

Regorafenib Versus Nivolumab After Sorafenib Failure: Real-World Data in Patients With Hepatocellular Carcinoma

Won-Mook Choi ¹, Jonggi Choi ¹, Danbi Lee,¹ Ju Hyun Shim ¹, Young-Suk Lim ¹, Han Chu Lee,¹ Young-Hwa Chung,¹ Young-Sang Lee,¹ Sook Ryun Park,² Min-Hee Ryu,² Baek-Yeol Ryoo,² So Jung Lee,³ and Kang Mo Kim¹

Regorafenib and nivolumab are drugs approved for second-line treatment of patients with hepatocellular carcinoma (HCC) after sorafenib failure. However, the effectiveness of regorafenib and nivolumab following sorafenib has not been directly compared. This study retrospectively evaluated 373 patients with HCC who were treated with regorafenib (n = 223) or nivolumab (n = 150) after sorafenib failure between July 2017 and February 2019. Progression-free survival (PFS; hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.69-1.06; *P* = 0.150), time to progression (TTP; HR, 0.95; 95% CI, 0.77-1.19; *P* = 0.680), and overall survival (OS; HR, 0.83; 95% CI, 0.64-1.07; *P* = 0.154) did not differ significantly between groups of patients treated with regorafenib and nivolumab, findings consistently observed by multivariable-adjusted, propensity score-matched, and inverse probability treatment weighting (IPTW) analyses. However, the objective response rate was significantly higher in the nivolumab than in the regorafenib group (13.3% vs. 4.0%; *P* = 0.002). When the effectiveness of regorafenib and nivolumab was compared in nonprogressors to treatment, defined as patients who achieved complete response, partial response, or stable disease after first response evaluation, PFS (HR, 0.50; 95% CI, 0.33-0.75; *P* = 0.001), TTP (HR, 0.48; 95% CI, 0.31-0.73; *P* < 0.001), and OS (HR, 0.51; 95% CI, 0.31-0.87; *P* = 0.013) were significantly longer in the 59 nonprogressors to nivolumab than in the 104 nonprogressors to regorafenib, findings also observed by multivariable-adjusted and IPTW analyses. **Conclusion:** Survival outcomes in patients treated with regorafenib and nivolumab after sorafenib failure did not differ significantly. However, nivolumab may be more effective than regorafenib in nonprogressors. (*Hepatology Communications* 2020;4:1073-1086).

Hepatocellular carcinoma (HCC) is the most common type of liver cancer and the second most common cause of cancer deaths in Korea and worldwide, leading to nearly 745,000 deaths each year.^(1,2) Despite regular HCC surveillance in at-risk populations, many patients are newly diagnosed with advanced-stage disease, limiting the

feasibility of locoregional therapy, such as surgical resection, ablation, or transarterial chemoembolization.^(3,4) Systemic treatment is therefore the only feasible therapeutic option in patients unsuitable for locoregional treatment. Sorafenib, an oral multikinase inhibitor, has been the standard of care since 2007 when a phase III study of sorafenib in patients

Abbreviations: AFP, α -fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; DCB, durable clinical benefit; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; FDA, U.S. Food and Drug Administration; HCC, hepatocellular carcinoma; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IQR, interquartile range; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PS, propensity score; PIVKA-II, protein induced by vitamin K absence or antagonist-II; TTP, time to progression.

Received December 3, 2019; accepted April 2, 2020.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1523/supinfo.

© 2020 The Authors. *Hepatology Communications* published by Wiley Periodicals, Inc., on behalf of the American Association for the Study of Liver Diseases. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep4.1523

Potential conflict of interest: Dr. Lim consults for, advises, is on the speakers' bureau for, and received grants from Gilead. The other authors have nothing to report.

with advanced hepatocellular carcinoma (SHARP trial) demonstrated that median overall survival (OS) was significantly longer in the sorafenib than in the placebo group (10.7 months vs. 7.9 months; hazard ratio [HR], 0.69; $P < 0.001$). These results were validated in a trial in the Asia-Pacific region.^(5,6) Lenvatinib, a new oral multikinase inhibitor, was found to be noninferior to sorafenib in median OS and has become another first-line therapeutic option for patients with HCC.⁽⁷⁾

Two second-line agents, regorafenib and nivolumab, have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of HCC. Regorafenib, an oral multikinase inhibitor that blocks angiogenesis, oncogenesis, metastasis, and tumor immunity,^(8,9) was shown to significantly improve OS in the second-line setting following sorafenib and was approved by the FDA in April 2017 for second-line treatment of patients with HCC.⁽¹⁰⁾ Nivolumab, a programmed cell death protein-1 (PD-1) inhibitor that showed durable responses and enhanced long-term survival after sorafenib failure, was approved by the FDA as a second-line treatment for HCC in September 2017.⁽¹¹⁾ To our knowledge, however, no studies have compared the effectiveness of regorafenib and nivolumab after sorafenib failure in patients with HCC. The aim of this study was to compare the effectiveness of regorafenib and nivolumab as a second-line treatment after sorafenib failure in a real-world setting in patients with HCC.

Patients and Methods

STUDY POPULATION

The study cohort retrospectively evaluated 436 consecutive patients with HCC who received regorafenib

or nivolumab after sorafenib failure at Asan Medical Center from July 2017 to February 2019. The diagnosis of HCC was based on pathological confirmation or noninvasive assessment by dynamic computed tomography and/or magnetic resonance imaging.⁽¹²⁾ Patients were included if they had Barcelona Clinic Liver Cancer (BCLC) stage B or C disease with documented radiologic progression during sorafenib treatment,⁽³⁾ were not eligible for locoregional therapy, and had at least one measurable target lesion based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST).⁽¹³⁾ However, in this real-world clinical study, patients with Child-Pugh class B liver function or an Eastern Cooperative Oncology Group (ECOG) performance status of 2 were allowed. Patients were excluded if they had Child-Pugh class C liver function ($n = 7$); ECOG performance status >2 ($n = 1$); or had been followed up for less than 2 weeks ($n = 11$). In addition, 29 patients treated with regorafenib and 15 treated with nivolumab were excluded because they had participated in a clinical trial after sorafenib failure and received regorafenib or nivolumab as a third- or fourth-line treatment. After excluding these 63 patients from the source population, 373 patients were analyzed; 223 of these patients had been treated with regorafenib and 150 had been treated with nivolumab.

The decision to treat with regorafenib or nivolumab after sorafenib failure was made by medical experts based on each patient's clinical situation. Treatment with the recommended dosages of regorafenib (160 mg once daily for the first 3 weeks of each 4-week cycle) and nivolumab (3 mg/kg every 2 weeks) was continued until disease progression, severe adverse events, or death. Dosage was adjusted according to each patient's tolerability. Clinical information, including

ARTICLE INFORMATION:

From the ¹Department of Gastroenterology, Liver Center; ²Department of Oncology; ³Department of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Kang Mo Kim, M.D., Ph.D.
Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine
88 Olympic-ro 43-gil

Songpa-gu, Seoul 05505, Republic of Korea
E-mail: kimkm70@amc.seoul.kr
Tel.: +82-02-3010-5812

demographic characteristics, laboratory results, and clinical outcomes, was collected from electronic medical records. The patients in both groups generally underwent radiologic investigation every 2–3 months. Additional radiologic examinations were performed when clinically indicated.

The study protocol was approved by the Institutional Review Board of Asan Medical Center, which waived the requirement for patient informed consent owing to the retrospective nature of this study.

OUTCOMES

Oncological outcomes analyzed in the intention to treat population included progression-free survival (PFS), defined as the time from initiation of medication to progression or death due to any cause; time to progression (TTP), defined as the time from initiation of medication to radiologic or clinical progression; and OS, defined as the time from initiation of medication to death due to any cause. Other efficacy outcomes included objective response rate (ORR), defined as patients with complete or partial response; disease control rate (DCR), defined as patients with complete response, partial response, or stable disease; and durable clinical benefit (DCB), defined as patients with complete response, partial response, or stable disease maintained continuously for a minimum of 6 months, assessed by mRECIST.⁽¹³⁾ Safety outcomes included treatment-related severe adverse events that led to discontinuation of therapy, as recorded in patients' electronic medical records.

STATISTICAL ANALYSIS

Categorical variables were compared using Fisher's exact test or the chi-square test. Continuous variables were expressed as mean and SD or median and interquartile range (IQR) and were compared using unpaired two-tailed *t* tests. Survival curves for time-to-event outcomes were determined using the Kaplan-Meier method. HRs for survival outcomes and their 95% confidence interval (CIs) were calculated using a Cox proportional hazard model or a log normal accelerated failure time model, as appropriate. Univariate and multivariable logistic regression analyses were performed to evaluate the association between clinical variables and treatment response.

Propensity score (PS) matching and inverse probability treatment weighting (IPTW) analyses were performed to minimize any selection biases and potential confounding variables. PS was calculated using logistic regression with the following variables: age, sex, concentrations of α -fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II), Child-Pugh class, ECOG performance status, BCLC stage, extent of HCC, and number of involved disease sites. For PS-matching analysis, a nearest neighbor 1:1 matching scheme with a caliper size of 0.2 was applied. In IPTW, individuals were weighted by the inverse probability of their treatment status. Moreover, stratified analysis of the PS-matched cohort was performed to evaluate the effectiveness of regorafenib and nivolumab in patient subgroups.

All statistical analyses were performed using R statistical software, version 3.5.0 (R Foundation Inc.; <http://cran.r-project.org>). All tests were two sided, with $P < 0.05$ considered statistically significant.

Results

BASELINE CHARACTERISTICS

The study included 373 patients, 223 who received regorafenib and 150 who received nivolumab as second-line treatment after sorafenib failure. The baseline demographic and clinical characteristics of the study population are shown in Table 1. The median concentration of albumin was significantly higher (3.5 vs. 3.4 g/dL; $P = 0.009$) whereas the median concentration of bilirubin was significantly lower (0.8 vs. 0.9 mg/dL; $P = 0.014$) in the regorafenib than in the nivolumab group. In addition, the percentages of patients with ECOG performance status ≥ 1 (37.2% vs. 46.7%; $P = 0.015$) and Child-Pugh class B (26.5% vs. 37.3%; $P = 0.034$) were significantly lower and the median duration of sorafenib treatment significantly longer (2.7 vs. 1.4 months; $P < 0.001$) in the regorafenib than in the nivolumab group. Because of these differences in baseline characteristics, PS matching was performed, resulting in 136 pairs of patients. Following PS matching, the baseline characteristics of the two groups were balanced, except that the duration of sorafenib treatment remained significantly longer in the regorafenib than in the nivolumab group (Table 1; Supporting Fig. S1).

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY POPULATION

Characteristics	Before Propensity Score Matching				After Propensity Score Matching*			
	Regorafenib	Nivolumab	Standardized Difference (%)	PValue	Regorafenib	Nivolumab	Standardized Difference (%)	PValue
Number of patients	223	150	–	–	136	136	–	–
Age, mean ± SD, years	58.5 ± 9.4	56.9 ± 10.0	–16.5	0.116	57.1 ± 9.8	57.6 ± 10.0	5.5	0.652
Male sex, n (%)	202 (90.6)	125 (83.3)	–21.7	0.054	118 (86.8)	118 (86.8)	0.0	1.000
ECOG performance status, n (%)			28.6	0.015			21.3	0.218
0	140 (62.8)	80 (53.3)			79 (58.1)	78 (57.4)		
1	83 (37.2)	66 (44.0)			57 (41.9)	55 (40.4)		
2	0 (0.0)	4 (2.7)			0 (0.0)	3 (2.2)		
Child-Pugh class, n (%)			23.5	0.034			–4.7	0.797
A	164 (73.5)	94 (62.7)			89 (65.4)	92 (67.6)		
B	59 (26.5)	56 (37.3)			47 (34.6)	44 (32.4)		
AFP, median (IQR), ng/mL	354.8 (7.9, 3,669.8)	463.9 (10.3, 13,806.6)	–6.9	0.551	493.5 (7.5, 4,569.4)	270.0 (8.4, 9,404.4)	–1.0	0.934
PIVKA-II, median (IQR), mAU/mL	2,150.0 (128.5, 12,666.0)	1,598.0 (176.5, 12,897.5)	7.0	0.507	2,241.5 (164.8, 18,656.0)	1,598.0 (171.3, 13,671.5)	1.9	0.876
Albumin, median (IQR), g/dL	3.5 (3.2, 3.9)	3.4 (3.0, 3.7)	–27.6	0.009	3.5 (3.0, 3.8)	3.4 (3.0, 3.8)	–12.9	0.288
Total bilirubin, median (IQR), mg/dL	0.8 (0.6, 1.2)	0.9 (0.6, 1.4)	24.2	0.014	0.8 (0.6, 1.2)	0.8 (0.5, 1.3)	–6.6	0.585
Etiology, n (%)			–17.6	0.278			–17.5	0.358
Hepatitis B	178 (79.8)	125 (83.3)			117 (86.0)	114 (83.8)		
Hepatitis C	14 (6.3)	4 (2.7)			7 (5.1)	4 (2.9)		
Other	31 (13.9)	21 (14.0)			12 (8.9)	18 (13.3)		
BCLC stage, n (%)			8.5	0.584			0.0	1.000
B (intermediate)	13 (5.8)	6 (4.0)			6 (4.4)	6 (4.4)		
C (advanced)	210 (94.2)	144 (96.0)			130 (95.6)	130 (95.6)		
Macroscopic portal vein invasion, n (%)	77 (34.5)	65 (43.3)	18.1	0.108	49 (36.0)	54 (39.7)	7.6	0.617
Extrahepatic spread, n (%)	197 (88.3)	136 (90.7)	7.6	0.588	126 (92.6)	122 (89.7)	–10.4	0.521
Involved disease sites, n (%)								
Liver	173 (77.6)	124 (82.7)	12.8	0.287	104 (76.5)	111 (81.6)	12.7	0.371
Lung	137 (61.4)	90 (60.0)	–2.9	0.865	88 (64.7)	78 (57.4)	–15.1	0.263
Number of involved disease sites per patient, n (%)			–9.5	0.431			–10.8	0.445
1-2	137 (61.4)	99 (66.0)			84 (62.5)	92 (67.6)		
≥3	86 (38.6)	51 (34.0)			51 (37.5)	44 (32.4)		
Duration of sorafenib treatment, months	2.7 (1.1, 5.4)	1.4 (0.5, 3.4)	–42.8	<0.001	2.9 (1.2, 6.5)	1.4 (0.5, 3.5)	–49.5	<0.001

*Matching variables: age, sex, AFP concentration, PIVKA-II concentration, Child-Pugh class, etiology, ECOG performance status, BCLC stage, extent of HCC, and number of involved disease sites.

Abbreviations: Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; mAU, milli-absorbance unit; PIVKA, protein induced by vitamin K absence or antagonist-II; SD, standard deviation.

TABLE 2. TUMOR RESPONSES IN THE STUDY POPULATION ACCORDING TO mRECIST

	Regorafenib (n = 223)	Nivolumab (n = 150)	P value*
Entire cohort			
Best overall response			
Complete response	0	1 (0.7)	
Partial response	9 (4.0)	19 (12.7)	
Stable disease	95 (42.6)	39 (26.0)	
Progressive disease	99 (44.4)	72 (48.0)	
Not evaluable [†]	20 (9.0)	19 (12.6)	
Objective response rate [‡]	9 (4.0)	20 (13.3)	0.002
Disease control rate [§]	104 (46.6)	59 (39.3)	0.198
Durable clinical benefit	34 (32.7)	30 (50.8)	0.035
	Regorafenib (n = 136)	Nivolumab (n = 136)	P value*
Propensity score-matched cohort			
Best overall response			
Complete response	0	1 (0.7)	
Partial response	5 (3.7)	18 (13.2)	
Stable disease	61 (44.9)	36 (26.5)	
Progressive disease	57 (41.9)	67 (49.3)	
Not evaluable [†]	13 (9.5)	14 (10.3)	
Objective response rate [‡]	5 (3.7)	19 (14.0)	0.005
Disease control rate [§]	66 (48.5)	55 (40.4)	0.222
Durable clinical benefit	24 (36.4)	29 (52.7)	0.105
	Regorafenib (n = 223)	Nivolumab (n = 150)	P value*
Entire cohort, IPTW analysis			
Best overall response			
Complete response	0	1 (0.7)	
Partial response	9 (4.0)	19 (12.7)	
Stable disease	95 (42.6)	39 (26.0)	
Progressive disease	99 (44.4)	72 (48.0)	
Not evaluable [†]	20 (9.0)	19 (12.6)	
Objective response rate [‡]	9 (4.0)	20 (13.3)	<0.001
Disease control rate [§]	104 (46.6)	59 (39.3)	0.446
Durable clinical benefit	34 (32.7)	30 (50.8)	0.012

*By χ^2 test or Fisher's exact test, as appropriate, for radiologic response.

[†]Due to death without radiologic disease progression or early drug discontinuation due to a severe adverse drug reaction.

[‡]Objective response rate, defined as the proportion of patients who had complete response or partial response.

[§]Disease control rate, defined as the proportion of patients who had complete response, partial response, or stable disease.

^{||}Durable clinical benefit, defined as the proportion of patients with complete response, partial response, or stable disease maintained continuously for a minimum of 6 months.

ONCOLOGICAL OUTCOMES

One patient (0.7%) in the nivolumab group but none in the regorafenib group achieved a complete response whereas 19 (12.7%) and 9 (4.0%) patients, respectively, achieved a partial response, as determined by mRECIST (Table 2). The ORR was significantly lower in the regorafenib than in the nivolumab group in both the entire cohort (4.0% vs. 13.3%; $P = 0.002$ by

unweighted analysis and $P < 0.001$ by IPTW analysis) and the PS-matched cohort (3.7% vs. 14.0%; $P = 0.005$). In subgroup analysis of patients stratified by underlying Child-Pugh classification, the ORR was significantly lower in patients with Child-Pugh A treated with regorafenib than in those treated with nivolumab (3.7% vs. 19.1%; $P < 0.001$ in the entire cohort and 3.4% vs. 18.5%; $P = 0.003$ in the PS-matched cohort), but there was no between-group difference in patients with

Child-Pugh B (Supporting Table S1). DCR did not differ significantly in the regorafenib- and nivolumab-treated groups before and after PS-matching analysis. Intriguingly, the proportion of patients with DCB, defined as complete response, partial response, or stable disease maintained continuously for a minimum of 6 months, was significantly lower in the regorafenib than in the nivolumab group in the entire cohort (32.7% vs. 50.8%; $P = 0.035$ by unweighted analysis and $P = 0.012$ by IPTW analysis) (Table 2).

During a maximum of 85.7 weeks of follow-up, 197 patients in the regorafenib group and 123 in the nivolumab group experienced disease progression or death. Median PFS by mRECIST was 12.0 weeks (95% CI, 9.1-13.3 weeks) in patients treated with regorafenib and 7.1 weeks (95% CI, 6.3-10.1 weeks) in patients treated with nivolumab. PFS in the two groups did not differ significantly on univariate analysis (HR, 0.85; 95% CI, 0.69-1.06; $P = 0.150$), multivariable analysis (HR, 0.93; 95% CI, 0.76-1.13; $P = 0.458$), and IPTW analysis (HR, 0.94; 95% CI, 0.73-1.21; $P = 0.621$) (Table 3; Fig. 1). Univariate analysis showed no significant differences in TTP (12.1 vs.

7.9 weeks; HR, 0.95; 95% CI, 0.77-1.19; $P = 0.680$) (Table 3; Fig. 1) and OS (30.9 vs. 32.6 weeks; HR, 0.83; 95% CI, 0.64-1.07; $P = 0.154$) between the regorafenib and nivolumab groups, results also observed by multivariable and IPTW analyses (Table 3; Fig. 1; Supporting Fig. S2). In the PS-matched cohort of 136 pairs, PFS (12.6 vs. 7.1 weeks; HR, 0.83; 95% CI, 0.64-1.08; $P = 0.170$), TTP (13.1 vs. 7.6 weeks; HR, 0.88; 95% CI, 0.68-1.14; $P = 0.330$), and OS (31.3 vs. 37.1 weeks; HR 0.94; 95% CI, 0.68-1.30; $P = 0.710$) (Table 3; Fig. 1) were comparable between the two groups. Subgroup analysis of the PS-matched cohort showed that PFS was comparable in all subgroups of the regorafenib and nivolumab groups (Fig. 2).

The rate of dose reductions due to intolerance was much higher in the regorafenib group than in the nivolumab group (75 [33.6%] vs. 5 [3.3%]). Moreover, the rate of toxicity-related discontinuation was significantly higher in the regorafenib than in the nivolumab group (15 [6.7%] vs. 3 [2.0%]). Of the 15 patients who discontinued in the regorafenib group, 5 discontinued because of severe nausea and vomiting; 3 because of fatigue and hand/foot skin reaction; and 1 because of

TABLE 3. SURVIVAL OUTCOMES OF THE STUDY POPULATION

Outcome	Median time (95% CI), weeks		HR (95% CI)*	P value
	Regorafenib (n = 223)	Nivolumab (n = 150)		
Entire Cohort, Univariate				
Progression-free survival	12.0 (9.1-13.3)	7.1 (6.3-10.1)	0.85 (0.69-1.06)	0.150
Time to progression	12.1 (10.6-14.6)	7.9 (7.0-15.3)	0.95 (0.77-1.19)	0.680
Overall survival	30.9 (28.9-35.6)	32.6 (21.7-42.9)	0.83 (0.64-1.07)	0.154
Outcome	Regorafenib (n = 223)	Nivolumab (n = 150)	HR (95% CI)*	P value
Entire cohort, multivariable adjusted				
Progression-free survival	–	–	0.93 (0.76-1.13)	0.458
Time to progression	–	–	0.96 (0.78-1.19)	0.699
Overall survival	–	–	1.03 (0.83-1.27)	0.809
Outcome	Regorafenib (n = 223)	Nivolumab (n = 150)	HR (95% CI)*	P value
Entire cohort, IPTW analysis				
Progression-free survival	–	–	0.94 (0.73-1.21)	0.621
Time to progression	–	–	0.90 (0.69-1.18)	0.451
Overall survival	–	–	0.82 (0.62-1.08)	0.149
Outcome	Regorafenib (n = 136)	Nivolumab (n = 136)	HR (95% CI)*	P value
Propensity score-matched cohort				
Progression-free survival	12.6 (10.6-15.7)	7.1 (6.1-11.1)	0.83 (0.64-1.08)	0.170
Time to progression	13.1 (11.0-17.1)	7.6 (6.7-14.9)	0.88 (0.68-1.14)	0.330
Overall survival	31.3 (24.6-42.0)	37.1 (22.4-49.0)	0.94 (0.68-1.30)	0.710

*Log normal accelerated failure time model for the nivolumab group with the regorafenib group as a reference. Abbreviations: CI, confidence interval; HR, hazard ratio.

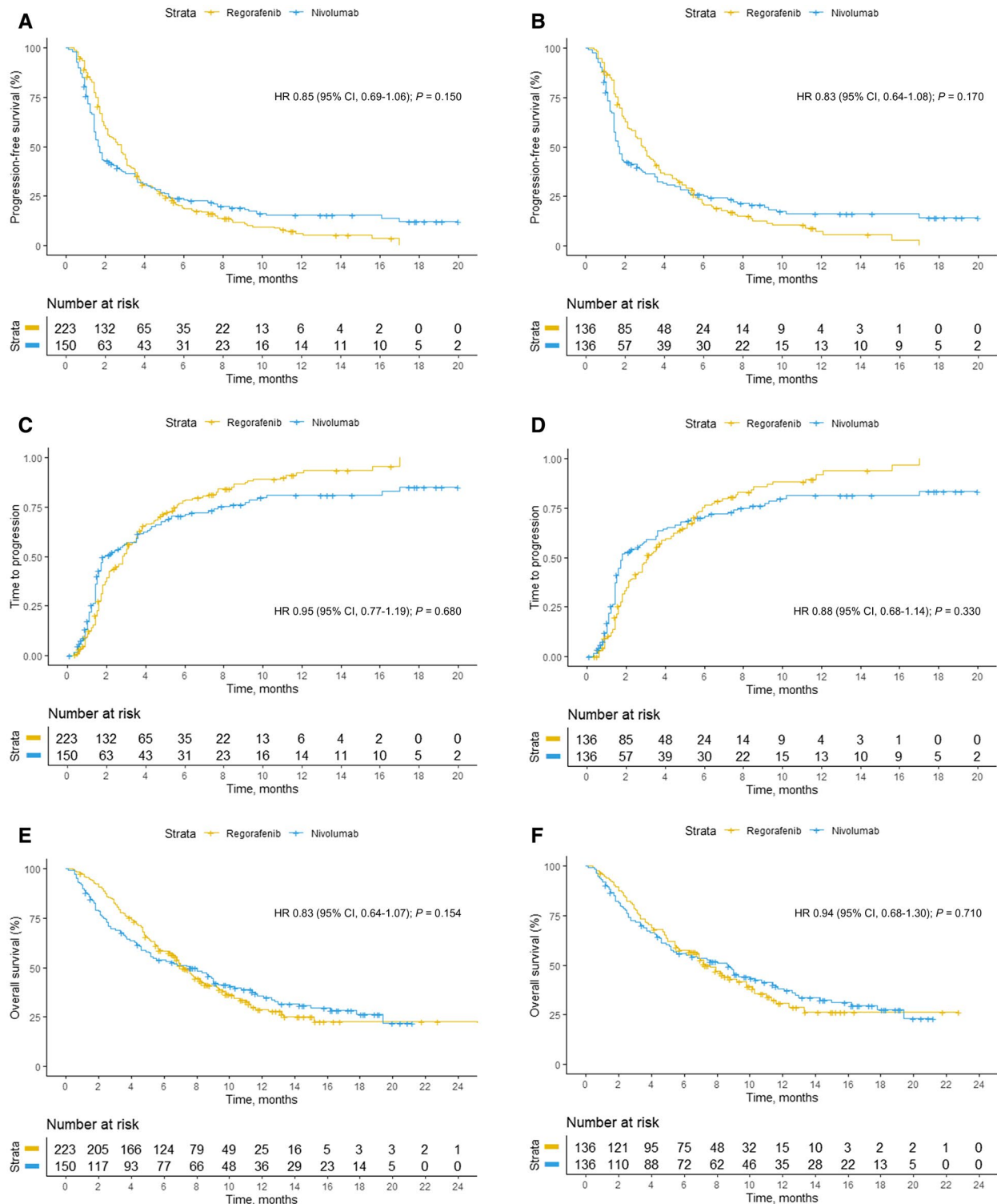


FIG. 1. Kaplan-Meier analyses of survival outcomes in patients treated with regorafenib and nivolumab. (A,B) PFS of patients treated with regorafenib and nivolumab in (A) the entire cohort (HR, 0.85; 95% CI, 0.69-1.06; $P = 0.150$) and (B) the PS-matched cohort (HR, 0.83; 95% CI, 0.64-1.08; $P = 0.170$). (C,D) TTP of patients treated with regorafenib and nivolumab in (C) the entire cohort (HR, 0.95; 95% CI, 0.77-1.19; $P = 0.680$) and (D) the PS-matched cohort (HR, 0.88; 95% CI, 0.68-1.14; $P = 0.330$). (E,F) OS of patients treated with regorafenib and nivolumab in (E) the entire cohort (HR, 0.83; 95% CI, 0.64-1.07; $P = 0.154$) and (F) the PS-matched cohort (HR, 0.94; 95% CI, 0.68-1.30; $P = 0.710$).

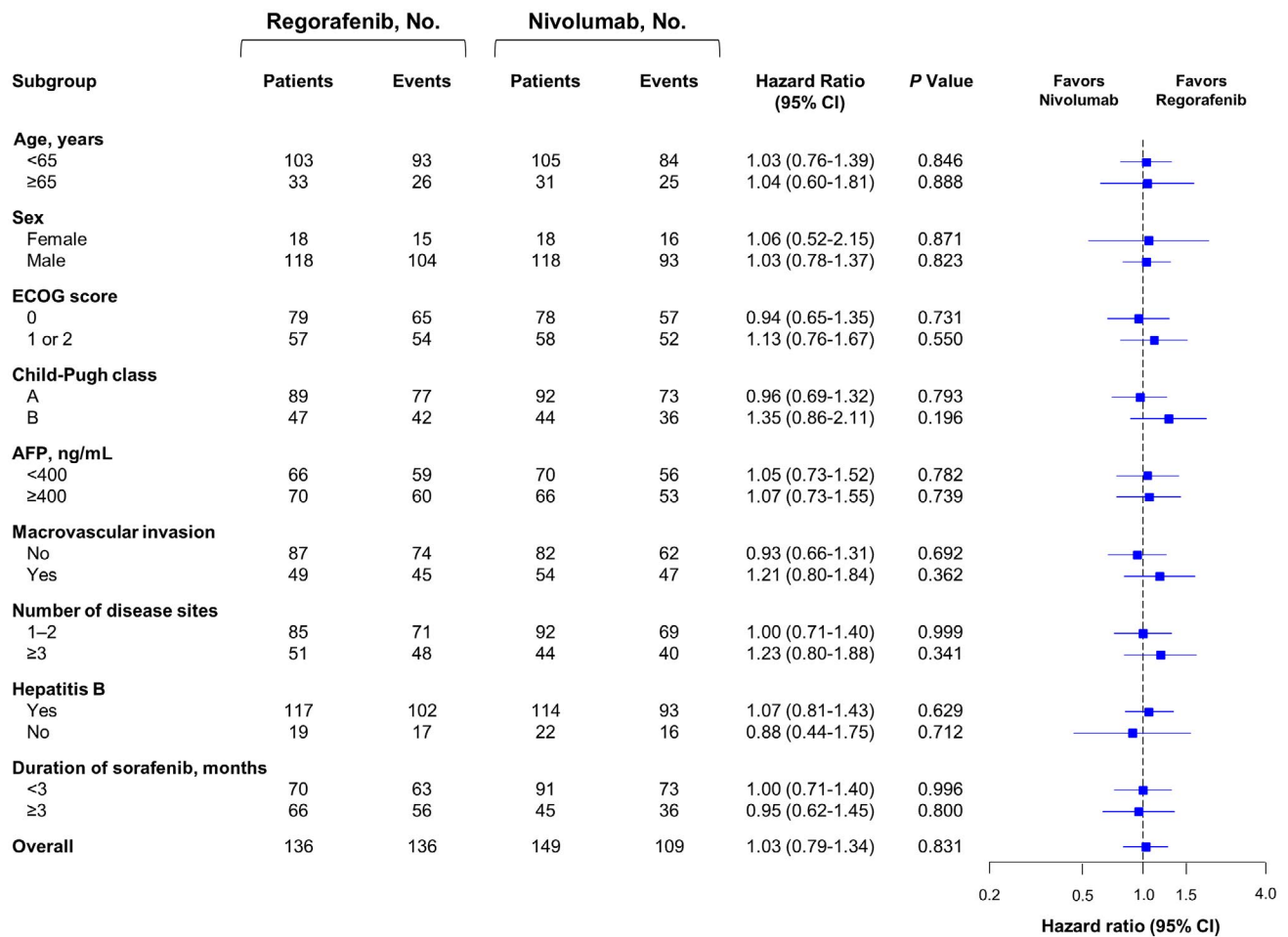


FIG. 2. Forest plot of PFS in subgroups of the PS-matched cohort.

abdominal pain, limb edema, interstitial pneumonia, and a cerebrovascular event. Of the 3 patients who discontinued in the nivolumab group, 2 discontinued because of pneumonitis and 1 because of hepatitis.

SUBCOHORT ANALYSES OF NONPROGRESSORS

As there were more patients with DCB in the nivolumab than in the regorafenib group, subgroup analysis was performed in nonprogressors to treatment, defined as those who achieved complete response, partial response, or stable disease after first response evaluation. The baseline characteristics of these two subgroups were generally well balanced, except for the duration of sorafenib treatment (Table 4).

Median PFS in nonprogressors was longer in those treated with nivolumab than with regorafenib (35.6

vs. 21.7 weeks), with significant between-group differences observed on univariate (HR, 0.50; 95% CI, 0.33-0.75; $P = 0.001$), multivariable (HR, 0.44; 95% CI, 0.28-0.69; $P < 0.001$), and IPTW (HR, 0.60; 95% CI, 0.40-0.91; $P = 0.016$) analyses. Univariate analyses showed that median TTP (HR, 0.48; 95% CI, 0.31-0.73; $P < 0.001$) and OS (HR, 0.51; 95% CI, 0.31-0.87; $P = 0.013$) in this subcohort were significantly longer in patients treated with nivolumab than with regorafenib, with similar results observed on multivariable-adjusted and IPTW analyses (Table 5; Fig. 3; Supporting Fig. S3).

PREDICTIVE FACTORS FOR TREATMENT RESPONSE

To find predictive factors of treatment responses to each drug, we compared the baseline characteristics

TABLE 4. BASELINE CHARACTERISTICS OF THE SUBCOHORT OF NONPROGRESSORS TO TREATMENT

Characteristics	Nonprogressors to Treatment			
	Regorafenib	Nivolumab	Standardized Difference (%)	P Value
Number of patients	104	59	–	–
Age, mean \pm SD, years	58.6 \pm 9.7	58.4 \pm 9.8	–2.3	0.889
Male sex, n (%)	94 (90.4)	48 (81.4)	–26.1	0.158
ECOG performance status, n (%)			14.6	0.474
0	79 (76.0)	41 (69.5)		
1	25 (24.0)	18 (30.5)		
Child-Pugh class, n (%)			9.4	0.707
A	85 (81.7)	46 (78.0)		
B	19 (18.3)	13 (22.0)		
AFP, median (IQR), ng/mL	103.1 (5.8, 1,283.3)	162.8 (5.2, 2,768.7)	19.9	0.207
PIVKA-II, median (IQR), mAU/mL	1,047.5 (98.3, 8,680.8)	880.0 (64.0, 4,831.5)	–17.2	0.311
Albumin, median (IQR), g/dL	3.6 (3.4, 3.9)	3.5 (3.0, 3.9)	–23.6	0.145
Total bilirubin, median (IQR), mg/dL	0.7 (0.6, 1.0)	0.7 (0.5, 1.1)	7.5	0.646
Etiology, n (%)			13.2	0.715
Hepatitis B	88 (84.6)	47 (79.7)		
Hepatitis C	3 (2.9)	2 (3.4)		
Other	13 (12.5)	10 (16.9)		
BCLC stage, n (%)			–8.4	0.863
B (intermediate)	5 (4.8)	4 (6.8)		
C (advanced)	99 (95.2)	55 (93.2)		
Macroscopic portal vein invasion, n (%)	25 (24.0)	17 (28.8)	10.8	0.629
Extrahepatic spread, n (%)	92 (88.5)	52 (88.1)	–1.0	1.000
Involved disease sites, n (%)				
Liver	70 (67.3)	41 (69.5)	4.7	0.910
Lung	60 (57.7)	30 (50.8)	–13.8	0.496
Number of involved disease sites per patient, n (%)			–22.1	0.250
1-2	69 (66.3)	45 (76.3)		
\geq 3	35 (33.7)	14 (23.7)		
Duration of sorafenib treatment, months	3.2 (1.4, 6.9)	2.3 (0.6, 3.7)	–46.8	0.003

*Matching variables: age, sex, AFP concentration, PIVKA-II concentration, Child-Pugh class, etiology, ECOG performance status, BCLC stage, extent of HCC, and number of involved disease sites.

Abbreviations: Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; mAU, milli-absorbance unit; PIVKA, protein induced by vitamin K absence or antagonist-II; SD, standard deviation.

of nonprogressors and progressors in both the regorafenib and nivolumab groups (Supporting Table S2). In both groups, patients with poor performance status (ECOG performance status, 1-2 vs. 0), advanced liver disease (Child-Pugh class, B vs. A), high levels of tumor marker and bilirubin, low levels of albumin, presence of portal vein invasion, liver involvement of HCC, and higher numbers of involved disease sites (\geq 3 vs. 1-2) were poorly responsive to each treatment. Moreover, in the regorafenib group, the treatment response was lower in patients with a shorter duration of previous sorafenib treatment (Supporting Tables S2 and S3).

However, in multivariable analyses, none of those factors were predictive of treatment responses to each drug except poor ECOG performance status in the regorafenib group.

Discussion

To our knowledge, this study is the first to compare oncological outcomes of second-line regorafenib and nivolumab in patients who experienced disease progression during sorafenib treatment. Unadjusted, multivariable-adjusted, PS-matched, and IPTW analyses

TABLE 5. SURVIVAL OUTCOMES IN NONPROGRESSORS TO TREATMENT

Outcome	Median time (95% CI), weeks		HR (95% CI)*	P value
	Regorafenib (n = 104)	Nivolumab (n = 59)		
Subcohort, univariate				
Progression-free survival	21.7 (18.3-25.4)	35.6 (22.4-NA)	0.50 (0.33-0.75)	0.001
Time to progression	21.7 (18.3-25.4)	35.6 (22.6-NA)	0.48 (0.31-0.73)	<0.001
Overall survival	48.6 (41.1-NA)	83.3 (61.3-NA)	0.51 (0.31-0.87)	0.013
Subcohort, multivariable adjusted				
Progression-free survival	-	-	0.44 (0.28-0.69)	<0.001
Time to progression	-	-	0.43 (0.28-0.68)	<0.001
Overall survival	-	-	0.43 (0.25-0.75)	0.003
Subcohort, IPTW analysis				
Progression-free survival	-	-	0.60 (0.40-0.91)	0.016
Time to progression	-	-	0.59 (0.39-0.90)	0.014
Overall survival	-	-	0.48 (0.29-0.80)	0.005

*Cox proportional hazards regression model for the nivolumab group with the regorafenib group as a reference. Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable.

all showed that there were no statistically significant between-group differences in PFS, TTP, and OS. However, nivolumab showed statistically meaningful improvements in the ORR (including 1 patient who achieved a complete response) and DCB compared with regorafenib. This led to subcohort analyses of nonprogressors to treatment, defined as those who achieved a complete response, partial response, or stable disease after first-response evaluation. In this subcohort, nivolumab significantly improved all oncological outcomes, including PFS, TTP, and OS, compared with regorafenib following application of the same robust statistical methods.

In our study, the median PFS and OS of patients treated with regorafenib were 12.0 and 30.9 weeks, respectively. These durations were much shorter than the median PFS (3.2 months) and OS (10.6 months) of patients with HCC treated with regorafenib in the phase 3 Regorafenib for Patients With Hepatocellular Carcinoma Who Progressed on Sorafenib Treatment (RESORCE) trial.⁽¹⁰⁾ The ORR of patients treated with regorafenib in our study (4.0%) was also much lower than that observed in the RESORCE trial (11.0%).⁽¹⁰⁾ Moreover, the ORR and DCR observed in patients treated with nivolumab in our study were 13.3% and 39.3%, respectively, lower than that observed in previous phase 1/2 trials.^(11,14) The differences in oncological outcomes between our study and these previous trials were likely due to differences

in baseline patient characteristics. Previous trials of nivolumab and regorafenib included small proportions of patients with Child-Pugh class B or only patients with Child-Pugh class A and ECOG performance status 0 or 1, whereas our study included a larger proportion of patients with Child-Pugh class B (29.5%) and ECOG performance status 2, reflecting real-world data. Moreover, the patients included in our study had more extensive lesions, including a higher proportion of patients with macroscopic vascular invasion and extrahepatic spread, than patients in previous clinical trials. The response rates and survival outcomes observed in our study were similar to those reported in real-world studies assessing the effectiveness of regorafenib or nivolumab.⁽¹⁵⁻¹⁸⁾

The pathway involving PD-1 and programmed death-ligand 1 (PD-L1) is an important mechanism of tumor-induced immune tolerance. PD-1 expression on effector phase cluster of differentiation (CD)8+ T cells has been reported to be greater in patients with HCC than in patients with cirrhosis and healthy controls.^(19,20) In addition to cancer cells, PD-L1 is highly expressed on peritumoral stromal cells, including Kupffer cells, hepatic stellate cells, and liver sinusoidal endothelial cells, resulting in the activation of the PD-L1/PD-1 pathway and the inhibition of anti-tumor T-cell responses.⁽²¹⁻²³⁾ These findings strongly support the use of PD-1 and PD-L1 inhibitors for the treatment of HCC. The phase 3 studies with

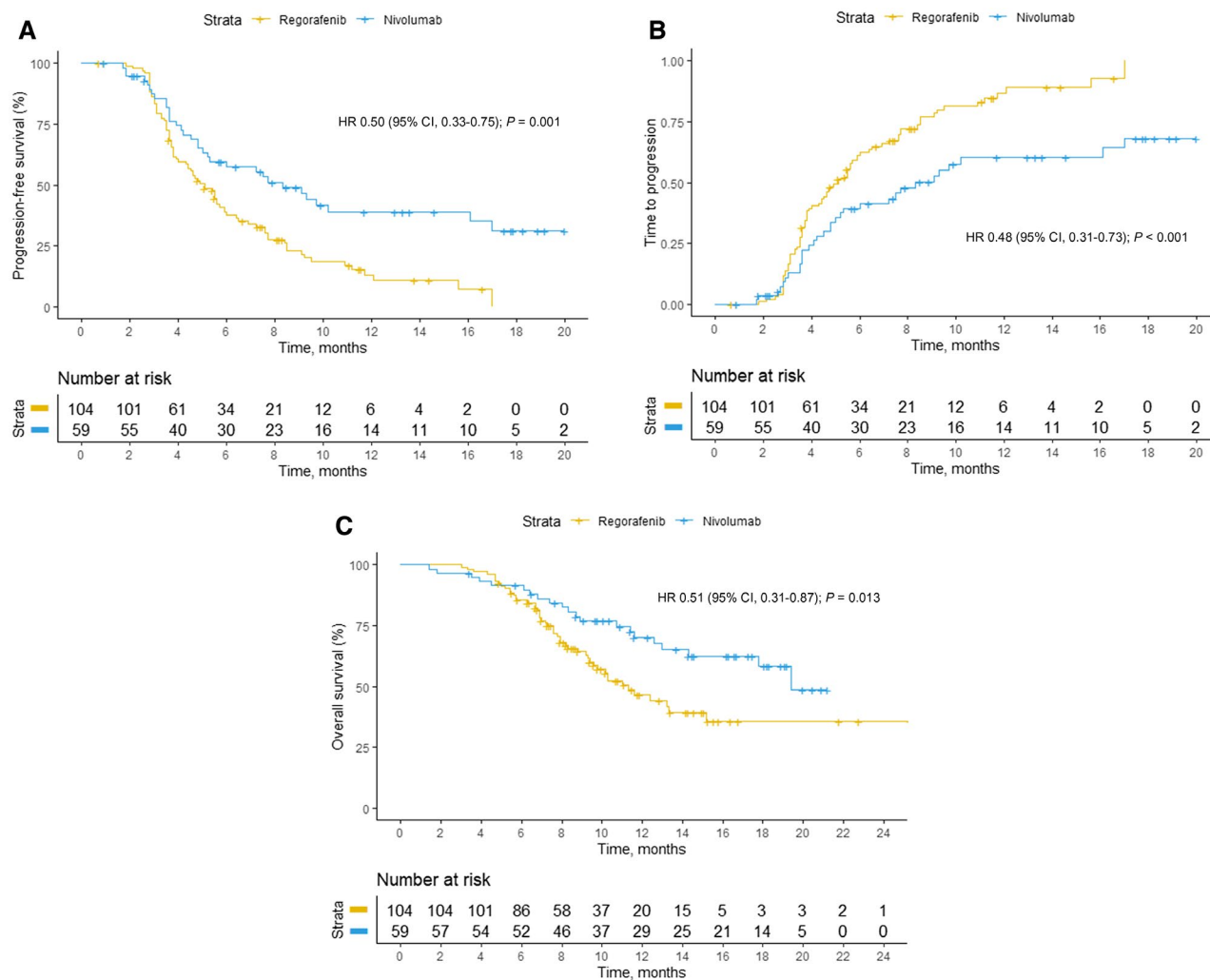


FIG. 3. Kaplan-Meier analyses of survival outcomes in nonprogressors to treatment with regorafenib and nivolumab before PS matching. (A) PFS (HR, 0.50; 95% CI, 0.33-0.75; $P = 0.001$). (B) TTP (HR, 0.48; 95% CI, 0.31-0.73; $P < 0.005$). (C) OS (HR, 0.51; 95% CI, 0.31-0.87; $P = 0.013$).

nivolumab and pembrolizumab (as a first- and second-line treatment for advanced HCC, respectively) yielded negative results. However, the results of both trials showed a clear trend toward improvement in oncological outcomes. In KEYNOTE-240, pembrolizumab improved OS (HR, 0.78; one-sided $P = 0.024$) and PFS (HR, 0.78; one-sided $P = 0.021$) versus placebo. The ORR was 16.9%, which is higher than in our study.⁽²⁴⁾ In CheckMate-459, nivolumab treatment showed a trend toward improvement in OS (HR, 0.85; 95% CI, 0.71-1.02; $P = 0.075$).⁽²⁵⁾ Thus, when both trials are examined in detail, it seems premature to consider immune checkpoint inhibitors for

the treatment of HCC as a failure; indeed, immune checkpoint inhibitors still appear to be effective for the treatment of advanced HCC.

However, driver oncogenes have not yet been accurately identified in HCC or used for the development of targeted therapy of this disease. Targeted agents currently used in patients with HCC, such as sorafenib, regorafenib, and lenvatinib, are multikinase inhibitors, which have lower response rates and higher therapeutic resistance than targeted therapy agents in other cancers.⁽²⁶⁾ Thus, targeted therapy of HCC may initially induce a higher rate of response with early improvements in survival curves than nivolumab, but

most responses are short lived due to the emergence of therapeutic resistance, resulting in unclear long-term survival benefits. By contrast, treatment with immune checkpoint inhibitors, such as nivolumab, results in tumor responses in a lower percentage of patients, but these responses are highly durable, resulting in longer term benefits.⁽²⁷⁾ Consistent with this, survival outcomes were significantly higher in nonprogressors to treatment with nivolumab than in nonprogressors to treatment with regorafenib. One patient in the nivolumab group but none of the patients in the regorafenib group achieved a complete response. Moreover, the proportion of patients with DCB, defined as a therapeutic effect lasting for at least 6 months, was higher in the nivolumab than in the regorafenib group. These results explain why the PFS, TTP, and OS curves of the regorafenib and nivolumab groups crossed over in our study. Moreover, this phenomenon has been confirmed in other types of cancer.⁽²⁸⁻³²⁾

Our finding, that nivolumab showed better survival outcomes than regorafenib when progressors to each were excluded, suggests that initial second-line treatment with nivolumab may be a good strategy to the predicted nonprogressors. The better tolerability and safety profile of nivolumab than of regorafenib observed in this study further support this strategy. However, no baseline clinical markers predictive of treatment response to nivolumab were identified in our study. PD-L1 expression is an established predictor of responses to immune checkpoint inhibitors in other types of solid tumors. In HCC, the combined positive score, calculated by dividing the number of PD-L1-positive cells by the total number of viable tumor cells and multiplying by 100, was predictive of a response to pembrolizumab in a previous trial.⁽³³⁾ However, because the association between the combined positive score and tumor response in HCC was based on a retrospective evaluation in a small subset of patients, further studies in larger populations are warranted.

This study had several limitations. First, it was a retrospective observational study, a design with inherent limitations, including bias and confounding. Although multiple statistical strategies, including multivariable adjustment, PS matching, and IPTW analyses, were employed to rigorously adjust for between-group differences in baseline characteristics, the duration of previous sorafenib treatment remained longer in the regorafenib than the nivolumab group, even after

PS matching. This resulted from the current guidance,⁽³⁴⁾ which recommends regorafenib for patients who tolerate sorafenib treatment well and nivolumab for patients who are intolerant to or progress rapidly under sorafenib treatment. However, a previous study demonstrated that the longer the duration of prior sorafenib, the longer the duration of time to progression on regorafenib.⁽³⁵⁾ Moreover, liver function and performance status were worse in patients treated with nivolumab than with regorafenib, making it unlikely that the possible selection bias in our study worked unfavorably against regorafenib to change the conclusion. Despite this limitation, the findings of this retrospective cohort study in a real-world setting are likely valuable in suggesting the design of future prospective studies comparing these two agents. A second limitation of this study was the inclusion of only patients at a single center, which limits the ability to draw general conclusions from the results. Most of the included patients were Asian, with HCC in most cases caused by hepatitis B virus infection, which may be associated with poor prognosis.⁽³⁶⁾ No previous study, however, has shown that etiology or ethnicity affects the efficacy of regorafenib or nivolumab treatment.^(10,14) Further studies on other ethnicities or etiologies are warranted to replicate these results. Finally, because the data in this study were collected retrospectively from electronic medical records, only side effects leading to drug discontinuation or dose reduction were compared. Mild side effects, however, were not identified or compared in the two groups.

The present study is the first to compare the effectiveness of regorafenib and nivolumab, approved as second-line treatment for HCC, in real-world patients after sorafenib failure. Although the ORR was higher in the nivolumab group than in the regorafenib group, there were no between-group differences in survival outcomes. In nonprogressors to treatment, nivolumab showed significant improvements in survival outcomes when compared with regorafenib, suggesting that nivolumab may be a better option for nonprogressors to treatment. Further studies predicting treatment response to nivolumab are warranted to increase the clinical significance of our results. Moreover, because this was a retrospective study, randomized controlled trials comparing the efficacies of nivolumab and regorafenib are needed to confirm our findings.

REFERENCES

- 1) Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359-E386.
- 2) Kim BH, Park JW. Epidemiology of liver cancer in South Korea. *Clin Mol Hepatol* 2018;24:1-9.
- 3) Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. *Gastroenterology* 2016;150:835-853.
- 4) Bertuccio P, Turati F, Carioli G, Rodriguez T, La Vecchia C, Malvezzi M, et al. Global trends and predictions in hepatocellular carcinoma mortality. *J Hepatol* 2017;67:302-309.
- 5) Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al.; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378-390.
- 6) Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, 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.
- 7) Kudo M, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, 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.
- 8) Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schütz G, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *Int J Cancer* 2011;129:245-255.
- 9) Abou-Elkacem L, Arns S, Brix G, Gremse F, Zopf D, Kiessling F, et al. Regorafenib inhibits growth, angiogenesis, and metastasis in a highly aggressive, orthotopic colon cancer model. *Mol Cancer Ther* 2013;12:1322-1331.
- 10) Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al.; RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;389:56-66.
- 11) El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017;389:2492-2502.
- 12) Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018;68:723-750.
- 13) Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010;30:52-60.
- 14) Yau T, Hsu C, Kim TY, Choo S-P, Kang YK, Hou MM, et al. Nivolumab in advanced hepatocellular carcinoma: sorafenib-experienced Asian cohort analysis. *J Hepatol* 2019;71:543-552. Erratum in: *J Hepatol* 2019;71:1278.
- 15) Yoo C, Park JW, Kim YJ, Yu SJ, Lim TS, Lee SJ, et al. Multicenter retrospective analysis of the safety and efficacy of regorafenib after progression on sorafenib in Korean patients with hepatocellular carcinoma. *Invest New Drugs* 2019;37:567-572.
- 16) Kuzuya T, Ishigami M, Ito T, Ishizu Y, Honda T, Ishikawa T, et al. Clinical characteristics and outcomes of candidates for second-line therapy, including regorafenib and ramucirumab, for advanced hepatocellular carcinoma after sorafenib treatment. *Hepatol Res* 2019;49:1054-1065.
- 17) Scheiner B, Kirstein MM, Huckle F, Finkelmeier F, Schulze K, von Felden J, et al. Programmed cell death protein-1 (PD-1)-targeted immunotherapy in advanced hepatocellular carcinoma: efficacy and safety data from an international multicentre real-world cohort. *Aliment Pharmacol Ther* 2019;49:1323-1333.
- 18) Finkelmeier F, Czauderna C, Perkhofer L, Ettrich TJ, Trojan J, Weinmann A, et al. Feasibility and safety of nivolumab in advanced hepatocellular carcinoma: real-life experience from three German centers. *J Cancer Res Clin Oncol* 2019;145:253-259.
- 19) Shi F, Shi M, Zeng Z, Qi RZ, Liu ZW, Zhang JY, et al. PD-1 and PD-L1 upregulation promotes CD8+ T-cell apoptosis and postoperative recurrence in hepatocellular carcinoma patients. *Int J Cancer* 2011;128:887-896.
- 20) Kim HD, Song GW, Park S, Jung MK, Kim MH, Kang HJ, et al. Association between expression level of PD1 by tumor-infiltrating CD8+ T cells and features of hepatocellular carcinoma. *Gastroenterology* 2018;155:1936-1950.e17.
- 21) Gao Q, Wang XY, Qiu SJ, Yamato I, Sho M, Nakajima Y, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. *Clin Cancer Res* 2009;15:971-979.
- 22) Wang BJ, Bao JJ, Wang JZ, Wang Y, Jiang M, Xing MY, et al. Immunostaining of PD-1/PD-Ls in liver tissues of patients with hepatitis and hepatocellular carcinoma. *World J Gastroenterol* 2011;17:3322-3329.
- 23) Greten TF, Sangro B. Targets for immunotherapy of liver cancer. *J Hepatol* 2017; pii:S0168-8278(17)32287-0.
- 24) Finn RS, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, et al. Results of KEYNOTE-240: phase 3 study of pembrolizumab (Pembro) vs best supportive care (BSC) for second line therapy in advanced hepatocellular carcinoma (HCC) [Abstract]. *J Clin Oncol* 2019;37(Suppl.):4004.
- 25) Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. CheckMate 459: a randomized, multi-center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). *Ann Oncol* 2019;30(Suppl. 5):v874-v875.
- 26) Chen S, Cao Q, Wen W, Wang H. Targeted therapy for hepatocellular carcinoma: challenges and opportunities. *Cancer Lett* 2019;460:1-9.
- 27) Ribas A, Hersey P, Middleton MR, Gogas H, Flaherty KT, Sondak VK, et al. New challenges in endpoints for drug development in advanced melanoma. *Clin Cancer Res* 2012;18:336-341.
- 28) Larkin J, Minor D, D'Angelo S, Neyns B, Smylie M, Miller WH, et al. Overall survival in patients with advanced melanoma who received nivolumab versus investigator's choice chemotherapy in CheckMate 037: a randomized, controlled, open-label phase III trial. *J Clin Oncol* 2018;36:383-390.
- 29) Overman MJ, Lonardi S, Wong KYM, Lenz HJ, Gelsomino F, Aglietta M, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol* 2018; 36:773-779.
- 30) Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al.;KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018;378:2078-2092.
- 31) Pons-Tostivint E, Latouche A, Vaflard P, Ricci F, Loirat D, Hescot S, et al. Comparative analysis of durable responses on immune checkpoint inhibitors versus other systemic therapies: a pooled analysis of phase III trials. *JCO Precis Oncol* 2019. <https://ascopubs.org/doi/pdf/10.1200/PO.18.00114>.
- 32) Powles T, Durán I, Van Der Heijden MS, Loriot Y, Vogelzang NJ, De Giorgi U, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3

randomised controlled trial. *Lancet* 2018;391:748-757. Erratum in: *Lancet* 2018;392:1402.

- 33) Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al.; KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol* 2018;19:940-952.
- 34) Vogel A, Cervantes A, Chau I, Daniele B, Llovet J, Meyer T, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019;30:871-873.
- 35) Finn RS, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, et al. Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: additional analyses from the phase III RESORCE trial. *J Hepatol* 2018;69:353-358.

- 36) Zucman-Rossi J, Villanueva A, Nault JC, Llovet JM. Genetic landscape and biomarkers of hepatocellular carcinoma. *Gastroenterology* 2015;149:1226-1239.e4.

Author names in bold designate shared co-first authorship.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1523/supinfo.