

# Outcomes of Post-Immunotherapy Durable Responders of Advanced Hepatocellular Carcinoma– with Emphasis on Locoregional Therapy for Oligoprogression

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## Keywords

Hepatocellular carcinoma · Immunotherapy · Durable response · Locoregional therapy · Oligoprogression

## Abstract

**Introduction:** The progression patterns, dispositions, and outcomes of patients with advanced hepatocellular carcinoma (HCC) who achieved durable responses with immu-

notherapy remain poorly characterized. **Methods:** Patients with advanced HCC who received immune checkpoint inhibitor (ICI)-based immunotherapy and achieved durable responses were retrospectively included. A durable response was defined as partial response (PR) or stable disease (SD) per RECIST 1.1 for more than 8 months after initiation of immunotherapy. Oligoprogression and polyprogression were defined as progression at  $\leq 3$  and  $>3$  lesions, respectively. **Results:** A total of 91 durable responders (63 PR and

28 SD) were identified. The majority had chronic viral hepatitis ( $n = 69, 75.8\%$ ). Forty-seven (51.6%) and 44 (48.4%) patients received the index immunotherapy as first-line and second- or beyond-line therapy, respectively. Fifty-four (59.3%) patients subsequently developed progression, with a predominant pattern of oligoprogression (66.7%). The median overall survival (OS) was 46.2 months (95% CI: 34.1–58.3). For patients with subsequent progression, employment of locoregional therapy (LRT) for progression was associated with prolonged OS (univariate analysis: hazard ratio [HR] 0.397,  $p = 0.009$ ; multivariate analysis: HR 0.363,  $p = 0.050$ ). Patients with oligoprogression who received LRT showed longer median OS than those who did not (48.4 vs. 20.5 months,  $p < 0.001$ ). In contrast, the median OS of patients with polyprogression who received LRT was not different from those without LRT (27.7 vs. 25.5 months,  $p = 0.794$ ). **Conclusion:** Approximately 60% of the post-immunotherapy durable responders of HCC subsequently develop progression. Proactive LRT may further rescue patients who develop subsequent oligoprogression. Prospective studies are mandatory to clarify the proper management of durable responders with subsequent progression.

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Published by S. Karger AG, Basel

## Introduction

Immune checkpoint inhibitors (ICIs) exhibit novel response patterns that are less commonly observed with cytotoxic chemotherapy or targeted therapies [1]. One of the novel response patterns is a durable response, predominantly characterized in patients with lung cancer and melanoma [2–4]. Durable responses have also been noted in patients with hepatocellular carcinoma (HCC) receiving ICI-based immunotherapies [5, 6]. Approximately 30% of patients receiving atezolizumab-bevacizumab in IMbrave150 trial experienced a partial response (PR) or stable disease (SD) for more than 6 months, with half of them eventually developing progression [7]. However, the progression patterns, associated dispositions, and long-term outcomes of these durable responders were less characterized in clinical trials and previous scientific literature.

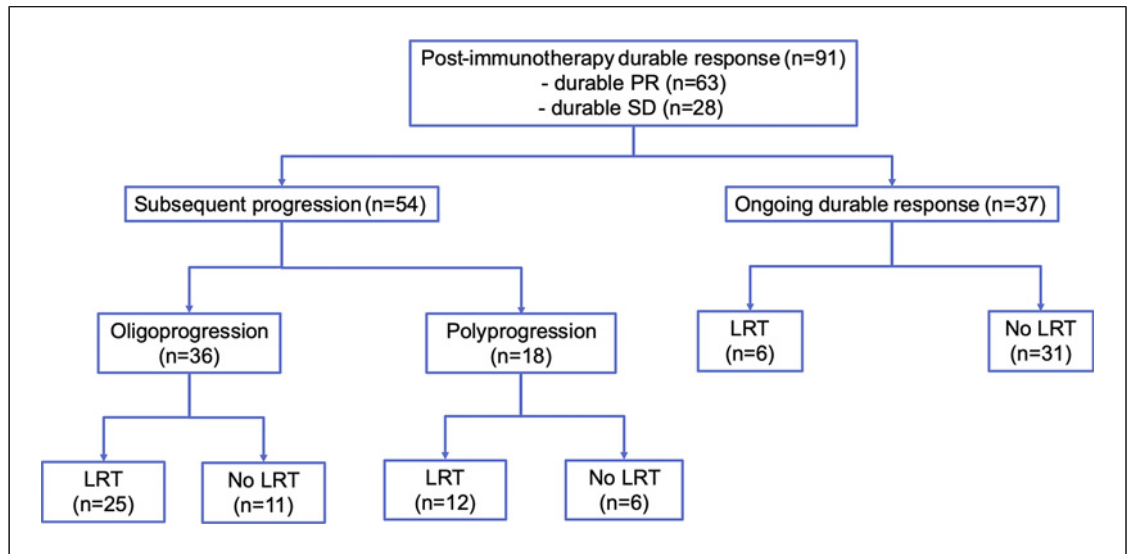
Locoregional therapies (LRTs), including resection, ablation, liver transplant, transarterial chemoembolization (TACE), transarterial radioembolization (TARE), stereotactic body radiation therapy, and hepatic arterial infusional chemotherapy (HAIC), have been commonly employed in the real-world practice, especially in Asia-Pacific regions, for the treatment of

patients with Barcelona Clinic Liver Cancer (BCLC) stage C HCC [8]. With the high local tumor control rates and immune-modulatory potentials [9–15], LRT may play novel roles in the era of immunotherapy. First, LRT may eradicate residual tumors after successful conversion immunotherapy, prevent immune escape, and potentially provide a cure to patients [16–19]. Second, LRT may rescue patients who developed subsequent progression after the initial response to immunotherapy, particularly in the absence of effective subsequent systemic therapy and in case of limited progression, referred to as “oligoprogression” [20–23]. Lastly, LRT in combination with immunotherapy may promote antitumor immune responses and further improve the efficacy of immunotherapy [15, 24]. Nevertheless, the survival benefits of LRTs with curative or palliative intent in the era of immunotherapy have yet to be defined. This retrospective multicenter study aimed to characterize the progression patterns, subsequent therapies with a particular focus on LRT, and outcomes in a large cohort of real-world durable responders with HCC following immunotherapy.

## Methods

### Study Design

This retrospective study was conducted by the Taiwan Liver Cancer Association Research Group in compliance with all applicable ethical standards and was approved by the Research Ethics Committee of each participating hospital. Patients with unresectable HCC who received ICI-based immunotherapy (referred to as the index immunotherapy) between August 2015 and March 2021 and achieved durable responses from 8 major referral hospitals were included for analysis. In this study, the term “index immunotherapy” refers to the specific immunotherapy regimen that resulted in the durable response being analyzed. Computed tomography or magnet resonance images were performed every 8–12 weeks according to the local guidelines, and the response was evaluated by individual treating physicians. A durable response is defined as PR or SD per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) for more than 8 months after initiation of the index immunotherapy. The data cutoff point was Oct 31, 2023. Retrospective medical record reviews were performed to collect the following data: age, gender, underlying viral hepatitis status, Child-Pugh classification, performance status, BCLC stage, extrahepatic spread, vascular invasion, serum alpha-fetoprotein (AFP) level, types of immunotherapies, previous line of systemic therapies, best tumor response, progression patterns, subsequent therapies, LRTs after the index immunotherapy, and death. LRTs include surgery, ablation, TACE, TARE, radiotherapy, and HAIC. The decision of LRT was made on the judgment of the treating physicians. Oligoprogression and



**Fig. 1.** Patient flowchart. The patient flowchart summarizes the progression patterns and LRT utilization in the entire cohort of durable responders.

polyprogession were defined as progression at  $\leq 3$  and  $> 3$  lesions, respectively. Data were de-identified for all statistical analyses.

#### Statistical Analysis

Overall survival (OS) was defined as the time from the initiation of the index immunotherapy to death of any causes. The Kaplan-Meier method was employed to analyze the OS curve, and the median survival time was reported with a 95% confidence interval (95% CI). The log-rank test was utilized to determine whether there were survival discrepancies among different patient subgroups. Univariate and multivariate analyses were conducted using the Cox proportional hazard model. The  $\chi^2$  test was employed to examine demographic differences between subgroups. All  $p$  values were based on a two-sided hypothesis, and those of  $< 0.05$  were considered statistically significant. All analyses were performed using SPSS software (version 29; International Business Machines Corporation).

## Results

### Patient Characteristics

A total of 91 durable responders were identified, with 63 classified as PR and 28 as SD (Fig. 1). The patient characteristics are shown in Table 1. The median age was 62.0 years, and the majority were male ( $n = 69$ , 75.8%). Chronic viral hepatitis was prevalent among most patients ( $n = 69$ , 75.8%), along with Child-Pugh class A liver function ( $n = 81$ , 89%), ECOG performance status  $\leq 2$  ( $n = 83$ , 91.2%), and BCLC stage C ( $n =$

81, 89%). Forty-one (45.1%) and 58 (63.7%) patients had vascular invasion and extrahepatic spread, respectively. Thirty-four (37.4%) patients had serum AFP levels  $\geq 400$  ng/mL. Forty-seven (51.6%) patients received the index immunotherapies as first-line therapy, while 44 (48.4%) patients received them as second-line therapy or beyond. The types of ICI-based immunotherapy included anti-programmed cell death-1 (PD-1)/programmed cell death ligand 1 (PD-L1) monoclonal antibody (mAb) plus anti-vascular endothelial growth factor (VEGF) mAb ( $n = 32$ , 35.2%), anti-PD-1/PD-L1 mAb alone ( $n = 24$ , 26.4%), anti-PD-1/PD-L1 mAb plus multitarget kinase inhibitor (MKI) ( $n = 23$ , 25.3%), anti-PD-1/PD-L1 mAb plus anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) mAb ( $n = 4$ , 4.4%), and others ( $n = 8$ , 8.8%).

### Subsequent Progression and Disposition

During a median follow-up time of 36.3 months (IQR: 20.8–46.2 months), 54 patients (59.3%), comprising 31 with initial PR and 23 with initial SD, experienced subsequent progression. Notably, subsequent progression was more common in patients with durable SD than those with durable PR (86.5 vs. 57.4%,  $p = 0.005$ ). Baseline patient characteristics were generally similar between patients with subsequent progression and those with ongoing durable responses, except for serum AFP level and ECOG status (online suppl. Table 1; for all online suppl. material, see <https://>

**Table 1.** Patient characteristics of all patients with durable responses

	N	%
Total	91	100.0
Age, years		
Mean (SD)	61.9 (10.8)	
Median (IQR)	62.0 (57–70)	
Gender		
Male	69	75.8
Female	22	24.2
Etiology		
Viral (HBV or HCV)	69	75.8
Nonviral	22	24.2
Child-Pugh class		
A	81	89.0
B	8	8.8
C	2	2.2
ECOG performance status		
≤2	83	91.2
>2	8	8.8
BCLC stage		
B	10	11.0
C	81	89.0
Extrahepatic spread and/or vascular invasion		
Vascular invasion	41	45.1
Extrahepatic spread	58	63.7
AFP ≥400 ng/mL	34	37.4
Prior line of systemic therapy		
0	47	51.6
1 or above	44	48.4
Types of ICIs		
Anti-PD-1/PD-L1 mAb alone	24	26.4
Anti-PD-1/PD-L1 mAb + anti-CTLA-4 mAb	4	4.4
Anti-PD-1/PD-L1 mAb + anti-VEGF mAb	32	35.2
Anti-PD-1/PD-L1 mAb + MKI	23	25.3
Others <sup>a</sup>	8	8.8
Best response (RECIST 1.1)		
PR	63	69.2
SD	28	30.8
Employment of LRT after the index immunotherapy		
Yes	43	47.3
No	48	52.7

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; ICI, immune checkpoint inhibitor; IQR, interquartile range; mAb, monoclonal antibody; MKI, multikinase inhibitors; LRT, locoregional therapy; PD-1, programmed death-1; PD-L1, programmed death ligand 1; RECIST 1.1, response evaluation criteria in solid tumors 1.1; SD, standard deviation; VEGF, vascular endothelial growth factor; y, year. <sup>a</sup>Other types of ICIs included anti-CTLA-4 alone, anti-PD-1 plus anti-ALK-1, anti-PD-L1 plus anti-glypican-3, anti-PD-1 plus anti-LAG-3 antibodies.

**Table 2.** Dispositions of patients with subsequent progression

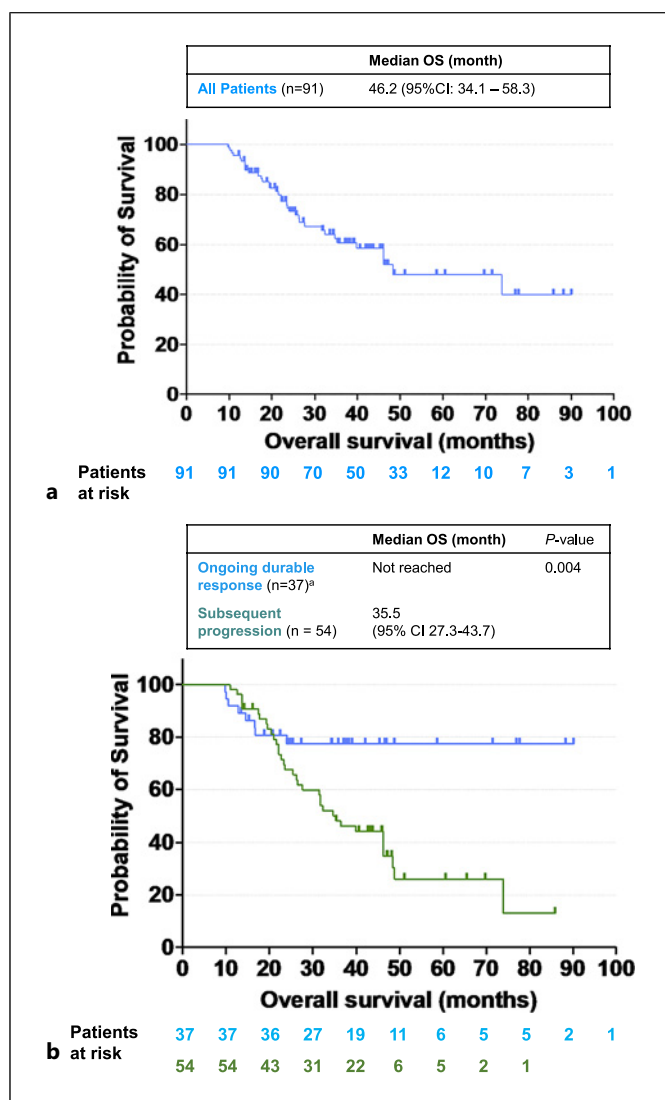
Treatment after progression	All progression		Oligoprogression		Polyprogression		p value
	N	%	N	%	N	%	
	54	100	36	100	18	100	
Systemic therapy							0.733
No	11	20.4	8	22.2	3	16.7	
Yes	43	79.6	28	77.8	15	83.3	
Continuing the index immunotherapy	15	27.8	10	27.8	5	27.8	
Switching to a different systemic therapy	28 <sup>a</sup>	51.9	18	50.0	10	55.6	
LRT							>0.999
No	17	31.5	11	30.6	6	33.3	
Yes	37	68.5	25	69.4	12	66.7	
For hepatic progression	20	37.0	13	36.1	7	38.9	
Hepatectomy	0	0	0	0	0	0	
Ablation alone	5	9.3	5	13.9	0	0	
TACE alone	9	16.7	5	13.9	4	22.2	
TACE + ablation	4	7.4	1	2.8	3	16.7	
Radiotherapy	2	3.7	2	5.6	0	0	
For extrahepatic progression	11	20.4	7	19.4	4	22.2	
Metastasectomy	4	7.4	4	11.1	0	0	
Radiotherapy	6	11.1	3	8.3	3	16.7	
Metastasectomy + radiotherapy	1	1.9	0	0	1	5.6	
For concurrent hepatic and extrahepatic progression	6	11.1	5	13.9	1	5.6	
Ablation (hepatic) + radiotherapy (extrahepatic)	1	9.1	1	2.8	0	0	
Hepatectomy + radiotherapy (extrahepatic)	1	9.1	1	2.8	0	0	
Radiotherapy (hepatic + extrahepatic)	1	9.1	1	2.8	0	0	
TACE (hepatic) + surgery (extrahepatic)	2	18.2	2	5.6	0	0	
TACE + TARE + HAIC (hepatic) + RT (extrahepatic)	1	9.1	0	0	1	5.6	

TACE, transarterial chemoembolization; TARE, transarterial radioembolization; HAIC, hepatic arterial infusional chemotherapy. <sup>a</sup>Eleven patients were treated with lenvatinib, 7 with sorafenib, 2 each with regorafenib and ramucirumab, 1 with cabozantinib, 2 with systemic chemotherapy, and 3 with different immunotherapy combinations.

doi.org/10.1159/000536549). Significantly fewer patients with subsequent progression had serum AFP  $\geq 400$  ng/mL before immunotherapy compared to those with ongoing durable responses (27.8 vs. 51.4%,  $p = 0.028$ ).

Among those patients with subsequent progression, 36 patients (66.7%) had oligoprogression, and 18 patients (33.3%) had polyprogression. Baseline patient characteristics and AFP responses within the first 4 weeks after treatment initiation were generally similar between patients with oligoprogression and those with polyprogression except for types of immunotherapies (online suppl. Table 2). Their subsequent therapies are presented in Table 2. Twenty-eight (51.9%) patients switched to a different systemic therapy, comprising 11 patients on lenvatinib, 7 on sorafenib, 2 each on regorafenib and ramucirumab, 1 on cabozantinib, 2 on

systemic chemotherapy, and 3 on different immunotherapy combinations. Meanwhile, 15 (27.8%) patients continued the index immunotherapy, and 11 (20.4%) patients did not receive any systemic therapy afterward. Thirty-seven (68.5%) patients received LRTs. The most employed LRT for hepatic progression alone was TACE (5 for oligoprogression and 4 for polyprogression), followed by ablation (5 for oligoprogression), TACE + ablation (1 for oligoprogression and 3 for polyprogression), and radiotherapy (2 for oligoprogression). In contrast, the most employed LRT for extrahepatic progression alone was radiotherapy (3 for oligoprogression and 3 for polyprogression), followed by metastasectomy (4 for oligoprogression) and a combination of metastasectomy plus radiotherapy (1 for polyprogression). Six patients received LRT for concomitant hepatic and extrahepatic progression with



**Fig. 2.** OS of all durable responders. **a** Kaplan-Meier OS curve of the entire cohort of patients who exhibited a durable response. **b** Kaplan-Meier OS curves depicting a comparison between 2 subgroups: patients who experienced ongoing durable responses and those who subsequently developed progression. OS, overall survival; CI, confidence interval. <sup>a</sup> There were 8 deaths noted in the ongoing durable response group. Six patients died of infection/pneumonia, and 1 each died of severe gastrointestinal bleeding and complications of cirrhosis.

varied approaches (Table 2). The employment rates of either systemic therapy or LRT were not different between patients with oligoprogession and those with polyprogession.

For patients with ongoing durable responses, all patients ( $n = 37$ , 100%) continued the index immunotherapy during the follow-up period. Three patients

received LRT to the responding hepatic lesions, including hepatectomy ( $n = 1$ ), TACE ( $n = 1$ ), and radiotherapy ( $n = 1$ ); 3 patients received LRT for responding extrahepatic lesions, including metastasectomy ( $n = 2$ ) and radiotherapy ( $n = 1$ ).

#### Survival and Risk Factors for Death

For the entire group ( $n = 91$ ), the median OS was 46.2 months (95% CI: 34.1–58.3) (Fig. 2a). The median OS of those with subsequent progression was 35.5 months (95% CI: 27.3–43.7), while the median OS of patients with ongoing durable response was not reached (Fig. 2b). The median OS was statistically different between patients who subsequently developed progression and patients who experienced ongoing durable response ( $p = 0.004$ ). Macrovascular invasion was found to be associated with shorter survival in univariate analysis (hazard ratio [HR] 2.047,  $p = 0.02$ ) but not in multivariate analysis (HR 1.983,  $p = 0.056$ ). Subsequent progression was found to be associated with shorter survival in both univariate analysis (HR 2.915,  $p = 0.007$ ) and multivariate analysis (HR 4.910,  $p < 0.001$ ). Employment of LRT after the index immunotherapy was associated with longer survival in multivariate analysis (HR 0.341,  $p = 0.004$ ) but not in the univariate analysis (HR 0.940,  $p = 0.840$ ) (Table 3a).

Among those patients with subsequent progression ( $n = 54$ ), LRT for progression but not progression pattern (oligoprogession vs. polyprogession) nor systemic therapy after progression was an independent risk factor for death through the Cox proportional hazard analysis (Table 3b). LRT for progression was associated with longer survival in both univariate analysis (HR 0.397,  $p = 0.009$ ) and multivariate analysis (HR 0.363,  $p = 0.050$ ).

The clinical characteristics of patients who subsequently progressed and received LRT or those who did not receive LRT were similar either at baseline or upon progression (Table 4). The median OS was longer for patients who received LRT than those who did not (46.2 vs. 22.2 months,  $p = 0.006$ ) (Fig. 3a). Eleven (29.7%) out of 37 patients who received LRT achieved complete response with LRT. The OS of the patients who did not achieve complete response with LRT was still longer than those who did not receive LRT for progression (online suppl. Fig. 1). Furthermore, patients with oligoprogession who received LRT showed a significantly longer median OS than those who did not (48.4 vs. 20.5 months,  $p < 0.001$ ). However, the median OS of patients with polyprogession who received LRT was not



**Table 3.** Univariate and multivariate analyses of risk factors associated with death

	Univariate analysis		Multivariate analysis	
	HR	<i>p</i> value	HR	<i>p</i> value
<b>a</b> All durable responders				
Age	1.001	0.966	0.988	0.370
Male	1.156	0.690	0.979	0.959
Viral etiology associated HCC	0.889	0.732	0.711	0.393
Macrovascular invasion	2.047	<b>0.020*</b>	1.983	0.056
Extrahepatic spread	0.664	0.193	0.980	0.956
AFP >400 ng/mL	0.666	0.235	0.648	0.280
Child-Pugh class A	0.613	0.312	0.563	0.265
No prior systemic therapy	0.896	0.723	1.352	0.375
Subsequent progression	2.915	<b>0.007*</b>	4.910	<b>&lt;0.001*</b>
LRT after the index immunotherapy	0.940	0.840	0.341	<b>0.004*</b>
<b>b</b> Durable responders with subsequent progression				
Age <sup>a</sup>	0.988	0.406	0.988	0.433
Male	0.799	0.582	1.129	0.819
Viral etiology associated HCC	0.795	0.548	0.496	0.189
Macrovascular invasion <sup>a</sup>	1.754	0.101	1.645	0.293
Extrahepatic spread <sup>a</sup>	0.615	0.167	0.741	0.514
AFP >400 ng/mL <sup>a</sup>	0.976	0.950	0.605	0.351
Oligoprogression <sup>a</sup>	0.678	0.275	0.477	0.141
LRT after the index immunotherapy	0.397	<b>0.009*</b>	0.363	<b>0.050*</b>
Systemic therapy after progression		0.110		0.685
Switching to a different systemic therapy	1		1	
Continuing the index immunotherapy	0.406	0.054	0.609	0.386
No more systemic therapy	0.518	0.231	0.880	0.847

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; HR, hazard ratio. <sup>a</sup>Analyzed based on the data upon progression. \*Denote *p* value < 0.05 which is considered statistically significant.

different from those without LRT (27.7 vs. 25.5 months, *p* = 0.794) (Fig. 3b). Among those patients who experienced ongoing durable responses, the median OS was not statistically different between patients who received LRT and those who did not (*p* = 0.687) (online suppl. Fig. 2).

## Discussion

To the best of our knowledge, this study is the first to characterize the subsequent progression patterns, dispositions, and long-term outcomes of patients who had unresectable HCC and achieved durable responses (defined as PR or SD lasting for more than 8 months) under ICI-based immunotherapy in the real-world setting. The findings of this study demonstrate that these durable responders had remarkably longer OS with a median of 46.2 months, despite approximately half of them eventually developing progression, pri-

marily in the form of oligoprogression. Furthermore, employment of LRT following the index immunotherapy was associated with prolonged OS, and this survival advantage was predominantly observed in patients receiving LRT for oligoprogression rather than those receiving LRT for polyprogression or ongoing durable response.

### *Subsequent Progression in Durable Responders*

The precise rate at which patients with advanced HCC experience subsequent progression after the initial response to immunotherapy remains uncertain. In a post hoc analysis of data from the atezolizumab-bevacizumab arm of the IMbrave150 trial, durable responders were defined as patients with PR or SD lasting for more than 6 months. Among these durable responders, 54 (59.3%) out of 97 experienced subsequent progression during a median follow-up period of 17.6 months [7]. Specifically, 41.7% of patients with durable PR and 47.9% of those with durable SD

**Table 4.** Patient characteristics of patient with subsequent progression according to the use of LRT

	Receiving LRT		Not receiving LRT		<i>p</i> value
Baseline characteristics (when receiving the index immunotherapy)					
	<i>N</i>	%	<i>N</i>	%	
Total	37	100.0	17	100.0	
Age, years					0.598
Mean (SD)	62.0 (10.1)		63.8 (14.3)		
Median (IQR)	61.0 (56.5–67.5)		67 (57.0–74.5)		
Gender					0.696
Male	30	81.1	13	76.5	
Female	7	18.9	4	23.5	
Etiology					0.512
Viral (HBV or HCV)	27	73.0	14	82.35	
Nonviral	10	27.0	3	17.65	
Child-Pugh class					0.321
A	34	91.9	15	88.2	
B	3	8.1	1	5.9	
C	0	0	1	5.9	
ECOG					0.315
≤2	37	100.0	16	94.1	
>2	0	0.0	1	5.9	
BCLC stage					0.645
B	3	8.1	2	11.8	
C	34	91.9	15	88.2	
Vascular invasion	17	45.9	9	52.9	0.633
Extrahepatic spread	26	70.3	8	47.1	0.101
AFP >400 ng/mL	10	27.0	5	29.4	0.856
Prior line of systemic Therapy					0.609
0	18	48.6	7	58.8	
1 or above	19	51.4	10	41.2	
Types of ICIs					0.856
Anti-PD-1/PD-L1 mAb alone	13	35.1	5	29.4	
Anti-PD-1/PD-L1 mAb + anti-CTLA-4 mAb	2	5.4	0	0.0	
Anti-PD-1/PD-L1 mAb + anti-VEGF mAb	10	27.0	5	29.0	
Anti-PD-1/PD-L1 mAb + MKI	10	27.0	6	35.3	
Others <sup>a</sup>	2	5.4	1	5.9	
Clinical characteristics upon progression					
	<i>N</i>	%	<i>N</i>	%	<i>p</i> value
Child-Pugh class					0.092
A	34	91.9	12	70.6	
B	3	8.1	5	29.4	
C	0	0	0	0	



**Table 4** (continued)

Clinical characteristics upon progression					
	N	%	N	%	p value
ECOG					
≤2	34	91.9	15	88.2	0.645
>2	3	8.1	2	11.8	
Vascular invasion	13	35.1	5	29.4	0.763
Extrahepatic spread	21	56.8	12	70.6	0.383
AFP >400 ng/mL	8	21.6	5	29.4	0.738

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; ICI, immune checkpoint inhibitor; IQR, interquartile range; mAb, monoclonal antibody; MKI, multikinase inhibitors; PD-1, programmed death-1; PD-L1, programmed death ligand 1; RECIST 1.1, response evaluation criteria in solid tumors 1.1; SD, standard deviation; VEGF, vascular endothelial growth factor; y, year. <sup>a</sup>Other types of ICIs include anti-CTLA-4 alone, anti-PD-1 plus anti-ALK-1, anti-PD-L1 plus anti-glypican-3, anti-PD-1 plus anti-LAG-3 antibodies.

experienced subsequent progression. In contrast, the current real-world study revealed that 54 (59.3%) out of 91 durable responders (57.4% of patients with durable PR and 86.5% of patients with durable SD) experienced subsequent progression during a median follow-up period of 36.3 months. Although the definitions of durable response, types of immunotherapies, and patient populations differed between the 2 studies, the data indicate that approximately 60% of durable responders develop subsequent progression despite initial disease control for at least 6–8 months under immunotherapy. Currently, no clinicopathological characteristics have been identified to predict subsequent progression. Therefore, it is of great interest that pathological specimen analysis of subsequently progressed lesions may help researchers gain insight into immune escape mechanisms and develop novel strategies to overcome resistance.

#### *LRT for Subsequent Progression*

This study revealed significant survival advantages associated with LRT for progression in durable responders who subsequently developed progression despite 70.3% of them having extrahepatic diseases at the time of progression (Table 3b, 4). Notably, the survival benefits of LRT were primarily observed in patients who received LRT for oligoprogression (Fig. 3b). The median OS for patients who received LRT for subsequent oligoprogression is 48.4 months (95% CI: 38.7–58.0), implicating the crucial role of LRT in addressing acquired immunotherapy resistance in HCC. These findings align with a growing concept that aggressive LRTs, with or without systemic therapy, can improve survival in patients with different types of metastatic cancers

experiencing oligoprogression following systemic therapies, including immunotherapy [20, 25–38].

In this study, the 3 most employed LRTs for oligoprogression were TACE alone ( $n = 5$ ) and ablation alone ( $n = 5$ ), followed by metastasectomy ( $n = 4$ ). Many patients received various combinations of these LRTs in our study, which underscores the commonly adopted and practiced concepts of utilizing LRTs along with systemic therapy in the Asia-Pacific region’s real-world practice. While the role of radiotherapy [25, 34, 36, 37], metastasectomy [21, 26, 30], and ablation [28, 38] in treating oligoprogression has been extensively investigated in other cancer types, the role of TACE for oligoprogression in HCC had not been reported before. Nevertheless, it is reasonable to expect that judicious TACE without compromising liver reserve may contribute to prolonged OS in cases of hepatic oligoprogression.

#### *Systemic Therapy for Subsequent Progression*

Systemic therapy switch is usually considered to manage subsequent progression following prior systemic therapy failure, particularly in the scenario of polyprogression, while LRT primarily serves a palliative role, aiming to relieve symptoms. However, the current study found that switching to a different systemic therapy was less common than the employment of LRT in durable responders who experienced subsequent progression, regardless of progression patterns (all progression: 51.9% switched systemic therapy vs. 68.5% received LRT; oligoprogression: 50.0 vs. 69.4%; polyprogression: 55.6 vs. 66.7%) (Table 2). The lower rate of switching to a different systemic therapy in this study can be attributed to the limited availability of subsequent



preexisting preference and extensive experiences in employing liver-directed LRT to treat advanced-stage HCC in the Asia-Pacific region [8]. Additionally, recent advancements in minimally invasive metastasectomy of lung metastases and stereotactic body radiation therapy contribute to the increased utilization of LRT for extrahepatic progression.

Furthermore, this study demonstrates that switching to a different systemic therapy did not provide any survival benefit for durable responders who encountered subsequent progression (Table 3b). In contrast, a global retrospective real-world study revealed that subsequent therapy ( $n = 165$ ), compared to best supportive care ( $n = 152$ ), is associated with prolonged OS in HCC patients who discontinued ICI-based immunotherapy primarily due to progressive disease [39]. The subsequent therapy following immunotherapy discontinuation included not only systemic therapies (MKIs/immunotherapy/chemotherapy: 66.1/12.7/5.5%) but also LRTs (radiotherapy/TACE or TARE/radiotherapy/ablation: 17/11.5/3.6/2.4%). Therefore, the OS benefits from subsequent therapy in that study were most likely derived from systemic therapies rather than LRTs. Another retrospective single-institute study demonstrated that subsequent MKI, compared to no subsequent MKI, was also associated with improved OS in multivariate analysis (HR 0.412,  $p = 0.0043$ ) in 77 HCC patients who received immunotherapy [40]. The varying impacts of subsequent systemic therapies on OS observed in these studies may be attributed to different patient populations (durable PR or SD to immunotherapy vs. any response to immunotherapy), varying proportions of prior MKI failure, and various patient selection biases.

### Limitations

Our study has several limitations that require acknowledgment. First, it is crucial to recognize that our analyses are retrospective in nature, which introduces the possibility of information bias, including selection bias, recall bias, or misclassification bias. Second, there is considerable heterogeneity in the immunotherapy combinations received by the durable responders, as well as significant variation in the types of subsequent LRTs utilized. Third, the limited size of our study population prevented us from conducting adequately powered comparisons between the different subgroups. Moreover, comprehensive information regarding treatment toxicities and co-medication, such as antibiotics, corticosteroids, immunosuppressants, or proton pump inhibitors, which can potentially impact the response to ICIs, was not fully available. Despite these limitations, our study's strength lies in being the first investigation, to the best of our knowledge, that comprehensively characterizes the progression patterns, dispositions, and outcomes of real-

world durable responders with advanced HCC treated with immunotherapies.

In conclusion, patients with advanced HCC who experienced durable responses after initiation of immunotherapy have excellent clinical outcomes. For this group of patients, proactive LRTs may further benefit or rescue patients who developed subsequent oligo-progression. Prospective studies are mandatory to clarify the proper management of durable responders with subsequent progression.

### Acknowledgment

We would like to acknowledge the service provided by the administrative office of the Taiwan Liver Cancer Association.

### Statement of Ethics

The study protocol was reviewed and approved by the Research Ethics Committee of National Taiwan University Hospital/National Taiwan University Cancer Center (approval number 202109071RINC), Taipei Veterans General Hospital (approval number TPEVGH IRB No.: 2023-08-010CC), E-Da Cancer Hospital (approval number EMRP-110-091), Chang Gung Memorial Hospital Linkou Branch (approval number 202002147BOC501), National Health Research Institute/National Cheng Kung University Hospital (approval number A-ER-112-215), Tri-Service General Hospital (approval number IRB-C202105167), National Taiwan University Hospital Yunlin Branch (approval number 202212015RINC), respectively, for each participating hospital. This is a retrospective clinical study and was exempted from individual patient informed consent. The raw data were first extracted from each participating hospital, and patients' identities, including names, screening IDs, patient IDs, and mobile phone numbers, were de-identified before the statistical analyses of aggregated de-identified data.

### Conflict of Interest Statement

The authors declare no conflicts of interest.

### Funding Sources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

### Author Contributions

Study design and concept: Tsung-Hao Liu, Ying-Chun Shen, and Ann-Lii Cheng; data collection and data interpretation and review and approval of the manuscript submission: Tsung-Hao

Liu, San-Chi Chen, Kun-Ming Rau, Li-Chun Lu, Po-Ting Lin, Yung-Yeh Su, Wei Teng, Shiue-Wei Lai, Ren-Hua Yeh, Tsui-Mai Kao, Pei-Chang Lee, Chi-Jung Wu, Chien-Hung Chen, Chih-Hung-Hsu, Shi-Ming Lin, Yi-Hsiang Huang, Li-Tzong Chen, Ann-Lii Cheng, and Ying-Chun Shen; and study analysis and manuscript writing: Tsung-Hao Liu and Ying-Chun Shen.

## Data Availability Statement

For ethical reasons, the data are not publicly available. The datasets generated and analyzed in this study are available from the corresponding author upon reasonable request. Further inquiries can be directed to the corresponding author.

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