed patients with advanced HCC who were treated with regorafenib plus PD-1 or regorafenib as second-line therapy between May 2019 and January 2022 at five independent medical institutions (The Fifth Medical Center of the PLA General Hospital, Beijing, China; Department of Tumor Intervention, Beijing Ditan Hospital, Capital Medical University, Beijing, China; Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Department of Liver Surgery, Peking Union Medical College Hospital, Beijing, China; Department of Intervention Therapy, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China) across China. After detailed discussions, the research group developed the following patient inclusion criteria: (I) aged between 18 and 75 years old; (II) have received TKIs alone or TKI combined with PD-1 and a candidate for regorafenib or regorafenib plus PD-1; (III) received systemic treatment for more than 8 weeks; (IV) liver function scored as Child-Pugh class A or B, (V) have at least one measurable tumor [according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria]; (VI) HCC diagnosis according to the China's 2022 *Guidelines for the diagnosis and treatment of primary liver cancer* (9); and (VII) complete imaging computed tomography (CT)/magnetic resonance imaging (MRI) and laboratory data examination indicators from the initial treatment until death or the study censor time (22 May 2022). The exclusion criteria were as follows: (I) a history of other malignant tumors in the past 5 years; (II) Child-Pugh score >8 points; (III) received other experimental drugs or medical apparatus/instruments within the past 4 weeks; (IV) underwent surgery within 4 weeks; (V) abdominal surgical complications (fistula, abscess) or gastrointestinal perforation within the past 4 weeks; (VI) active bleeding within the past 4 weeks; (VII) incomplete follow-up or lost to follow-up. The study protocol was approved by the China Ethics Committee of Registering Clinical Trials (No. ChiECRCT20210376). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

Study procedures

Treatment protocol: the choice of regorafenib alone or regorafenib plus PD-1 inhibitors was dependent on the following factors: the guidelines recommended at the time, the drug supply at each medical institution, and the patient's condition and economic status. An oral regorafenib dose of 80–160 mg/day, once/day, was administered. Also, the PD-1 inhibitors were not limited to certain brands, and the dosage was set according to the manufacturer's instructions, once every 3 weeks. If grade III treatment-related adverse events (TRAEs) occurred, symptomatic treatment was given and the duration of medication was held. If grade IV TRAEs occurred, the drug was discontinued immediately, and the medication could be resumed after symptomatic treatment, which lasted until the TRAEs fell below grade III. The drug was permanently discontinued if grade IV TRAEs recurred.

The following baseline characteristics were collected for each patient: age, surgery, ablation, intervention, radiation, first-line therapy, cirrhosis, Eastern Cooperative Oncology Group (ECOG) performance status, metastatic sites, and amount of ascites.

Follow-up and assessment

Patients were followed up every 3–6 weeks after receiving

second-line therapy. The follow-up included a detailed medical history, physical examination, contrast-enhanced CT or MRI of the upper abdomen and plain chest CT scan, and laboratory tests (complete blood count, prothrombin time, alpha-fetoprotein, aspartate aminotransferase, alanine aminotransferase, total bilirubin, serum albumin, alkaline phosphatase, and creatinine). The therapeutic response was evaluated according to the modified RECIST guidelines (14).

Outcomes

The present study aimed to evaluate the short-term efficacy of the later-line treatment regimens, and thus, we selected PFS as the primary endpoint. The secondary endpoints were OS, tumor ORR, DCR, and safety analysis (including the overall incidence of adverse reactions, the incidence of grade 3/4 adverse reactions, the types of adverse reactions, etc.). Adverse reactions were graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

After 8–12 weeks of treatment, efficacy and treatment-related adverse reactions evaluations were performed. Response rate was evaluated according to the RECIST v1.1 criteria (11). Two radiologists with more than 15 years of experience respectively measured the axial image data. Complete response (CR) was defined as tumor arterial phase enhancement on imaging, partial response (PR) was defined as the sum of the diameters of the tumor arterial phase enhanced imaging reduced by ≥30%, stable disease (SD) was defined as tumor arterial phase enhanced imaging shrinkage that does not reach PR or enlargement that does not reach PD, and progressive disease (PD), was defined as a ≥20% increase in the sum of the diameters of the contrast-enhanced sections of the tumor during the arterial phase or the appearance of new lesions.

Statistical methods

Continuous variables were expressed as the mean ± interquartile range (IQR), and categorical variables were expressed as percentages. The chi-square test was used for categorical variables, and analysis of variance (ANOVA) or the Kruskal-Wallis test was applied for continuous variables. The Kaplan-Meier method and log-rank test were used to analyze survival between the four groups of patients. A P value of <0.05 was considered statistically significant. R software for Windows (version 3.6.3; https://www.r-project.org/) was used for all statistical analyses.

Results

Patient characteristics

A total of 223 patients who received regorafenib plus PD-1 and 159 patients who received regorafenib alone were screened. A total of 94 patients in the regorafenib plus PD-1 group and 39 patients in the regorafenib monotherapy group were included in the final analytic cohort (*Figure 1*). A total of 133 of these subjects (94.3%) completed the follow-up.

The baseline clinicopathological characteristics of the included patients in each group are depicted in *Table 1*. The composition of both groups was similar and included 30.85% of patients in the regorafenib plus PD-1 inhibitors group and 30.77% in the regorafenib group with Child-Pugh B liver disease, respectively. Overall, 42.55% of patients in the regorafenib plus PD-1 inhibitors group and 84.62% in the regorafenib group had received TKIs as the first-line treatment (P=0.79).

There were no significant differences in the baseline clinical characteristics of the two groups, except for the composition of first-line therapy. Furthermore, we performed detailed subgroup analyses on primary and secondary outcomes, and also summarized the status of first-line therapy in each group (*Table 1*).

Overall therapeutic outcomes

The censor date for this study was 05/21/2020. The mPFS was 4.0 months [95% confidence interval (CI), 3.6–4.7 months] in the regorafenib group and 9.0 months (95% CI, 7.5–15.7 months) in the regorafenib plus PD-1 inhibitors group (P<0.0001) (*Figure 2*). However, mOS did not differ between the regorafenib and regorafenib plus PD-1 groups [mOS, 12.0 months (95% CI, 10.0–22.0 months) *vs.* 14.0 months (95% CI, 14.0–16.0 months), P=0.32] (*Figure 3*). Moreover, we simultaneously performed subgroup analyses of survival by Barcelona Clinic Liver Cancer (BCLC), Child-Pugh score, and age. We observed significant differences in OS between the regorafenib and regorafenib plus PD-1 inhibitors groups in patients with BCLC-C stage, Child-Pugh B class, and age <50 years old (Figures S1-S3).

Subgroup analysis

In the subgroup analysis of patients who had received

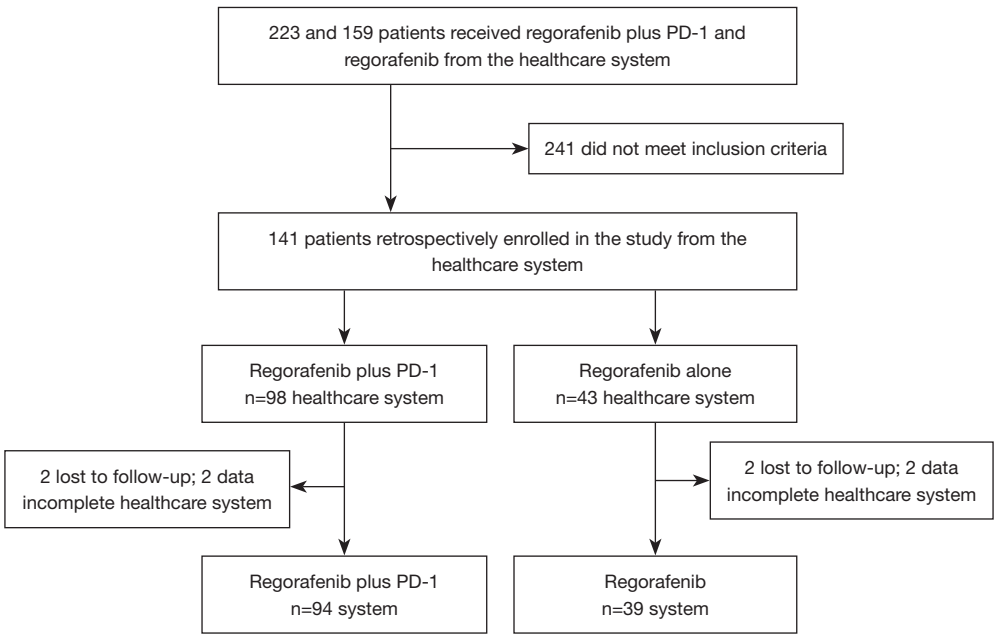

Figure 1 Patient selection flowchart. PD-1, programmed death-1.

first-line treatment according to the TKI strategy, the PFS still exhibited a highly significant difference between the two groups (P=0.0018) (*Figure 4*): the mPFS was 4.0 months (95% CI, 3.6–6.8 months) in the regorafenib group and 10.0 months (95% CI, 7.2–32.4 months) in the combination group. As for efficacy outcomes, the ORR in the combination group was 37.50% compared to that of 12.12% observed in the monotherapy group (P=0.014). Moreover, the DCR in the combination group reached 92.50% and was higher than that in the monotherapy group (92.50% *vs.* 69.70%, P=0.011) (*Table 2*).

In the subgroup of patients who received first-line treatment according to the TKI plus ICIs strategy, the PFS was still significantly different between the two groups (*Figure 5*): the mPFS was 3.4 months (95% CI, 2.0–5.8 months) in the monotherapy group and 8.8 months (95% CI, 7.1–12.4 months) in the combination group (P<0.01). Also, the ORR in the combination group was 16.67%, which was dramatically higher than the ORR of 0.00% observed in the monotherapy group (P=0.278). Furthermore, the DCR in the combination group reached 83.33% and was also higher than that in the monotherapy group (83.33% *vs.* 50.00%, P=0.001) (*Table 2*). The details of first-line therapy are shown in Table S1.

Safety profiles

During the follow-up period, all TRAEs could be alleviated to below grade II after symptomatic treatment and delayed administration, and no fatalities were observed. There were no significant differences in the total incidence of TRAEs or the incidence of grade 3/4 serious adverse reactions between the two groups, as shown in *Table 3*.

For the regorafenib group, the common TRAEs of any grade included hand-foot syndrome (HFS) (n=11, 28.21%), fatigue (n=7, 20.69%), and diarrhea (n=4, 10.26%). Conversely, in the regorafenib plus ICIs group, the common TRAEs of any grade were HFS (n=24, 25.53%), pain (n=13, 13.83%), and fatigue (n=10, 10.64%). The incidence of any treatment-related grade 3 or higher AE was low in both groups. The overall incidence of AEs was similar between the regorafenib and regorafenib plus ICIs groups (any grade: 71.79% *vs.* 78.72%, P=0.39; grade 3/4: 5.13% *vs.* 18.09%, P=0.19). Moreover, the overall incidence of AEs showed no significant difference between the Child-Pugh A and B groups (any grade: 80.00% *vs.* 75.86%, P=0.09; grade 3/4: 9.23% *vs.* 34.48%, P=0.12) (Table S2).

Table 1 Baseline characteristics of the included HCC patients

Characteristics	Regorafenib (n=39)	Regorafenib plus ICIs (n=94)	P value
Age (years), median [IQR]	58.00 [51.50, 63.00]	55.50 [48.00, 62.75]	0.66
Sex, n (%)			0.81
Female	5 (12.82)	9 (9.57)	
Male	34 (87.18)	85 (90.43)	
Surgery, n (%)			0.29
No	23 (58.97)	66 (70.21)	
Yes	16 (41.03)	28 (29.79)	
Ablation, n (%)			0.71
No	22 (56.41)	58 (61.70)	
Yes	17 (43.59)	36 (38.30)	
Intervention, n (%)			0.47
No	9 (23.08)	15 (15.96)	
Yes	30 (76.92)	79 (84.04)	
Radiation, n (%)			0.87
No	24 (61.54)	61 (64.89)	
Yes	15 (38.46)	33 (35.11)	
First-line therapy, n (%)			0.79
TKI monotherapy	33 (84.62)	40 (42.55)	
TKI plus ICIs	6 (15.38)	54 (57.45)	
Cirrhosis, n (%)			0.61
No	7 (17.95)	12 (12.77)	
Yes	32 (82.05)	82 (87.23)	
ECOG, n (%)			0.92
0	16 (41.03)	37 (39.36)	
1	21 (53.85)	52 (55.32)	
2	2 (5.13)	4 (4.26)	
3	0 (0.00)	1 (1.06)	
Ascites, n (%)			0.08
No	23 (58.97)	38 (40.43)	
Yes	16 (41.03)	56 (59.57)	
Total bilirubin (μmol/L), median [IQR]	17.20 [12.45, 25.65]	15.00 [11.93, 20.58]	0.26
Albumin (g/L), median [IQR]	36.00 [34.00, 38.00]	36.00 [33.00, 39.00]	0.89
ALBI score, median [IQR]	−2.26 [−2.45, −2.03]	−2.30 [−2.64, −1.97]	0.63
ALBI grade, n (%)			0.45
1	7 (17.95)	25 (26.60)	
2	29 (74.36)	65 (69.15)	
3	3 (7.69)	4 (4.26)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Regorafenib (n=39)	Regorafenib plus ICIs (n=94)	P value
Child-Pugh, n (%)			>0.99
A	27 (69.23)	65 (69.15)	
B	12 (30.77)	29 (30.85)	
Child-Pugh score, n (%)			0.60
5	14 (35.90)	27 (28.72)	
6	13 (33.33)	38 (40.43)	
7	6 (15.38)	20 (21.28)	
8	5 (12.82)	6 (6.38)	
9	1 (2.56)	3 (3.19)	
AFP (ng/mL), median [IQR]	151.20 [4.70, 1,206.00]	138.90 [6.92, 1,857.00]	0.55
Lymph node metastasis, n (%)			0.85
No	29 (74.36)	73 (77.66)	
Yes	10 (25.64)	21 (22.34)	
Extrahepatic metastasis, n (%)			0.63
No	17 (43.59)	47 (50.00)	
Yes	22 (56.41)	47 (50.00)	
Tumor thrombus, n (%)			0.36
No	24 (61.54)	48 (51.06)	
Yes	15 (38.46)	46 (48.94)	
BCLC stage, n (%)			0.46
A	3 (7.69)	3 (3.19)	
B	5 (12.82)	16 (17.02)	
C	31 (79.49)	75 (79.79)	

HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; IQR, interquartile range; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

Discussion

To our knowledge, this was the largest cohort study to date evaluating the efficacy and safety of regorafenib combined with PD-1 inhibitors *vs.* regorafenib monotherapy. Our study showed that regorafenib combined with PD-1 has a similar safety profile and superior efficacy to regorafenib alone. Previous studies have reported a higher efficacy of regorafenib combined with immunotherapy compared to a regorafenib monotherapy regimen in patients with advanced disease. However, these studies were typically case reports and only analyzed specific immune drugs combined with regorafenib, and thus, have important limitations in terms of their application and reliability (15-17).

Although the PD-1 inhibitor combination therapy has promoted the short-term efficacy of treatment in HCC patients, most patients will experience tumor progression and will need to alter their anticancer regimen given the average PFS of 6–9 months (3). As for second-line therapy, both the NCCN and Chinese guidelines similarly propose that almost all of the high-quality evidence-based drug/regimen recommendations, such as regorafenib, cabozantinib, ramucirumab, apatinib, pembrolizumab, tislelizumab, etc., are based on first-line monotherapy; that is, either TKI or chemotherapy treatment, with no immunotherapy. However, given the rapid introduction of first-line systemic HCC treatment

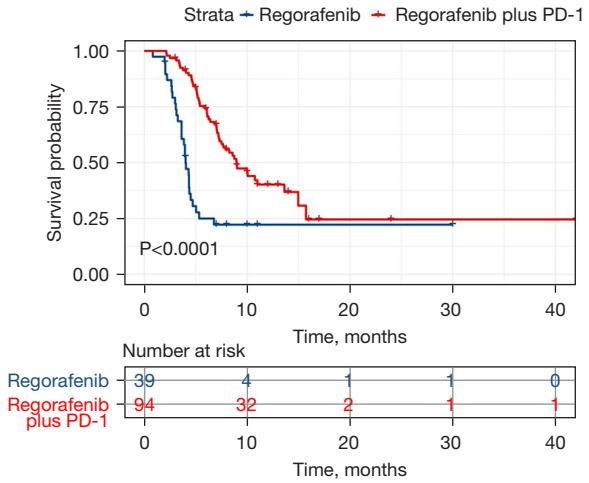

Figure 2 Comparison of PFS between the regorafenib and regorafenib plus PD-1 groups. PD-1, programmed death-1; PFS, progression-free survival.

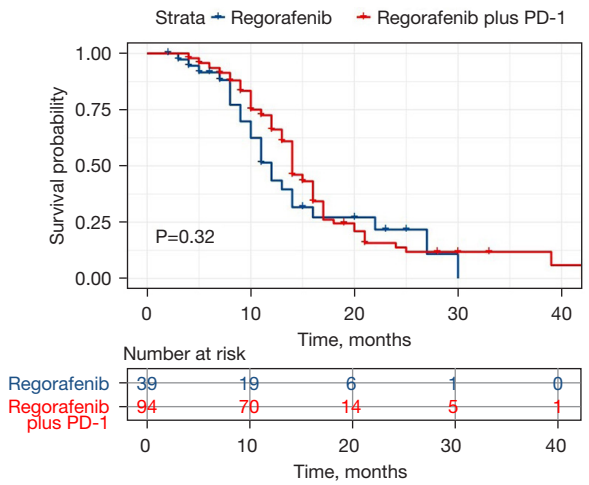

Figure 3 OS comparison between the regorafenib and regorafenib plus PD-1 groups. PD-1, programmed death-1; OS, overall survival.

into the era of immunologic combination therapy, later-line HCC treatment needs to be changed accordingly. As for the former single TKI first-line treatment, there are questions regarding whether PD-1 can be used in addition to the TKI switch-over strategy, as well as which of the approaches is superior. As for the first-line PD-1 combination therapy, questions surrounding how to design a second-line treatment regimen need to be answered. Potential options are changing the TKI or PD-1 or altering

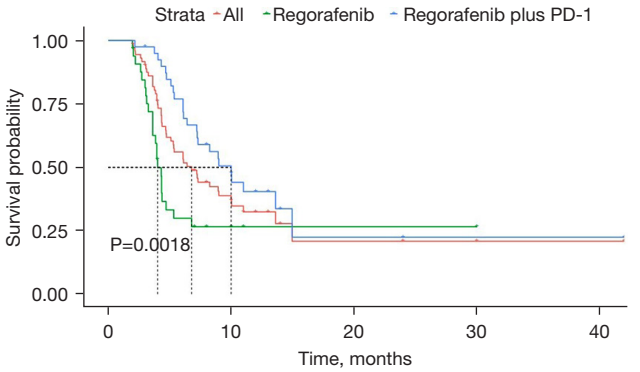

Figure 4 PFS comparison between the regorafenib and regorafenib plus PD-1 groups using first-line TKI treatment. PD-1, programmed death-1; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

both, switching to other kinds of PD-1 combination. It needs to be explored whether there is a universal second-line regimen that can be utilized for all kinds of first-line treatment failure in HCC patients or dependent on the previous first line treatment.

In the subgroup analysis of patients who received previous treatment according to the TKI strategy, the PFS still showed very significant differences between the two groups: the mPFS was 4.0 months in the regorafenib group and 10.0 months in the regorafenib plus PD-1 inhibitors group. Also, in the subgroup of patients who received previous treatment based on the TKI plus PD-1 inhibitors strategy, the PFS was still markedly different between the two groups: the mPFS was 3.4 months in the regorafenib group and 8.8 months in the regorafenib plus PD-1 group. In the context of advocating precision therapy, the second-line therapy of HCC patients who have failed first-line therapy is characterized by significant differences in their subsequent line treatment approaches. The regorafenib combined with PD-1 regimen not only has advantages over the regorafenib monotherapy regimen but also has a wide range of applications and is not constrained by previous first-line therapies. Moreover, the ORR and PFS of the regorafenib combined with PD-1 inhibitors regimen in our study were not only significantly higher than the second-line regorafenib regimens employed in a previous study (18), but were also higher than those reported in a second-line immunotherapy regimens study (19). To maximize the survival benefits of patients, it is recommended that regorafenib combined with PD-1 should be used as early as second-line for HCC patients who have failed first-line

Table 2 Best tumor responses in the total cohort and the subgroups

Investigator review	Total cohort			Former treatment with TKI regimens			Former treatment with TKI plus ICIs regimens		
	Reg (n=39)	Reg plus ICIs (n=94)	P value	Reg (n=33)	Reg plus ICIs (n=40)	P value	Reg (n=6)	Reg plus ICIs (n=54)	P value
CR	3 (7.69)	2 (2.13)	–	3 (9.10)	1 (0.03)	–	0 (0.00)	1 (1.85)	–
PR	1 (2.56)	22 (23.40)	–	1 (3.03)	14 (35.00)	–	0 (0.00)	8 (14.81)	–
SD	22 (56.41)	58 (61.70)	–	19 (57.58)	22 (55.00)	–	3 (50.00)	36 (66.67)	–
PD	13 (33.33)	12 (12.77)	–	10 (30.30)	3 (7.50)	–	3 (50.00)	9 (16.67)	–
ORR	4 (10.26)	24 (25.53)	0.015	4 (12.12)	15 (37.50)	0.014	0 (0.00)	9 (16.67)	0.278
DCR	26 (66.67)	82 (87.23)	0.006	23 (69.70)	37 (92.50)	0.011	3 (50.00)	45 (83.33)	0.001

Data are presented as n (%). TKI, tyrosine kinase inhibitor; ICIs, immune checkpoint inhibitors; Reg, regorafenib; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

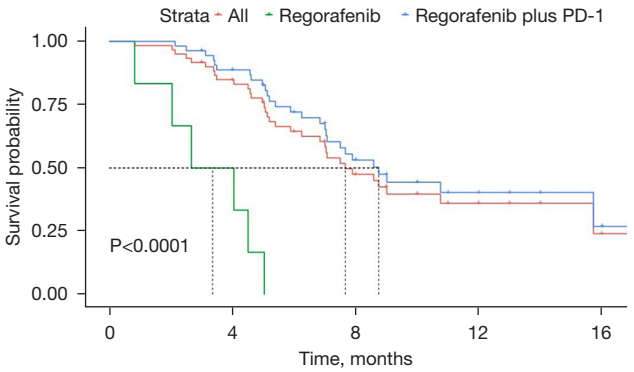

Figure 5 PFS comparison between the regorafenib and regorafenib plus PD-1 groups using first-line TKI plus PD-1 treatment. PD-1, programmed death-1; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

therapy.

Our results showed potential mechanisms of favorable results include immune potentiation, which has been shown to include inhibiting vascular endothelial growth factor receptor (VEGFR)1/2/3, platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR)1/2 anti-angiogenesis targets (20); inhibiting the colony stimulating factor 1 receptor (CSF-1R) target, which can exert an anti-immunosuppressive effect; and by blocking various protein kinases and inhibiting proto-oncogene receptor tyrosine kinase (KIT), rheumatoid arthritis factor (RAF), and other targets that play an important role in cell proliferation and anti-tumor cell proliferation, etc. (21).

The mOS in the regorafenib group was 12.0 months,

Table 3 TRAEs

AEs	Regorafenib (n=39)	Regorafenib plus ICIs (n=94)	P value
All grades			
HFS	11 (28.21)	24 (25.53)	0.75
Hair loss	0 (0.00)	2 (2.13)	0.36
Pain	1 (3.45)	13 (13.83)	0.05
Fatigue	7 (20.69)	10 (10.64)	0.25
Hypertension	2 (3.45)	8 (8.51)	0.50
Bleeding gums	1 (2.56)	2 (2.13)	0.88
Loss of appetite	3 (7.69)	5 (5.32)	0.60
Diarrhea	4 (10.26)	9 (9.57)	0.90
Fever	1 (2.56)	3 (3.19)	0.85
Rash	1 (2.56)	0 (0.00)	0.12
Elevated bilirubin	0 (0.00)	4 (4.26)	0.19
Elevated transaminases	0 (0.00)	1 (1.06)	0.52
Hypothyroidism	0 (0.00)	1 (1.06)	0.52
Overall incidence	28 (71.79)	74 (78.72)	0.39
Grade 3/4			
HFS	0 (0.00)	5 (6.94)	0.14
Diarrhea	1 (3.45)	3 (1.39)	0.85
Hypothyroidism	1 (0.00)	3 (4.17)	0.85
Hypertension	0 (0.00)	3 (4.17)	0.26
Elevated transaminases	0 (0.00)	1 (1.39)	0.52
Elevated bilirubin	0 (0.00)	1 (1.39)	0.52
Pain	0 (0.00)	3 (1.39)	0.26
Overall incidence	2 (5.13)	12 (18.09)	0.19

Data are presented as n (%). No treatment-related deaths occurred. TRAEs, treatment-related adverse events; AEs, adverse events; ICIs, immune checkpoint inhibitors; HFS, hand-foot syndrome.

which was consistent with the mOS of 10.3–12.1 months for second-line regorafenib treatment reported by a previous study, indicating that although our study included Child-Pugh A and B patients, the results were stable and comparable (22). Moreover, we simultaneously performed subgroup analyses of survival by BCLC, Child-Pugh score, and age. We speculate that the different responses to immune drugs among patients with BCLC-C stage, Child-Pugh B class, and aged <50 years old may be due to differences in the immune status of HCC patients at different stages of disease development.

A retrospective study conducted by Huang *et al.* compared the efficacy of regorafenib and regorafenib plus sintilimab combination therapy in second-line HCC treatment, and their result demonstrated that the regorafenib-sintilimab group had a higher ORR (36.2% *vs.* 16.4%), a longer PFS (median 5.6 *vs.* 4.0 months), and a better OS (median 13.4 *vs.* 9.9 months) than the regorafenib group (23). Although their first-line treatments were all involved TKI monotherapy, they still achieved the same conclusion; that is, ICI combination therapy was a superior later-line treatment to TKI monotherapy.

In terms of treatment-related safety, the overall incidence of TRAEs in this study was similar to that reported in the RESORCE study (24). The number of grade 3/4 AEs in the combination group was only marginally higher than that in the single-drug group. There are two possible reasons for this: (I) the effect of PD-1 inhibitors; and (II) the number of cases in the combination group was significantly higher than that in the single-drug group. In the regorafenib plus anti-PD-1 subgroup, the incidence of TRAEs did not differ between the Child-Pugh A and B patients. Among the patients enrolled in this study, 69% were of Child-Pugh A grade and nearly 1/3 were Child-Pugh B grade (score <8), which indicated that regorafenib plus anti-PD-1 inhibitors treatment was safe and effective for HCC patients with more advanced liver disease.

Nevertheless, our study still has some limitations that should be noted. Firstly, retrospective studies cannot avoid selection bias in the treatment recommendations of medical personnel, which may also explain the superior effect of the target-free combined therapy in Child-Pugh B patients. Second, the timeline of study cases enrolled lasted for nearly 4 years, resulting in different treatment strategies at various periods. For instance, early-stage patients received first-line treatment mainly with TKI monotherapy, while later-stage patients were mainly treated with TKI plus PD-1 inhibitors, which resulted in an uneven number of patients in the two groups, and this imbalance was more obvious in the subgroup analysis. Third, since this was a retrospective study, we did not restrict the types of PD-1 inhibitors. Although the efficacy of PD-1 inhibitors from various manufacturers is currently considered to be similar, there are no direct cross-sectional comparisons, so we cannot exclude the possibility that differences between the PD-1 inhibitors affected the final results. Lastly, the sample size of this study was small. Prospective studies with larger sample sizes can obtain more precise differences in the clinical response rates. Also, extension of the follow-up period may lead to more meaningful results.

Conclusions

According to guideline recommendations, after standard first-line HCC treatment progress, most patients will receive regorafenib as a follow-up treatment. Our study indicated that regorafenib plus PD-1 inhibitors could be used as a preferable second-line therapy regimen for HCC following several kinds of first-line treatment failure, and provide patients with a superior ORR and PFS. It is also safe for patients with more advanced liver disease including those with Child-Pugh B.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6614/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6614/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6614/coif). TBC received honoraria from BMS and Bayer for advisory boards and lectures. 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 protocol was approved by the China Ethics Committee of Registering Clinical Trials (No. ChiECRCT20210376). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

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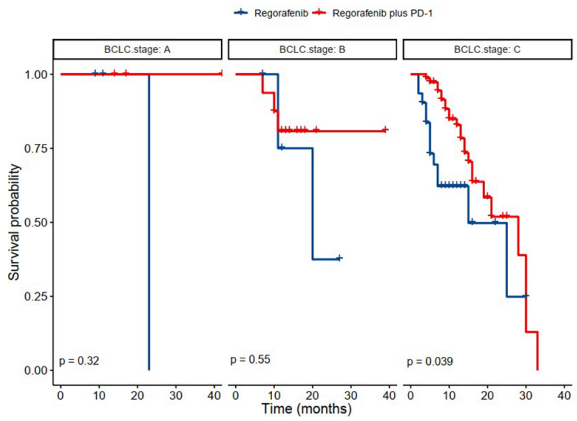

Figure S1 OS comparison between the regorafenib and regorafenib plus PD-1 groups in the BCLC subgroup. BCLC, Barcelona Clinic Liver Cancer; PD-1, programmed death-1; OS, overall survival.

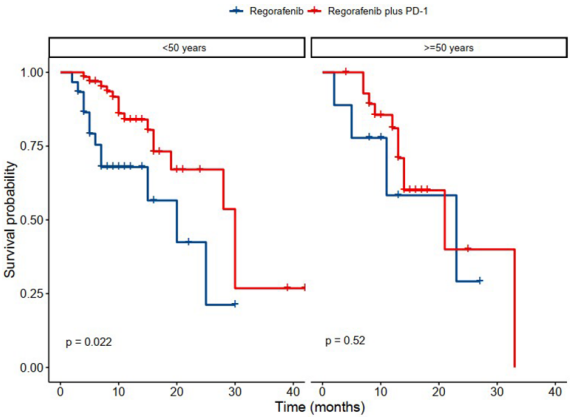

Figure S3 OS comparison between the regorafenib and regorafenib plus PD-1 groups in the age subgroup. PD-1, programmed death-1; OS, overall survival.

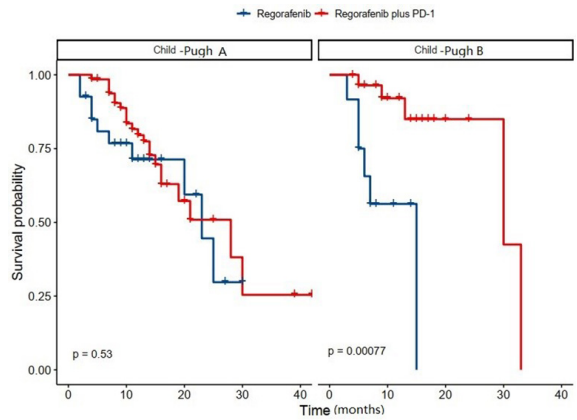

Figure S2 OS comparison between the regorafenib and regorafenib plus PD-1 groups in the Child-Pugh subgroup. PD-1, programmed death-1; OS, overall survival.

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Table S1 Characteristics of front line therapy

Drugs	Regorafenib (n=39)	Regorafenib plus ICIs (n=94)	P value
Anlotinib plus sintilimab	0 (0.0)	1 (1.1)	–
Apatinib & lenvatinib plus toripalimab	0 (0.0)	1 (1.1)	–
Apatinib plus carelizumab	0 (0.0)	1 (1.1)	–
Bevacizumab & erlotinib	0 (0.0)	1 (1.1)	–
Donafinil	0 (0.0)	1 (1.1)	0.50
Lenvatinib	11 (28.2)	14 (14.9)	0.88
Lenvatinib & sorafenib plus toripalimab	1 (2.6)	3 (3.2)	0.60
Lenvatinib plus carelizumab	1 (2.6)	4 (4.3)	0.90
Lenvatinib plus pembrolizumab	0 (0.0)	2 (2.1)	0.85
Lenvatinib plus sintilimab	2 (5.1)	30 (31.9)	0.12
Lenvatinib plus toripalimab	0 (0.0)	3 (3.2)	0.19
Sintlimab plus bevacizumab	2 (5.1)	1 (1.1)	0.52
Sorafenib & Lenvatinib	2 (5.1)	3 (3.2)	0.52
Sorafenib & Lenvatinib plus pembrolizumab	0 (0.0)	1 (1.1)	0.14
Sorafenib & Lenvatinib plus sintilimab	0 (0.0)	3 (3.2)	0.85
Sorafenib & Lenvatinib plus toripalimab	0 (0.0)	3 (3.2)	0.85
Sorafenib	20 (51.3)	22 (23.4)	0.26

Data are presented as n (%). ICIs, immune checkpoint inhibitors.

Table S2 Treatment-emergent AEs in regorafenib plus ICIs group

AEs	Child-Pugh A (n=65)	Child-Pugh B (n=29)	P value
All grades			
Overall incidence	52 (80.00)	22 (75.86)	0.09
Grade 3/4			
Overall incidence	6 (9.23)	6 (34.48)	0.12

Data are presented as n (%). No treatment-related deaths occurred. AEs, adverse events; ICIs, immune checkpoint inhibitors.

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