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Comparison between Nivolumab and Regorafenib as Second-line Systemic Therapies after Sorafenib Failure in Patients with Hepatocellular Carcinoma

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Purpose: Nivolumab and regorafenib are second-line therapies for patients with advanced hepatocellular carcinoma (HCC). We aimed to compare the effectiveness of nivolumab and regorafenib.

Materials and Methods: We retrospectively reviewed patients with HCC treated with nivolumab or regorafenib after sorafenib failure. Progression-free survival (PFS) and overall survival (OS) were analyzed. An inverse probability of treatment weighting using the propensity score (PS) was performed to reduce treatment selection bias.

Results: Among the 189 patients recruited, 137 and 52 patients received regorafenib and nivolumab after sorafenib failure, respectively. Nivolumab users showed higher Child-Pugh B patients (42.3% vs. 24.1%) and shorter median sorafenib maintenance (2.2 months vs. 3.5 months) compared to regorafenib users. Nivolumab users showed shorter median OS (4.2 months vs. 7.4 months, p=0.045) than regorafenib users and similar median PFS (1.8 months vs. 2.7 months, p=0.070). However, the median overall and PFS did not differ between the two treatment groups after the 1:1 PS matching (log-rank p=0.810 and 0.810, respectively) and after the stabilized inverse probability of treatment weighting (log-rank p=0.445 and 0.878, respectively). In addition, covariate-adjusted Cox regression analyses showed that overall and PFS did not significantly differ between nivolumab and regorafenib users after 1:1 PS matching and stabilized inverse probability of treatment weighting (all p>0.05).

Conclusion: Clinical outcomes of patients treated with nivolumab and regorafenib after sorafenib treatment failure did not differ significantly.

Key Words: Carcinoma, hepatocellular; immune checkpoint inhibitors; antineoplastic agents, immunological; nivolumab; angiogenesis inhibitors; regorafenib

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cause of cancer death with an increasing incidence worldwide.[1] In South Korea, HCC remains the second-largest cause of cancer mortality and is the most economically burdensome cancer, contributing to an increasing number of annual deaths and crude death rate due to liver cancer since 2013.[2,3] Despite improvements in periodic surveillance to detect early stages of HCC,[4] it is usually asymptomatic and often detected at an unresectable and advanced stage, resulting in poor clini-

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cal outcomes.[5,6]

Therapeutic advances have allowed the proposal of standard treatment for patients with advanced HCC involving vascular invasion, major portal vein tumor thrombosis, or extrahepatic metastases with preserved liver function.[7-9] For decades, the first-line therapy for advanced HCC has involved sorafenib and lenvatinib, which are similar oral multi-tyrosine kinase inhibitors (TKIs) with well-evidenced modest survival benefits.[10,11] However, despite the fact that the recently approved combination therapy of atezolizumab and bevacizumab, a programmed death-ligand 1 inhibitor and a vascular endothelial growth factor receptor inhibitor, respectively, promises a new era of first-line therapy for HCC due to its superior outcome compared to sorafenib in patients with treatment-naïve advanced HCC,[12] a considerable proportion of patients still experience disease progression or drug intolerance after first-line therapy, necessitating second-line therapy.

Currently, second-line therapy is approved only following sorafenib, as lenvatinib was approved much later than sorafenib (in 2018 and 2007, respectively). Recently, multi-TKIs, such as regorafenib, cabozantinib, and ramucirumab, along with nivolumab, a programmed cell death protein 1 inhibitor, have become available after sorafenib failure, based on their safety profiles and efficacy.[13-16] The question regarding which therapy should come after sorafenib for patients with advanced HCC remains critical. Since the approval of both regorafenib and nivolumab in 2017, the accumulation of clinical experience has allowed direct comparisons between the two drugs. Recent hospital-based studies have demonstrated promising treatment outcomes of both without significant difference,[17-19] though nivolumab may be beneficial in a subset of patients without progression and with sorafenib-intolerance.[18,19]

In the present study, we aimed to compare the clinical outcomes of nivolumab and regorafenib as second-line therapies after sorafenib treatment failure in patients with advanced HCC.

MATERIALS AND METHODS

Selection and description of study participants

Patients with advanced HCC who subsequently received regorafenib or nivolumab as second-line systemic therapy after sorafenib failure between August 2017 and December 2021 at Severance Hospital, Yonsei University College of Medicine, a tertiary academic hospital in Seoul, South Korea, were recruited retrospectively. The exclusion criteria were as follows: 1) age <18 years; 2) receiving systemic treatment for HCC other than sorafenib; 3) Barcelona Clinical Liver Cancer stage D;[20] 4) combined with another malignant disease; 5) Eastern Cooperative Oncology Group performance status ≥3; 6) history of organ transplantation before sorafenib use; and 7) insufficient data. The study protocol was in accordance with the guidelines of the 1975 Declaration of Helsinki. The need for written informed consent was waived owing to the retrospective nature of this study. The study procedure was approved by the Institutional Review Board of the Yonsei University Health System (IRB No. 4-2021-1268).

HCC was diagnosed based on histological evidence or by dynamic computed tomography and/or magnetic resonance imaging findings (nodule >1 cm with arterial hypervascularity and portal-/delayed-phase washout).[7,21,22] Advanced HCC was defined as having more than one of the following conditions: major vessel invasions, such as a portal vein or hepatic vein; extrahepatic metastasis; or refractoriness to multiple trials of locoregional therapy.[20] Sorafenib failure was defined as a definite progression after sorafenib use and/or side effects resulting in the discontinuation of sorafenib treatment.

Procedures

The decision to treat with regorafenib or nivolumab after sorafenib failure was made by medical experts based on the clinical situation of each patient. Regorafenib users received 160 mg of regorafenib (four 40 mg tablets) orally once daily for the first 3 weeks of each 4-week cycle.[13] Treatment interruptions within 14 days and dose reductions (to 120 mg, then 80 mg) were permitted to manage toxicity.[13] Nivolumab was administered intravenously to patients every 2 weeks, with each dose consisting of 3 mg/kg of the drug.[16]

Treatment response was evaluated using the modified Response Evaluation Criteria in Solid Tumors,[23] with imaging follow-up performed every 2–3 months. Treatment was discontinued when the patient experienced definite disease progression, unacceptable toxicity, systemic deterioration (including decreased liver function), or death.

Definitions and outcomes

Hypertension was defined as a systolic blood pressure of >140 mm Hg, a diastolic blood pressure of >90 mm Hg, or the current use of anti-hypertensive agents. Diabetes mellitus was defined as a fasting serum glucose level of ≥126 mg/dL or the current use of anti-diabetic agents. Significant alcohol intake was defined as alcohol intake of >210 g/week in males and >140 g/week in females.[24] Cirrhosis was histologically or clinically diagnosed as follows: 1) a platelet count of $<150\times10^9$/L and/or imaging findings suggestive of cirrhosis, including a blunted nodular surface accompanied by splenomegaly (>12 cm); or 2) clinical signs of portal hypertension, such as esophageal varix.[25] Objective response (OR) was defined as experiencing complete response (CR) and partial response (PR) as the best response during the treatment, and disease control (DC) was defined to as experiencing CR, PR, and stable disease (SD) as the best response. OR rate (ORR) and DC rate (DCR) were defined as the proportion of patients who achieved an OR and DC, respectively, among the total patients including those whose response could not be evaluated.

The primary endpoint was overall survival (OS), defined as

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the length of time from the start date of regorafenib or nivolumab treatment to the date of the patient's death. The secondary endpoint was progression-free survival (PFS), defined as the length of time from the start date of second-line therapy to the date of confirmed disease progression or patient death.

Statistical analysis

To account for possible factors that could have influenced the attending physician's choice of second-line therapy, we performed 1:1 propensity score (PS) matching to balance the patients' baseline characteristics between the treatment groups. The PS was determined using logistic regression with the greedy nearest neighbor matching technique without replacement and a caliper of 0.1 standard deviations. Covariates in the PS model included baseline age, sex, etiology of HCC, cirrhosis, hypertension, diabetes mellitus, previous liver resection, previous locoregional therapy, sorafenib maintenance, the reason for sorafenib failure, tumor behavior, platelet count, prothrombin time, total bilirubin, serum albumin, aspartate aminotransferase (AST), alanine aminotransferase, alkaline phosphatase (ALP), alpha-fetoprotein (AFP), protein induced by vitamin K absence or antagonist II, and Child-Pugh score. The balance between groups was assessed using absolute standardized mean differences (ASMDs), with <0.1 deemed ideal and <0.2 deemed acceptable.[26]

Additionally, stabilized inverse probability treatment weighting (IPTW) was adopted to preserve the sample size of the original data. Using the generated PSs, the IPTW created a "pseudo-sample" consisting of identical subjects in the original sample, but each subject in the pseudo-sample was assigned a weight derived from the IPTW to minimize the impact of treatment selection bias and other potential confounders. Additionally, IPTW was stabilized by multiplying IPTW by the marginal probability of receiving each treatment.[27]

Continuous variables, such as laboratory test results, were expressed as the median (interquartile range, IQR) and compared using the Student's t-test or the Mann–Whitney U test, depending on their distribution. Categorical variables are expressed as numbers (percentage) and were evaluated using the chi-squared test or Fisher's exact probability test. The cumulative incidence of death and progression was evaluated using the Kaplan–Meier method, and the calculated OS and PFS were compared using the log-rank test to verify the significant difference between regorafenib and nivolumab users. Univariate and multivariate Cox regression analyses were performed to assess the association between the treatment group and outcomes. The data are expressed as hazard ratios (HR) with 95% confidence intervals (CIs). Kaplan–Meier and Cox regression analyses were also performed after 1:1 PS matching and weighted using the IPTW method.

All statistical analyses were performed using R (version 4.2.3; http://cran.r-project.org/). Two-sided p values <0.05 were considered to indicate statistical significance.

RESULTS

Baseline characteristics

After exclusion, 137 (72.5%) regorafenib users and 52 (27.5%) nivolumab users were selected for statistical analysis (Supplementary Fig. 1, only online). Most of the patients were male (n=165, 87.3%) and had cirrhosis (n=160, 84.7%), hepatitis B virus (HBV) infection (n=143, 75.7%), and significant alcohol intake (n=121, 64.0%). Sorafenib was discontinued after a median of 2.8 months of maintenance, primarily due to disease progression (n=168, 88.9%). At the start of second-line therapy, 55 (42.3%) and 26 (13.8%) patients had Vp3–4 portal vein tumor thrombosis and hepatic invasion, respectively, and 162 (85.7%) patients had extrahepatic metastasis (Table 1). Before matching, nivolumab users were younger than regorafenib users (median age, 59 years vs. 63 years), had shorter sorafenib maintenance (median, 2.2 months vs. 3.5 months), and had a higher proportion of Child-Pugh scores ≥7 (42.3% vs. 24.1%, respectively) (all p<0.05).

Adverse events

Regorafenib users experienced more adverse events compared to those using nivolumab (50.4% vs. 19.2%, p<0.001) (Table 1 and Supplementary Table 1, only online). Grade 3 or higher adverse events, such as hand-foot syndrome, diarrhea, nausea, vomiting, and mucositis, were also predominantly observed in regorafenib patients. Meanwhile, one nivolumab user developed severe hepatitis, leading to the discontinuation of treatment.

Overall tumor response

Response evaluation was not possible in 25 (18.2%) regorafenib users and 13 (25.0%) nivolumab users due to early discontinuation caused by adverse events or follow-up discontinuation due to patient death and transfer to another hospital. ORR were higher in nivolumab users; however, the difference was not statistically significant (13.5% vs. 7.3%, p=0.117). DCR were similar between regorafenib (32.9%) and nivolumab (28.9%) users (p=0.681) (Table 2).

Comparison of outcomes between regorafenib and nivolumab users

A total of 147 (77.8%) patients died during the follow-up period (median=5.8 months; IQR=2.5–13.0; max=48.8), divided among 104 (75.9%) deaths in regorafenib users and 43 (82.7%) in nivolumab users. The median follow-up duration was 6.7 months (IQR=3.2–13.4; max=40.0) in regorafenib users and 3.3 months (IQR=1.4–10.5; max=48.8) in nivolumab users (p=0.010). The median OS and PFS in all patients were 6.9 months (95% CI=5.7–8.3) and 2.4 months (95% CI=1.9–2.7), respectively. Before matching, the median OS in regorafenib users was 7.4 months (95% CI=5.9–9.9), significantly higher than that in nivolumab users (4.2 months; 95% CI=2.7–8.5; log-rank p=

Table 1. Baseline Characteristics of Patients with Advanced Hepatocellular Carcinoma Who Received Second-line Therapy after Sorafenib Failure

Variable	Total (n=189)	Regorafenib (n=137; 72.5%)	Nivolumab (n=52; 27.5%)	*p* value
Age (yr)	62 (55–69)	63 (57–69)	59 (53–66)	0.020
Male sex	165 (87.3)	120 (87.6)	45 (86.5)	>0.999
HBV infection	143 (75.7)	100 (73.0)	43 (82.7)	0.231
HCV infection	8 (4.2)	6 (4.4)	2 (3.8)	>0.999
Significant alcohol intake	121 (64.0)	86 (62.8)	35 (67.3)	0.682
Cirrhosis	160 (84.7)	115 (83.9)	45 (86.5)	0.829
Hypertension	77 (40.7)	57 (41.6)	20 (38.5)	0.820
Diabetes mellitus	67 (35.4)	52 (38.0)	15 (28.8)	0.318
Previous liver resection	50 (26.5)	38 (27.7)	12 (23.1)	0.643
Previous locoregional therapy	155 (82.0)	115 (83.9)	40 (76.9)	0.363
Sorafenib maintenance (month)	2.8 (1.9–5.5)	3.5 (2.0–6.7)	2.2 (1.4–2.9)	<0.001
Reason for second-line change				
Progression/Adverse event	168 (88.9)/21 (11.1)	128 (93.4)/9 (6.6)	40 (76.9)/12 (23.1)	0.003
Portal vein invasion (Vp3–4)	55 (42.3)	35 (25.5)	20 (38.5)	0.117
Hepatic vein invasion	26 (13.8)	18 (13.1)	8 (15.4)	0.870
Extrahepatic metastasis	162 (85.7)	119 (86.9)	43 (82.7)	0.618
Lymph node	89 (47.1)	63 (46.0)	26 (50.0)	0.741
Bone	38 (20.1)	31 (22.6)	7 (13.5)	0.230
Lung	98 (51.9)	73 (53.3)	25 (48.1)	0.633
Other organ	54 (28.6)	40 (29.2)	14 (26.9)	0.898
Laboratory test results				
Platelet count ($\times 10^9$/L)	130 (90–194)	125 (89–187)	140 (105–230)	0.203
Prothrombin time (INR)	1.07 (1.02–1.17)	1.07 (1.02–1.14)	1.12 (1.03–1.21)	0.044
Total bilirubin (mg/dL)	0.9 (0.6–1.3)	0.9 (0.7–1.2)	0.8 (0.6–1.8)	0.753
Serum albumin (g/dL)	3.7 (3.2–4.2)	3.8 (3.3–4.2)	3.4 (3.0–3.9)	0.005
AST (IU/L)	52 (36–78)	49 (34–71)	68 (42–130)	0.005
ALT (IU/L)	30 (20–46)	29 (21–43)	30 (19–51)	0.540
Alkaline phosphatase (IU/L)	137 (100–201)	133 (98–191)	150 (110–239)	0.206
Serum creatinine (mg/dL)	0.79 (0.66–0.96)	0.78 (0.67–0.98)	0.81 (0.65–0.93)	0.584
AFP (ng/mL)	142.1 (10.8–2929.8)	125.3 (7.5–2178.8)	348.0 (30.3–3509.5)	0.306
PIVKA-II (mAU/mL)	3009 (351–22255)	2846 (411–15462)	3600 (110–35520)	0.724
Child-Pugh score	6 (5–7)	5 (5–6)	6 (5–8)	0.005
Child-Pugh score ≥7	55 (29.1)	33 (24.1)	22 (42.3)	0.014
Second-line therapy				
Treatment duration (month)	2.1 (1.1–4.5)	2.4 (1.4–4.7)	1.8 (0.8–3.9)	0.053
Adverse events	79 (41.8)	69 (50.4)	10 (19.2)	<0.001
Follow-up duration (month)	5.8 (2.5–13.0)	6.7 (3.2–13.4)	3.3 (1.4–10.5)	0.010

HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist II.
Values are expressed as numbers (percentages) or median (interquartile range).

0.045) (Fig. 1A). The median PFS did not differ between regorafenib users (2.7 months; 95% CI=2.2–3.2) and nivolumab users (1.8 months; 95% CI=1.5–2.4; log-rank *p*=0.070) (Fig. 1B).

In the multivariate analyses including either OR or DC, the use of nivolumab (vs. regorafenib) did not show an independent association with reduced OS (*p*=0.216 including OR and 0.377 including DC), despite showing a significant relationship in the univariate analysis (HR=1.436; 95% CI=1.006–2.050; *p*=0.046) (Table 3 and Supplementary Table 2, only online). Other variables that were independently associated with OS included lymph node metastasis, AST level, ALP (only when OR was included), and a Child-Pugh score ≥7, along with achieving an OR (HR=0.216) and DC (HR=0.228) (all *p*<0.05) (Table 3). The use of nivolumab (vs. regorafenib) was not associated with PFS, both in the univariate (*p*=0.068) and multivariate analyses (*p*=0.377) (Table 4 and Supplementary Table 3, only online). Factors such as HBV infection, AST level, and achieving an OR were independently associated with PFS (all

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Table 2. Comparison of Overall Best Response after Second-Line Therapy

Best response*	Total (n=189)	Regorafenib (n=137; 72.5%)	Nivolumab (n=52; 27.5%)	*p* value
Cannot evaluate	38 (29.1)	25 (18.2)	13 (25.0)	
Complete response	1 (0.5)	0 (0.0)	1 (1.9)	
Partial response	16 (8.5)	10 (7.3)	6 (11.6)	0.234
Stable disease	44 (23.3)	35 (25.6)	9 (17.3)	
Progressive disease	90 (47.6)	67 (48.9)	23 (44.2)	
Objective response†	17 (9.0)	10 (7.3)	7 (13.5)	0.117
Disease control‡	61 (32.3)	45 (32.9)	15 (28.9)	0.681

Values are expressed as numbers (percentages).
*Treatment response was evaluated using the modified Response Evaluation Criteria in Solid Tumors (mRECIST); †Objective response was defined as achieving a complete response or a partial response; ‡Disease control was defined as achieving a complete response, a partial response, or a stable disease.

p<0.05) (Table 4).

Comparison of outcome after PS matching

A 1:1 PS matching with a caliper of 0.1 standard deviation yielded 34 pairs in the regorafenib and nivolumab groups, with a close balance between the two matched groups in terms of baseline covariates for almost all pairs included in the PS model (ASMDs<0.2), except for serum creatinine (ASMD=0.253) (Supplementary Fig. 2 and Supplementary Table 4, only online). Between the matched regorafenib and nivolumab groups, the median OS (6.7 months; 95% CI=4.3–13.1 vs. 6.7 months; 95% CI=3.4–11.2; log-rank p=0.810) and PFS (1.8 months; 95% CI=1.6–3.6 vs. 1.8 months; 95% CI=1.6–2.8; log-rank p=0.810) were similar after matching (Fig. 1C and D).

In the PS-matched cohort, ORR were higher in the matched nivolumab users; however, the difference was not statistically significant (17.6% vs. 2.9%, p=0.105) (Supplementary Table 5, only online). DCR were similar between the matched regorafenib (32.4%) and nivolumab (35.3%) users (p>0.999). The use of nivolumab (vs. regorafenib) was not significantly associated with OS and PFS, both in the univariate (p=0.796 and 0.927) and multivariate analyses (p=0.315 and 0.981, respectively) after PS matching (Supplementary Tables 6–9, only online). OS was independently associated with AST level, a Child-Pugh score ≥7, and achieving DC (Supplementary Table 7, only online), and PFS was independently associated with AST level (all p<0.05) (Supplementary Table 9, only online).

Comparison of outcomes after stabilized IPTW

After incorporating stabilized IPTW [ASMDs <0.2, except for hepatitis C virus (HCV) infection, ASMD=0.300], the weighted regorafenib (n=153; 63.7%) and nivolumab users (n=87; 36.3%) did not show any statistical differences in baseline characteristics (Supplementary Table 10, only online). The median OS was similar between the weighted regorafenib and nivolumab groups (7.4 months; 95% CI=5.9–9.9 vs. 4.2 months; 95% CI=2.7–8.5; log-rank p=0.445) (Fig. 1E), and the median PFS was also similar between the two groups (2.6 months; 95% CI=1.9–3.0 vs. 1.8 months; 95% CI=1.7–not applicable; log-rank p=0.878) (Fig. 1F).

In the IPTW cohort, regorafenib and nivolumab users showed similar prevalence of ORR (5.9% and 13.6%, respectively, p=0.187) and DCR (31.4% and 35.2%, respectively, p=0.848) (Supplementary Table 11, only online). The use of nivolumab (vs. regorafenib) was not significantly associated with OS and PFS, both in the univariate (p=0.423 and 0.927, respectively) and multivariate analyses (for OS, p=0.053 including OR and 0.086 including DC, and for PFS, p=0.168) after IPTW (Supplementary Tables 12–15, only online). OS was independently associated with AST, ALP, AFP (only when OR was included) levels, and a Child-Pugh score ≥7, along with achieving an OR (HR=0.265) and DC (HR=0.222) (all p<0.05) (Supplementary Table 13, only online). PFS was independently associated with HBV infection (HR=1.991), HCV infection (HR=0.274), AST level (HR=1.007), and achieving an OR (HR=0.269) (all p<0.05) (Supplementary Table 15, only online).

DISCUSSION

After introducing the robust clinical outcome of combination therapy for patients with advanced HCC by the previous clinical trial,[12] various systemic therapeutic options have been approved by regulatory agencies across the world and are undergoing clinical trials. However, treatments approved as second-line therapy after prior systemic therapy are still functionally only possible following sorafenib treatment.[20] Although ramucirumab and cabozantinib has been also approved as second-line multikinase inhibitors following sorafenib treatment in South Korea, regorafenib was the only reimbursed second-line systemic therapy by the Korean National Health Insurance Service in 2018, and nivolumab was the only available systemic immune checkpoint inhibitor for patients with HCC after sorafenib treatment. Therefore, regorafenib and nivolumab are the most commonly used second-line therapies for patients with HCC after sorafenib treatment in South Korea.[28] However, the demonstrated efficacy of the two therapies was not significantly different in this study.

To summarize the results of previous studies that compared the clinical outcomes between regorafenib and nivolumab, the

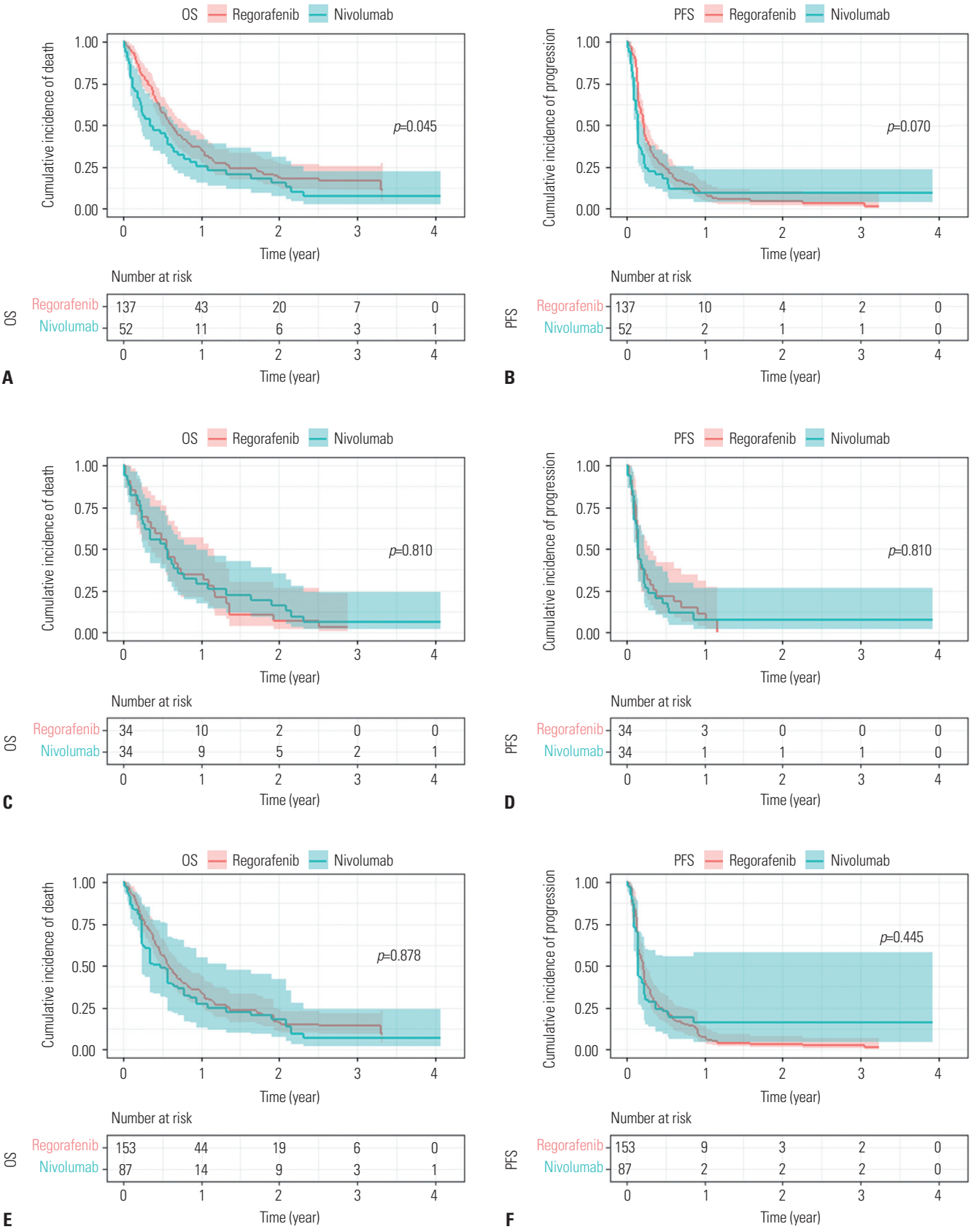

Fig. 1. Kaplan–Meier curves with survival analysis for regorafenib and nivolumab users. (A) OS and (B) PFS of the unmatched cohort, (C) OS and (D) PFS of the 1:1 propensity score-matched cohort, and (E) OS and (F) PFS of the covariate-adjusted cohort after the stabilized inverse probability of treatment weighting. OS, overall survival; PFS, progression-free survival.

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Table 3. Multivariate Cox Regression Analysis for Overall Survival

Variable	Univariate	Multivariate analysis		Multivariate analysis	
	p value	*p* value	HR (95% CI)	*p* value	HR (95% CI)
Nivolumab (vs. Regorafenib)	0.046	0.216	1.286 (0.864, 1.916)	0.377	1.201 (0.800, 1.804)
Previous liver resection	0.003	0.436	0.847 (0.557, 1.287)	0.340	0.809 (0.523, 1.251)
Portal vein invasion (Vp3–4)	<0.001	0.995	0.999 (0.640, 1.557)	0.588	1.129 (0.727, 1.754)
Lymph node metastasis	0.002	0.038	1.446 (1.021, 2.048)	0.037	1.446 (1.022, 2.046)
AST (IU/L)	<0.001	<0.001	1.008 (1.005, 1.011)	<0.001	1.007 (1.004, 1.010)
ALT (IU/L)	<0.001	0.461	0.998 (0.992, 1.004)	0.250	0.997 (0.991, 1.003)
Alkaline phosphatase (IU/L)	<0.001	0.002	1.003 (1.001, 1.005)	0.054	1.002 (1.000, 1.004)
AFP (ng/mL)	0.008	0.417	1.000 (1.000, 1.000)	0.834	1.000 (1.000, 1.000)
PIVKA-II (mAU/mL)	<0.001	0.583	1.000 (1.000, 1.000)	0.362	1.000 (1.000, 1.000)
Child-Pugh score ≥7	<0.001	0.007	1.818 (1.176, 2.810)	<0.001	2.516 (1.605, 3.943)
Adverse events after second-line therapy	0.001	0.135	0.745 (0.506, 1.096)	0.090	0.712 (0.481, 1.055)
Objective response	<0.001	<0.001	0.216 (0.101, 0.461)	-	-
Disease control	<0.001	-	-	<0.001	0.228 (0.149, 0.347)

HR, hazard ratio; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist II.

Table 4. Multivariate Cox Regression Analysis for Progression-Free Survival

Variable	Univariate	Multivariate analysis	
	p value	*p* value	HR (95% CI)
Nivolumab (vs. Regorafenib)	0.068	0.377	1.189 (0.810, 1.746)
Age (yr)	0.007	0.633	0.995 (0.976, 1.015)
HBV infection	0.001	0.006	1.835 (1.188, 2.833)
Sorafenib duration (month)	0.019	0.747	0.996 (0.973, 1.020)
Portal vein invasion (Vp3–4)	0.070	0.471	0.865 (0.582, 1.284)
Lymph node metastasis	<0.001	0.060	1.386 (0.987, 1.947)
AST (IU/L)	<0.001	<0.001	1.006 (1.003, 1.009)
ALT (IU/L)	<0.001	0.638	1.001 (0.996, 1.007)
Alkaline phosphatase (IU/L)	<0.001	0.075	1.002 (1.000, 1.003)
Child-Pugh score ≥7	0.002	0.186	1.320 (0.874, 1.994)
Adverse events after second-line therapy	0.036	0.556	0.903 (0.643, 1.268)
Objective response	<0.001	<0.001	0.249 (0.136, 0.456)

HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

prognosis was not significantly different when the data were analyzed with reduced selection bias through appropriate matching and weighting, although nivolumab was administered to more patients with reduced liver function relative to regorafenib and showed a greater change in achieving an OR. Lee, et al.[18] retrospectively analyzed 150 study patients (120 regorafenib users and 48 nivolumab users), of whom 3.9%–18.8% had Child-Pugh class B liver function, and found that nivolumab users had higher ORRs compared to regorafenib users (16.7% vs. 5.9%; p=0.04) and prolonged OS (adjusted HR=0.54; p=0.04), which was maintained after IPTW. Choi, et al.[19] also reported a retrospective study including 223 regorafenib users and 150 nivolumab users, of whom 26.5%–37.3% had Child-Pugh class B liver function, and found that the nivolumab users showed a significantly higher ORR compared to regorafenib users; however, it was not associated with a longer OS, PFS, or time to progression before and after PS matching and IPTW analysis (median OS before matching=30.9 weeks in regorafenib users vs. 32.6 in nivolumab, p=0.154). Another retrospective study by Kuo, et al.[17] included 67 regorafenib users and 52 nivolumab users, of whom 3.4%–21.9% had Child-Pugh class B liver function, and the median OS did not significantly differ between regorafenib and nivolumab users (11 months vs. 14 months; p=0.763). The study also showed that nivolumab users had a higher ORR, although the difference was not statistically significant (16% vs. 6.4%; p=0.190).[17]

Our study presents similar findings that regorafenib and nivolumab, as post-sorafenib systemic therapies for advanced HCC, showed similar therapeutic benefits, even if nivolumab might be beneficial in achieving an OR. The ORR tended to be higher in nivolumab users (13.5% vs. 7.3%), even if the difference was not significant (p=0.117). A higher proportion of extrahepatic lesions (85.7%) and Child-Pugh class B liver function (29.1%) resulted in a lower ORR compared to those observed in randomized trials for regorafenib (11.0%) and nivolumab (13.3%).[13,16] The median OS in regorafenib users was significantly longer (7.4 months vs. 4.2 months, p=0.045), which may be due to a higher proportion of patients with Child-Pugh class B liver function in nivolumab users (42.3% vs. 24.1%). However, ORR and DCR did not differ between regorafenib and nivolumab users after 1:1 PS matching and stabilized IPTW.

Moreover, covariate-adjusted Cox regression analyses in the PS-matched and IPTW cohorts also revealed that the selection of second-line treatment was not associated with clinical outcomes, whereas the reduced liver function, disease extension, such as lymph node metastasis, and achieving an OR and DC were associated with patient prognosis, although there were slight variations among individual analyses. Furthermore, a

considerable proportion of the patients were unable to evaluate their treatment response (29.1%) due to early mortality and severe adverse events. Although our study involved a retrospective review over an extended period (up to 48.8 months), which is longer compared to previous studies, the median follow-up duration for our study cohort was similarly short (5.8 months) due to early mortality. Therefore, it is important to adequately exclude patients with advanced HCC who are not expected to tolerate treatment, especially patients with a reduced liver function,[29] and develop a treatment strategy that maximizes efficacy without compromising safety.

Our study had several limitations. First, although this study attempted to overcome the potential differences between untreated and treated patients using PS matching and IPTW, unmeasured confounding factors may have influenced the selection of second-line therapy, considering the different reimbursements in South Korea. However, since our results were similar to those presented in previous studies using two separate methods, PS matching and IPTW, this bias may have been negligible. Second, the indication for nivolumab monotherapy as a second-line systemic therapy was withdrawn in late April 2021 by the United States Food and Drug Administration, and a clinical trial supported the approval of a combination treatment with nivolumab and ipilimumab,[30] which may limit the clinical utility of our findings. However, nivolumab monotherapy after sorafenib treatment failure is still an available treatment strategy in some countries such as South Korea, the data presented in this study can be a helpful indicator for clinicians for the time being. Since the combination therapy of nivolumab and ipilimumab has been reported to have a higher rate of adverse effects than nivolumab monotherapy, a comparison of the efficacy and safety with regorafenib is needed in the future.

In conclusion, second-line regorafenib and nivolumab showed similar OS, PFS, and DCR in patients with advanced HCC after sorafenib failure. Clinical decision-making for second-line therapy should be based on the patient's condition, including liver function and disease extent.

DATA TRANSPARENCY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, Do Young Kim. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

AUTHOR CONTRIBUTIONS

Conceptualization: Hong Jun Lee, Jae Seung Lee, and Do Young Kim. Data curation: Hong Jun Lee, Jae Seung Lee, and Hyesung So. Formal analysis: Hong Jun Lee, Jae Seung Lee, and Hyesung So. Funding acquisition: Do Young Kim. Investigation: Hong Jun Lee, Jae Seung Lee, Ja Kyung Yoon, and Jin-Young Choi. Methodology: Hong Jun Lee and Jae Seung Lee. Project administration: Do Young Kim. Resources: Jae Seung Lee, Hye Won Lee, Beom Kyung Kim, Seung Up Kim, Jun Yong Park, Sang Hoon Ahn, and Do Young Kim. Supervision: Jae Seung Lee and Do Young Kim. Visualization: Hong Jun Lee and Jae Seung Lee. Writing—Original draft: Hong Jun Choi, Jae Seung Lee, and Do Young Kim. Writing—Review and Editing: all authors. Approval of final manuscript: all authors.

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