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Original Article

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A Real-World Experience on a Chinese Population of Patients With Unresectable Hepatocellular Carcinoma Treated With Nivolumab

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Abstract

Background: For unresectable hepatocellular carcinoma (HCC), nivolumab (anti-programmed death receptor-1 (PD-1)) is used as non-curative interventions. The aim of the study was to focus on the real-world experience of nivolumab applied to patients with HCC.

Methods: Unresectable HCC patients receiving nivolumab treatments at Taichung Veterans General Hospital, from June 2018 to May 2020, were recruited. Exclusion criteria were Child-Pugh stage C, poor performance status, a lack of compliance or intolerable to drug treatments. The tumor radiological responses and survival outcomes of enrolled patients were collected and analyzed.

Results: Among a total of 57 patients, most of them were classified as Child-Pugh stage A (70.2%) and Barcelona Clinic Liver Cancer (BCLC) stage C (66.7%). Nivolumab was given to 14 (24.6%) as the primary-line, and 43 patients (75.4%) as the secondary-line systemic treatments. The mean therapeutic duration was 6.5 months. Objective response rate (ORR) was 24.6%, and disease control rate (DCR) was 42.1%. The overall median progression-free survival (PFS) was 5.8 months (95% confidence interval (CI): 1.1 - 10.6), and overall survival (OS) was 11.5 months (95% CI: 4.3 - 17.8). Immune-related adverse event (IRAE) was 8.8%. Presence of alpha-fetoprotein (AFP) response (a decline in AFP ≥ 10% from baseline) during therapy predicted the tumor radiological response (to objective response: hazard ratio (HR): 4.89, 95% CI: 1.14 - 21.00; to disease control: HR: 4.71, 95% CI: 1.32 - 16.81). Those with tumor radiological responses showed longer PFS and OS.

Conclusions: Decline in AFP during therapy has a predicting role on HCC radiological responses to nivolumab. Achieving radiological responses had better survival outcomes.

Keywords: Alpha-fetoprotein; Hepatocellular carcinoma; Nivolumab

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Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related morbidity worldwide, and most HCC cases occur with chronic liver inflammation [1]. Treatments of HCC depend on disease stages, typically according to the Barcelona Clinic Liver Cancer (BCLC) staging, which considers prognosis-related factors, such as tumor burden, liver function and performance status [2, 3]. In patients with intermediate (BCLC stage B) or advanced (BCLC stage C) HCC, non-curative interventions are used, with the aim to prolong survival by slowing tumor progression. These interventions are as follows: for patients with intermediate HCC, transarterial chemoembolization (TACE) [4], and for patients with advanced HCC or intermediate HCC with unsuitable for locoregional therapy, systemic therapy with tyrosine kinase inhibitor (TKI) or immunotherapeutic agents [5, 6].

Currently, four first-line treatments options are available, which include sorafenib (SOR), lenvatinib (LEN), the combination of atezolizumab with bevacizumab (Beva), and the combination of tremelimumab with durvalumab, based on the successful phase 3 studies [7].

Two common immunotherapies clinically used for second-line therapies on patients with HCC are nivolumab and pembrolizumab, which both target programmed death receptor-1 (PD-1) [6]. According to the phase 1/2 CheckMate 040 trial, nivolumab is effective as the second-line therapies for patients with HCC after failed responses to SOR [8].

The aim of our study was to focus on the real-world experience of nivolumab in treating patients with unresectable HCC.

Materials and Methods

HCC patients, diagnosed at Taichung Veterans General Hospital in accordance with American Association for the Study of Liver Disease (AASLD) guideline [9], were recruited for study during the period from June 2018 to May 2020. The inclusion criterion was unresectable HCC receiving nivolumab treatments. Exclusion criteria were those with cirrhotic Child-Pugh stage C, poor performance status, a lack of compliance or intolerability to drugs within the following day or missing any follow-ups. Clinical parameters were collected for all enrolled patients, including age, gender, liver function such as total bilirubin, albumin, alpha-fetoprotein (AFP), presence of chronic hepatitis B virus (HBV), hepatitis C virus (HCV), macroscopic vascular invasion (MVI), extrahepatic spread (EHS), cirrhotic Child-Pugh stage, albumin-bilirubin (ALBI) grade and BCLC stage. During the study period, the uses of combined TKI, such as SOR or LEN, or local-regional therapy (LRT), such as TACE or radiofrequency ablation (RFA), were also recorded.

After initial administration of nivolumab, patients returned for follow-up appointments at the outpatient clinic every 2 weeks and received continuous nivolumab treatments. The dosage of nivolumab each patient received was determined by the hepatologist. Nivolumab usage was discontinued if tumor progression had been found from follow-up imaging studies. The therapeutic duration, as well as dosage of nivolumab for each of the enrolled patients were recorded.

Throughout the study period, patients were assessed every 4 to 8 weeks by dynamic imaging. Any death, disease progression or treatment failure with nivolumab were recorded. Immune-related adverse events (IRAEs) were also recorded. AFP response was defined as a decline in AFP level $\geq$ 10% from baseline during therapy. To assess tumor responses, mRECIST criteria [10] was adapted and classified in four response categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Patients with CR or PR were considered having objective response, and patients with CR, PR or SD were considered having disease control. Objective response rate (ORR) and disease control rate (DCR) were calculated. Progression-free survival (PFS) was defined as the time from the start of study until disease progression or death. Overall survival (OS) was defined as the time from the start of study until death within the study period.

Data were expressed as mean and standard deviation of each measured parameter. The positive rates of individual stratified groups were expressed as percentages of the individual groups. Statistical comparisons were made using univariate or multivariate logistic regression to determine strengths of association between clinical parameters and tumor responses following nivolumab. Hazard ratio (HR) and 95% confidence interval (CI) were calculated, and statistical significance was set at $P \leq 0.05$. Survival analyses were carried out using the Kaplan-Meier method.

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of Taichung Veterans General Hospital approved this study (CF21236B).

Results

A total of 57 patients were enrolled for study. Their characteristics are shown in Table 1. Their median age was 66.7 years, with male predominance (84.2%). Chronic HBV was found in 28 patients (49.1%) and HCV infection in 14 patients (24.6%). The majority of them were classified as cirrhotic Child-Pugh stage A (70.2%), and BCLC stage C (66.7%) at the time of enrollment. ALBI grade 1 was found in 25 cases (43.9%), grade 2 in 30 cases (52.6%) and grade 3 in two cases (3.5%).

There were 21 patients (36.8%) with MVI, and 25 patients (43.9%) with EHS. Among all patients, 14 received nivolumab as the primary systemic therapy (24.6%), and 43 as the secondary-line treatment (75.4%). During the nivolumab therapeutic course, nine patients (15.8%) had combined TKI, and eight patients (14.0%) had LRT. The average nivolumab dosage was 2.5 mg/kg, and the mean duration of medication was 6.5 months.

Therapeutic responses of these patients with nivolumab are listed in Table 2. The radiological responses are as follows: two (3.5%) with CR, 12 (21.1%) with PR, 10 (17.5%) with SD, and 33 cases (57.9%) with PD. Overall, ORR was 24.6%, and DCR was 42.1%. For all patients, their median PFS was 5.8 months (95% CI: 1.1 - 10.6), and OS was 11.5 months (95% CI: 4.3 - 17.8). Only five patients (8.8%) reported IRAE to nivolumab treatments, which included three cases of skin-related adverse effects and two with hepatic adverse effects. Positive AFP responses were noted in 17 patients (30.4%).

Logistic analyses of the patients with objective responses to nivolumab are listed in Table 3. According to the univariable analysis, presence of HCV infection (HR: 5.14, 95% CI: 1.36 - 19.33, P = 0.015) and AFP response (HR: 7.65, 95% CI: 2.01 - 29.14, P = 0.003) had significant positive impacts to achieve the tumor objective response. Patients with age $\leq$ 65 years old (HR: 0.17, 95% CI: 0.03 - 0.88, P = 0.034) had a negative impact. After adjustments by the multivariable analysis, AFP response (HR: 4.89, 95% CI: 1.14 - 21.00, P = 0.033) still had the statistical strength in predicting the tumor objective response.

Logistic analyses of patients with disease control to nivolumab are listed in Table 4. According to the multivariable analysis, AFP response (HR: 4.71, 95% CI: 1.32 - 16.81, P = 0.017) also had the statistical strength in predicting tumor disease control.

Logistic analyses of OS of patients are listed in Table 5. According to the logistic analysis, none of the clinical parameters, including age, gender, Child-Pugh stage, ALBI grade, BCLC stage, presence of MVI and EHS, and baseline or during therapy AFP levels, was associated with the length of OS. Similarly, as primary or secondary-line systemic therapy, dosage of nivolumab, presence of IRAE, and combination of TKI or LRT had no impacts to the OS of our patients.

As shown in Figure 1 and Table 6, the median PFS for patients with tumor objective response to nivolumab was 8.4 months (95% CI: 2.5 - 14.3), and for those without such re-

Table 1. The General Data of Patients

	All (n = 57)	
	Mean ± SD	N (%)
Age (years)	66.7 ± 9.8	
≤ 65		34 (59.6%)
> 65		23 (40.4%)
Gender		
Male		48 (84.2%)
Female		9 (15.8%)
Viral hepatitis		
HBV		26 (45.5%)
HCV		12 (21.1%)
HBV/HCV		2 (3.5%)
Nil		17 (29.9%)
Child-Pugh stage		
A		40 (70.2%)
B		17 (29.8%)
ALBI grade		
1		25 (43.9%)
2		30 (52.6%)
3		2 (3.5%)
BCLC stage		
B		19 (33.3%)
C		38 (66.7%)
MVI		21 (36.8%)
EHS		25 (43.9%)
Systemic therapy line		
First-line		14 (24.6%)
Second-line		43 (75.4%)
Combined TKI		9 (15.8%)
Combined LRT		8 (14.0%)
Nivolumab dosage (mg/kg)	2.5 ± 0.7	
≤ 2 mg/kg		19 (33.3%)
> 2 mg/kg		38 (66.7%)
Nivolumab duration (months)	6.5 ± 5.9	
Total bilirubin (mg/dL)	1.0 ± 0.7	
Albumin (g/dL)	3.7 ± 0.6	
NLR		
> 5		14 (24.6%)
≤ 5		43 (75.4%)
AFP (ng/mL)	10,544.1 ± 46,120.1	
> 400 ng/mL		18 (31.6%)
≤ 400 ng/mL		39 (68.4%)

BCLC: Barcelona Clinic Liver Cancer; AFP: alpha-fetoprotein; EHS: extrahepatic spread; HBV: hepatitis B virus; HCV: hepatitis C virus; LRT: local regional therapy; MVI: microscopic vascular invasion; N: number of patients; NLR: neutrophil to lymphocyte ratio; SD: standard derivation; TKI: tyrosine kinase inhibitor; ALBI: albumin-bilirubin.

Table 2. The Therapeutic Responses of Patients Treated With Nivolumab

	All (n = 57)		
	Mean	95% CI	N (%)
Radiological tumor responses			
CR			2 (3.5%)
PR			12 (21.1%)
SD			10 (17.5%)
PD			33 (57.9%)
ORR			14 (24.6%)
DCR			24 (42.1%)
OS (months)	11.5	4.3 - 17.8	
PFS (months)	5.8	1.1 - 10.6	
IRAE			5 (8.8%)
AFP response[a]			17 (30.4%)

[a]Defined as decline AFP level over 10% from baseline during nivolumab therapy. AFP: alpha-fetoprotein; CR: complete response; DCR: disease control rate; IRAE: immune-related adverse event; N: number of patients; ORR: objective response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; SD: stable disease; CI: confidence interval.

sponse, it was 4.9 months (95% CI: 0.8 - 9.0). Their difference was statistically significant (HR: 2.63, 95% CI: 1.23 - 5.66, P = 0.013). For those with tumor disease control to nivolumab, their mean PFS was 8.3 months (95% CI: 2.7 - 13.9), and for those without such control, it was 3.9 months (95% CI: 0.8 - 7.0). Again, their difference was statistically significant (HR: 2.89, 95% CI: 1.56 - 5.37, P = 0.008).

As shown in Figure 2 and Table 6, patients with tumor disease control to nivolumab had significantly longer OS than those without (median OS: 13.8 vs. 9.8 months, HR: 2.09, 95% CI: 1.07 - 4.08, P = 0.032). However, no significant difference was found between those with tumor objective response to nivolumab and those without (median OS: 13.5 vs. 10.8 months, HR: 1.53, 95% CI: 0.71 - 3.34, P = 0.284).

Discussion

Liver cancer is a common cancer worldwide, and HCC accounts for 90% of primary liver cancer cases. It occurs predominantly in patients with underlying chronic liver disease and cirrhosis [11]. For the treatment of unresectable HCC, LRT with TACE and systemic therapy with targeted or immunotherapeutic agents are recommended [4-6].

SOR was the first TKI approved for clinical use as the first-line treatment for unresectable HCC. Its application started in 2007 according to two phase 3 studies [5, 12]. Another TIK, LEN, was also approved for first-line treatment of advanced or unresectable HCC based on a phase 3 non-inferiority report [13]. More recently, atezolizumab in combination with bevacizumab was also reported effective in the first-line treatment of unresectable HCC according to a phase 3 trial evaluation [14].

Table 3. The Strength of Association Between Clinical Parameters and Tumor Objective Response Following Nivolumab Usage

	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (≤ 65 vs. > 65 years old)	0.17	0.03 - 0.88	0.034	0.25	0.04 - 1.38	0.110
Gender (male vs. female)	0.86	0.16 - 4.70	0.859			
HBV (HbsAg + vs. -)	0.72	0.21 - 2.42	0.590			
HCV (anti-HCV + vs. -)	5.14	1.36 - 19.33	0.015	2.98	0.64 - 13.73	0.162
Child-Pugh stage (B vs. A)	0.31	0.61 - 1.58	0.159			
ALBI grade (2/3 vs. 1)	0.72	0.21 - 2.42	0.595			
BCLC stage (C vs. B)	0.87	0.25 - 3.08	0.828			
Baseline AFP (> 400 vs. ≤ 400 ng/mL)	1.94	0.55 - 6.77	0.300			
AFP response[a] (yes vs. no)	7.65	2.01 - 29.14	0.003	4.89	1.14 - 21.00	0.033
MVI (yes vs. no)	0.61	0.16 - 2.27	0.463			
EHS (yes vs. no)	0.95	0.28 - 3.20	0.931			
Systemic therapy (second-line vs. first-line)	0.76	0.19 - 2.95	0.737			
Combined TKI (yes vs. no)	1.68	0.36 - 7.85	0.508			
Combined LRT (yes vs. no)	1.03	0.18 - 5.78	0.975			
Nivolumab dosage (> 2 vs. ≤ 2 mg/kg)	1.34	0.36 - 5.00	0.664			
NLR (≤ 5 vs. > 5)	1.26	0.30 - 5.37	0.754			
IRAE (yes vs. no)	5.59	0.83 - 37.71	0.077			

[a]Defined as decline AFP level over 10% from baseline during nivolumab therapy. BCLC: Barcelona Clinic Liver Cancer; AFP: alpha-fetoprotein; CI: confidence interval; EHS: extrahepatic spread; HBV: hepatitis B virus; HCV: hepatitis C virus; HR: hazard ratio; IRAE: immune-related adverse event; LRT: local regional therapy; MVI: microscopic vascular invasion; NLR: neutrophil to lymphocyte ratio; TKI: tyrosine kinase inhibitor; ALBI: albumin-bilirubin.

Table 4. The Strength of Association Between Clinical Parameters and Tumor Disease Control Following Nivolumab Usage

	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (≤ 65 vs. > 65 years old)	0.31	0.10 - 0.99	0.048	0.41	0.12 - 1.40	0.156
Gender (male vs. female)	0.64	0.14 - 2.88	0.564			
HBV (HbsAg + vs. -)	0.60	0.21 - 1.72	0.338			
HCV (anti-HCV + vs. -)	2.25	0.66 - 7.67	0.195			
Child-Pugh stage (B vs. A)	0.75	0.24 - 2.35	0.622			
ALBI grade (2/3 vs. 1)	0.87	0.30 - 2.51	0.798			
BCLC stage (C vs. B)	0.72	0.24 - 2.20	0.569			
Baseline AFP (> 400 vs. ≤ 400 ng/mL)	2.23	0.72 - 6.96	0.166			
AFP response[a] (yes vs. no)	5.40	1.55 - 18.76	0.008	4.71	1.32 - 16.81	0.017
MVI (yes vs. no)	0.56	0.18 - 1.71	0.308			
EHS (yes vs. no)	0.85	0.30 - 2.48	0.776			
Systemic therapy (second-line vs. first-line)	0.65	0.19 - 2.20	0.492			
Combined TKI (yes vs. no)	1.91	0.45 - 8.02	0.378			
Combined LRT (yes vs. no)	0.80	0.17 - 3.73	0.776			
Nivolumab dosage (> 2 vs. ≤ 2 mg/kg)	1.39	0.45 - 4.30	0.570			
NLR (≤ 5 vs. > 5)	1.53	0.45 - 5.14	0.492			
IRAE (yes vs. no)	6.40	0.70 - 61.42	0.108			

[a]Defined as decline AFP level over 10% from baseline during nivolumab therapy. BCLC: Barcelona Clinic Liver Cancer; AFP: alpha-fetoprotein; CI: confidence interval; EHS: extrahepatic spread; HBV: hepatitis B virus; HCV: hepatitis C virus; HR: hazard ratio; IRAE: immune-related adverse event; LRT: local regional therapy; MVI: microscopic vascular invasion; NLR: neutrophil to lymphocyte ratio; TKI: tyrosine kinase inhibitor; ALBI: albumin-bilirubin.

Table 5. The Strength of Association Between Clinical Parameters and Overall Survival Following Nivolumab Usage

	Univariable analysis		
	HR	95% CI	P value
Age (≤ 65 vs. > 65 years old)	0.60	0.32 - 1.13	0.112
Gender (male vs. female)	0.59	0.27 - 1.29	0.187
HBV (HbsAg + vs. -)	0.74	0.40 - 1.40	0.356
HCV (anti-HCV + vs. -)	2.36	1.02 - 5.40	0.043
Child-Pugh stage (B vs. A)	0.75	0.38 - 1.49	0.418
ALBI grade (2/3 vs. 1)	0.58	0.30 - 1.11	0.101
BCLC stage (C vs. B)	0.61	0.30 - 1.27	0.187
Baseline AFP (> 400 vs. ≤ 400 ng/mL)	0.80	0.41 - 1.57	0.523
AFP response[a] (yes vs. no)	1.38	0.69 - 2.80	0.364
MVI (yes vs. no)	0.86	0.45 - 1.64	0.646
EHS (yes vs. no)	0.58	0.31 - 1.10	0.095
Systemic therapy (second-line vs. first-line)	0.85	0.42 - 1.75	0.667
Combined TKI (yes vs. no)	1.34	0.61 - 2.92	0.463
Combined LRT (yes vs. no)	1.75	0.68 - 4.50	0.245
Nivolumab dosage (> 2 vs. ≤ 2 mg/kg)	1.03	0.53 - 2.00	0.921
NLR (≤ 5 vs. > 5)	1.17	0.57 - 2.41	0.663
IRAE (yes vs. no)	5.58	0.76 - 40.88	0.091

[a]Defined as decline AFP level over 10% from baseline during nivolumab therapy. BCLC: Barcelona Clinic Liver Cancer; AFP: alpha-fetoprotein; CI: confidence interval; EHS: extrahepatic spread; HBV: hepatitis B virus; HCV: hepatitis C virus; HR: hazard ratio; IRAE: immune-related adverse event; LRT: local regional therapy; MVI: microscopic vascular invasion; NLR: neutrophil to lymphocyte ratio; TKI: tyrosine kinase inhibitor; ALBI: albumin-bilirubin.

Since 2017, other multi-kinase inhibitors, like regorafenib, cabozantinib and ramucirumab (AFP ≥ 400 ng/mL), have been approved for treating advanced HCC after prior SOR treatment [15-17].

Nivolumab is a recombinant anti-PD-1 monoclonal antibody. It is administered through intravenous infusion. In a single-arm phase 1/2 CheckMate 040 trial, it was designed as a second-line therapy for HCC who did not respond to SOR. The ORR with nivolumab was 20%, and DCR was 64% [7, 18, 19]. Thus, the drug received accelerated approval as a second-line therapy for unresectable HCC. However, in the phase 3 CheckMate 459 trial, aimed as a potential first-line systemic treatment for HCC, the OS of patients with nivolumab treatments was not statistically better than those with SOR treatments (HR: 0.85, 95% CI: 0.72 - 1.02; P = 0.0752) [20].

Some real-world studies were reported, focusing on the

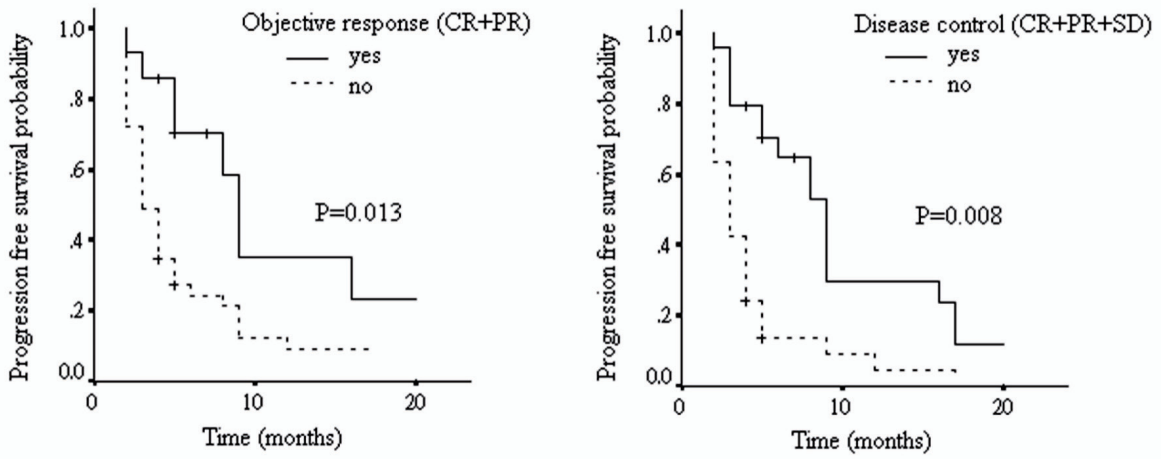

Figure 1. The progression-free survival of patients with different tumor radiological responses (CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease).

Table 6. The Strength of Association Between Survival Outcomes and Best Tumor Radiological Responses Following Nivolumab Usage

	Univariable analysis		
	HR	95% CI	P value
Progression-free survival			
OR vs. non-OR	2.63	1.23 - 5.66	0.013
DC vs. non-DC	2.89	1.56 - 5.37	0.008
Overall survival			
OR vs. non-OR	1.53	0.71 - 3.34	0.284
DC vs. non-DC	2.09	1.07 - 4.08	0.032

CI: confidence interval; DC: disease control; HR: hazard ratio; OR: objective response.

effectiveness of nivolumab in patients with unresectable HCC. One international, multicenter, real-world cohort, enrolled 64 patients with advanced HCC, who were given PD-1 immunotherapy, including nivolumab (n = 34) or pembrolizumab (n = 31). They found ORR of 12%, and DCR of 49%. Their median PFS was 4.6 months (95% CI: 3.0 - 6.2), and median OS was 11.0 months (95% CI: 8.2 - 13.8). Further investigations found significantly shorter OS in cases with Child-Pugh stage B compared with cases with stage A (8.6 vs. 16.7 months, P = 0.065) [21]. Another retrospective single-center study was conducted in Taiwan, on 95 patients with unresectable HCC receiving PD-1 immunotherapy, including nivolumab (n = 92) and pembrolizumab (n = 3). They found ORR of 24.4%, and DRR of 36.7%. Declines in AFP > 10% within 4 weeks was the independent predictor of achieving tumor objective response (HR: 7.259, P = 0.001). Their median OS was 11.9 months (95% CI: 5.6 - 18.2), and early decline AFP, ALBI grade and Child-Pugh stage were also independent factors associated with OS [22].

One recent international multicenter observational study, on 233 patients receiving nivolumab as HCC treatment, reported ORR of 22.4%, and DCR of 52.1%. Their median PFS was 10.1 months (95% CI: 6.1 - 14.2), and OS was 12.2 months (95% CI: 8.4 - 16.0). The OS was shorter for those in Child-Pugh stage B than in stage A (7.3 vs. 16.3 months, P < 0.001), and also in post-first line use (10.4 vs. 16.3 months, P = 0.05). Achievements of tumor objective response were predictive of improved OS (25.4 vs. 13.2 months, P < 0.001) [23]. One retrospective single-center study in Korea evaluated 203 patients with advanced HCC under nivolumab treatment. They found a shorter ORR for patients in Child-Pugh stage B than in stage A (2.8% vs. 15.9%, P = 0.010). Their median OS was also shorter in Child-Pugh stage B patients (11.3 vs. 42.9 weeks, adjusted hazard ratio (aHR) 2.10, P < 0.001) [24]. Another retrospective study was conducted in Taiwan on 87 patients with unresectable HCC over a median nivolumab treatment period of 2.53 months. Their final outcomes were ORR of 19.5%, and DCR of 39.1%, respectively. Declined AFP levels of ≥ 20% within the first 3 months of treatment was a predictor of achieving OR (OR: 5.997, P = 0.042). Their median PFS was 2.67 months, and OS was 5.87 months. The lack of MVI, combination therapy, and AFP response were predictors of PFS. Cancer of the Liver Italian Program (CLIP) scores of 0 to 2 (HR: 3.717, P = 0.004) and grade 1 to 2 IRAE (HR: 2.217, P = 0.049) were also predictors of OS [25].

Our present findings in our patients show an ORR of 24.6% and DCR of 42.1%, which are comparable to previous studies. The only significant factor of radiological responses to the HCC patients receiving nivolumab treatments was the AFP response. That was defined as a decline AFP levels ≥ 10% with reference to baseline during nivolumab therapy. Other factors, including age, gender, Child-Pugh stage, ALBI grade, BCLC stage, presence of MVI and EHS, baseline AFP, whether nivolumab was used as primary or secondary-line systemic therapy, dosage of nivolumab, presence of IRAE, combination of TKI or LRT, were not at all found to be associated with the best tumor radiological responses.

The median PFS and OS of all our enrolled cases were 5.8 and 11.5 months, respectively. Achievements of tumor objective response or disease control were associated with longer PFS, and achievements of tumor disease control predicted better OS. Therefore, in absence of molecular predictors, the

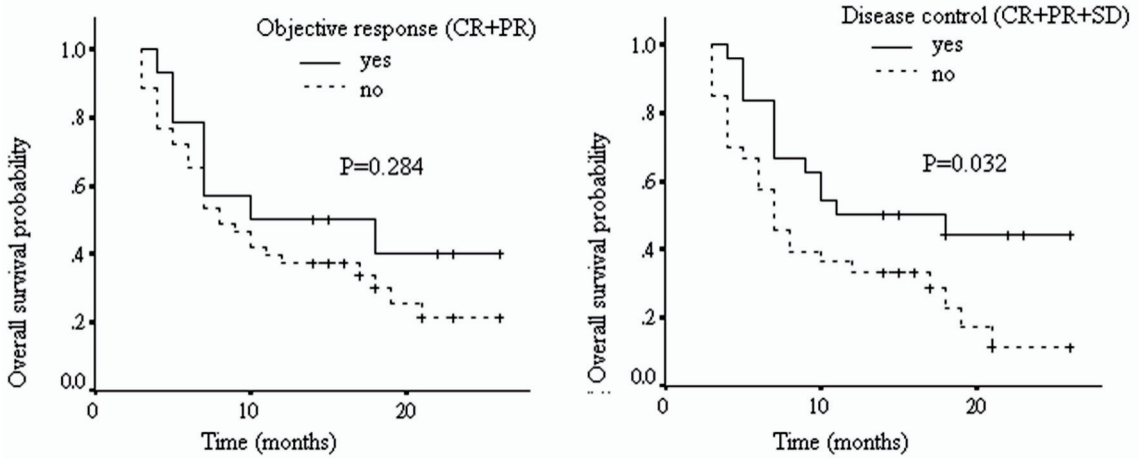

Figure 2. The overall survival of patients with different tumor radiological responses (CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease).

achievement of radiological response following nivolumab can help clinicians identify patients who are likely to derive long-term benefit from nivolumab therapy.

Different from previous studies, our results found no association between OS and Child-Pugh stage (B vs. A: 9.9 vs. 12.1 months, HR: 0.75, 95% CI: 0.38 - 1.49, P = 0.418). The reason could be related to the limited ample size and short follow-up periods. We also found a lower ratio of IRAE (8.8%) with nivolumab compared with previous studies. For example, in the phase 3 CheckMate 459 trial, they found a ratio of 22% grade 3/4 IRAE, which led to a 4% discontinuation [20]. The explanation of the discrepancy in results could be due to the exclusion of patients intolerant to nivolumab in our study, resulting in an underestimated incidence of IRAE.

Our study had several limitations. First, this is a retrospective study, and selection or reporting bias may have existed. Second, our sample size was relatively small, and the follow-up period was relatively short. Third, the PD-L1 expression in the tumor or immune cells was not assessed. Further prospective studies are needed on more patients and with more variables.

In conclusion, we found that the efficacy of nivolumab for unresectable HCC is acceptable. The decline in AFP during therapy is a predictor of tumor radiological responses, and achieving radiological responses predicted better survival outcomes.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

This study was designed and conducted in accordance with the IRB and consisted of retrospective chart review. The information in the manuscript is fully confidential and does not contain any individual patient identifiers. All the informed consents from the patients for publication of the manuscript were obtained.

Author Contributions

SW Lee and TY Lee designed and coordinated this study. SW Lee, SS Yang and TY Lee were responsible for chart review and data collection. SW Lee and TY Lee wrote the manuscript and all subsequent revisions. SW Lee performed the statistical analysis and created all tables and figures for publication.

Data Availability

The authors declare that data supporting the findings of this study are available within the article. Furthermore, the raw data supporting the findings of this study are available from the corresponding author upon reasonable request.

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