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ORIGINAL ARTICLE

Outcome and management of patients with hepatocellular carcinoma who achieved a complete response to immunotherapy-based systemic therapy

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Abstract

Background and Aims: The outcome of patients with HCC who achieved complete response (CR) to immune-checkpoint inhibitor (ICI)–based systemic therapies is unclear.

Approach and Results: Retrospective study of patients with HCC who had CR according to modified Response Evaluation Criteria in Solid Tumors (CR-mRECIST) to ICI-based systemic therapies from 28 centers in Asia, Europe, and the United States. Of 3933 patients with HCC treated with ICI-based noncurative systemic therapies, 174 (4.4%) achieved CR-mRECIST, and 97 (2.5%) had CR according to RECISTv1.1 (CR-RECISTv1.1) as well. The mean age of the total cohort (male, 85%; Barcelona-Clinic Liver Cancer-C, 70%) was 65.9 ± 9.8 years. The majority (83%) received ICI-based combination therapies. Median follow-up was 32.2 (95% CI: 29.9–34.4) months. One- and 3-year

Abbreviations: BCLC-C, Barcelona-Clinic Liver Cancer stage C; CR, complete response; ctDNA, circulating tumor DNA; ICI, immune checkpoint inhibitor; CR-mRECIST, CR according to modified Response Evaluation Criteria in Solid Tumors; CR-RECISTv1.1, CR according to RECISTv1.1; NE–NE, not evaluable–not evaluable.

B.S. and B.K. shared the first authorship; H.J.C. and M.P. shared the last authorship.

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overall survival rates were 98% and 86%. One- and 3-year recurrence-free survival rates were excellent in patients with CR-mRECIST-only and CR-RECISTv1.1 (78% and 55%; 70% and 42%). Among patients who discontinued ICIs for reasons other than recurrence, those who received immunotherapy for ≥ 6 months after the first mRECIST CR had a longer recurrence-free survival than those who discontinued immunotherapy earlier ($p = 0.008$). Of 9 patients who underwent curative surgical conversion therapy, 8 (89%) had pathological CR (CR-RECISTv1.1, n = 2/2; CR-mRECIST-only, n = 6/7).

Conclusions: Overall survival and recurrence-free survival of patients with CR-mRECIST-only and CR-RECISTv1.1 were excellent, and 6 of 7 patients with CR-mRECIST-only who underwent surgical conversion therapy had pathological CR. Despite potential limitations, these findings support the use of mRECIST in the context of immunotherapy for clinical decision-making. When considering ICI discontinuation, treatment for at least 6 months beyond CR seems advisable.

Keywords: immune checkpoint inhibitor, liver cancer, RECIST, systemic therapy

INTRODUCTION

HCC is one of the most common and deadliest cancers globally.[1] HCC is frequently diagnosed at locally advanced or metastatic stages, where systemic therapy is recommended, provided that liver function is preserved.[2] Immune checkpoint inhibitor (ICI)–based therapies represent the reference standard in the systemic first-line treatment of patients with advanced-stage HCC.[2] Even though considered non-curative therapies, ICIs have the potential to induce deep and durable responses.[3–6] This may enable right-to-left sequential treatment stage migration and even allow potential curative conversion therapy (eg, resection or liver transplantation) in selected patients with HCC who were initially diagnosed at advanced stages.[7–9]

A small proportion of patients can even achieve a complete response (CR) with ICI-based combination therapies.[3,4] Little is known about the outcome of patients who have CR to immunotherapy, and no guidance exists on how to manage patients with HCC after achieving a CR. There are several open questions, including whether and when it is safe to stop immunotherapy after CR, and if these patients should undergo curative conversion therapy or simply be observed closely for recurrence. It is also unknown whether mRECIST[10] is appropriate to identify complete necrosis in the context of immunotherapy or whether only the complete disappearance of all tumor lesions, as required by RECISTv1.1,[11] reflects "true" CR can translate into unprecedented long-term survival.

In this large retrospective, international, multicenter study, we aimed to shed light on the outcome and management of this particular group of patients with HCC who achieved CR to ICI-based systemic therapies.

METHODS

Patients

We included patients with radiologically or histologically diagnosed HCC who achieved radiological CR according to mRECIST[10] with ICI-based systemic therapy from 28 centers in Asia, Europe, and the United States. We only included patients who received ICI-based therapies as definitive therapies in a non-curative setting as per the decision of the local multidisciplinary team. Patients who received immunotherapy in a curative setting as (neo-)adjuvant therapy before/after resection or ablation or in combination with locoregional therapies were excluded. Locoregional therapy prior to immunotherapy initiation was allowed, but all patients had to have viable tumors at the time of ICI initiation.

Data were collected retrospectively from medical records. The date of initiation of the immunotherapy regimen leading to complete response was the baseline of this study. This study was conducted in accordance with the Declarations of Helsinki and Istanbul and approved by the Ethics Committee of the Medical University of Vienna. The need for written informed consent was waived due to the retrospective nature of the study.

Definitions

"CR-mRECIST-only" refers to patients who only achieved radiological complete response according to mRECIST (= disappearance of any intratumoral arterial enhancement in target and nontarget lesions).[10] "CR-RECISTv1.1" refers to patients with radiological CR according to RECISTv1.1 (= disappearance of all target and nontarget lesions),[11] who by nature also have CR according to mRECIST. "Curative conversion treatment" was defined as any kind of treatment performed in patients with ongoing CR (according to either mRECIST or RECISTv1.1) with the aim of inducing long-term remission. In patients who underwent resection or liver transplantation, local histopathological reports were used to assess the presence or absence of complete pathological response defined as no viable tumor tissue within the specimen. Any treatment performed after tumor recurrence was considered as "treatment of recurrence." Supplemental Figure S1, http://links.lww.com/HEP/J634, demonstrates key dates and end points evaluated for this study.

Statistical methods

Baseline characteristics were presented using descriptive statistics. Median estimated follow-up time was calculated using the reverse Kaplan-Meier method.[12] Median treatment duration was defined as time from the date of immunotherapy initiation until the date of last administration; patients who were still receiving immunotherapy at the last follow-up were censored.

Calculations involving the date of first radiological complete response were handled as follows: when referring to the whole cohort or patients with CR-mRECIST-only, the date of first radiological complete response according to mRECIST was used; when referring to the CR-RECISTv1.1 group, the date of first radiological complete response according to RECISTv1.1 was used.

Recurrence-free survival was defined as the time from the date of first radiological CR until the date of first tumor recurrence or death, whatever came first; patients alive without recurrence were censored at the date of last contact. Duration of response was defined as the time from the first CR until the date of tumor recurrence; patients who died prior to tumor recurrence were censored at the date of death, and patients alive without tumor recurrence were censored at the date of last contact. Overall survival (OS) was defined as the time from ICI start until death; patients still alive or lost to follow-up were censored at the date of last contact. Survival curves were calculated using the Kaplan-Meier method and compared by the Log-rank Test.

Univariable and multivariable analyses were performed using Cox regression. Variable selection in the multivariable model was based on stepwise backward elimination. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 26.0 (SPSS Inc., Chicago, IL), R 4.3.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria), and GraphPad Prism 10.2.1 (GraphPad Software, San Diego, CA).

RESULTS

Patients

Of 3933 patients with HCC treated with ICI-based noncurative systemic therapies, 174 (4.4%) patients achieved CR according to mRECIST (CR-mRECIST), and 97 (2.5%) patients had CR according to RECISTv1.1 (CR-RECISTv1.1) as well. The total cohort included 174 patients who initiated immunotherapy-based systemic therapy between September 2015 and November 2023.

The mean age was 65.9 ± 9.8 years, 147 (85%) were male, and the majority had Child-Pugh class A (n = 158, 91%). While 70% of patients had Barcelona-Clinic Liver Cancer (BCLC) stage C (n = 122), 26% had BCLC stage B and 6 patients had BCLC stage A (3%). Patients with BCLC stage A received ICI-based therapies for the following reasons: patient wish (n = 3, partially due to a history of repeated recurrences after several sessions of locoregional therapy), tumor location unsuitable for locoregional therapy (n = 2), and suspected unfavorable tumor biology based on high alpha-fetoprotein (AFP) levels and paraneoplastic polycythemia (n = 1). Viral hepatitis was the most common etiology of liver disease as 58 patients (33.3%) had HBV−, and 36 patients (20.7%) had HCV-associated liver disease.

While 50 patients with HBV (86.2%) were already receiving antiviral treatment, antiviral therapy was started in 4 patients (6.9%) at the time of ICI initiation or thereafter. The remaining 4 patients (6.9%) had negative HBV DNA at baseline and did therefore not receive antiviral therapy. At baseline, only 8 patients (22.2%) had positive HCV RNA, of which 3 individuals (8.3%) received anti-HCV treatment at ICI start or thereafter. The remaining 5 patients (13.9%) remained without HCV-specific treatment. One hundred thirty-nine patients (80%) had undergone previous surgical or locoregional therapies. The median time interval between the last surgical or locoregional therapy and initiation of the ICI-based regimen was 4.8 (IQR: 2.4–10.6) months.

The majority (n = 145, 83%) received ICI-based combination therapies (atezolizumab/bevacizumab: n = 104, 60%; durvalumab/tremelimumab, n = 10, 6%; nivolumab/ipilimumab: n = 10, 6%; anti-PD-(L)1+TKI combinations: n = 19, 11%; anti-programmed cell death protein 1+anti-cytotoxic T-lymphocyte associated protein 4 (CTLA-4)+TKI: n = 1, 1%), and 29 (17%) received programmed cell death ligand 1 monotherapy. Detailed patient characteristics are displayed in Table 1.

TABLE 1 Patient characteristics

	All patients (n = 174)	CR-RECISTv1.1 (n = 97)	CR-mRECIST-only (n = 77)
Age (y), mean ± SD	65.9 ± 9.8	64.7 ± 9.6	67.3 ± 9.8
Male, n (%)	147 (85)	80 (83)	67 (87)
Etiology, n (%)			
Viral	94 (54)	58 (60)	36 (47)
MASLD	30 (17)	13 (13)	17 (22)
ALD	29 (17)	13 (13)	16 (21)
Other	21 (12)	13 (13)	8 (10)
Cirrhosis, n (%)	136 (78)	75 (77)	61 (79)
Child-Pugh class, n (%)			
A	158 (91)	90 (93)	68 (88)
B	15 (9)	6 (6)	9 (12)
C	1 (1)	1 (1)	0
Presence of varices, n (%)[a]	52 (29.9)	30 (30.9)	21 (27.3)
Small varices	31 (17.8)	18 (18.6)	13 (16.9)
Medium/large varices	21 (12.1)	12 (12.4)	8 (10.4)
History of variceal bleeding, n (%)	5 (2.9)	5 (5.2)	0
Prophylaxis of variceal bleeding, n (%)	32 (18.4)	18 (18.6)	14 (18.2)
NSBB treatment	19 (10.9)	8 (8.2)	11 (14.3)
Endoscopic treatment	7 (4.0)	5 (5.2)	2 (2.6)
NSBB + endoscopic treatment	6 (3.4)	5 (5.2)	1 (1.3)
ECOG PS, n (%)			
0	107 (62)	60 (62)	47 (61)
1	67 (39)	37 (38)	30 (39)
Macrovascular invasion, n (%)	54 (31)	25 (26)	29 (38)
Extrahepatic metastases, n (%)	62 (36)	35 (36)	27 (35)
BCLC stage, n (%)			
A	6 (3)	4 (4)	2 (3)
B	45 (26)	29 (30)	16 (21)
C	122 (70)	63 (65)	59 (77)
D	1 (1)	1 (1)	0
Any prior treatment, n (%)	139 (80)	87 (90)	52 (68)
Previous TACE	90 (52)	60 (62)	30 (39)
Previous resection	66 (38)	48 (50)	18 (23)
Previous ablation	41 (24)	22 (23)	19 (25)
Previous systemic therapy	41 (24)	26 (27)	15 (20)
Previous radiotherapy	25 (14)	15 (16)	10 (13)
Previous TARE	9 (5)	5 (5)	4 (5)
No. any previous lines of treatment, n (%)	2 (IQR: 1–2)	2 (IQR: 1–2)	1 (IQR: 0–2)
No pretreatment	36 (21)	10 (10)	26 (34)
One previous treatment line	46 (26)	25 (26)	21 (27)
Two previous lines of treatment	57 (33)	38 (39)	19 (25)
Three or more lines of previous treatment	35 (20)	24 (25)	11 (14)
Line of ICI treatment, n (%)			
First-line	133 (76)	71 (73)	62 (81)
Second-line	31 (18)	21 (22)	10 (13)
Further line	10 (6)	5 (5)	5 (7)
Type of ICI regimen, n (%)			
Atezolizumab+bevacizumab	104 (60)	52 (54)	52 (68)
Anti-PD-(L)1 monotherapy	29 (17)	19 (20)	10 (13)

TABLE 1. (*continued*)

	All patients (n = 174)	CR-RECISTv1.1 (n = 97)	CR-mRECIST-only (n = 77)
Anti-PD-(L)1+TKI	19 (11)	12 (12)	7 (9)
Tremelimumab+durvalumab	10 (6)	7 (7)	3 (4)
Nivolumab+ipilimumab	10 (6)	5 (5)	5 (7)
Durvalumab+bevacizumab	1 (1)	1 (1)	0
Anti-PD-1+anti-CTLA-4+TKI	1 (1)	1 (1)	0
CRP ≥1 mg/dL[b]	39 (22)	13 (13)	26 (34%)
AFP (ng/mL), median (IQR)	39.8 (4.7–1767.0)	49.8 (5.0–790.5)	26.8 (4.2–3310.9)

[a]Unknown, n = 43 (24.7%).
[b]Missing, n = 37.
Abbreviations: AFP, alpha-fetoprotein; ALD, alcohol-associated liver disease; BCLC, Barcelona-Clinic Liver Cancer; CR-mRECIST, complete response according to modified Response Evaluation Criteria in Solid Tumors; CRP, C-reactive protein; CR-RECISTv1.1, complete response according to Response Evaluation Criteria in Solid Tumors version 1.1; CTLA-4, Cytotoxic T-lymphocyte associated protein 4; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; MASLD, metabolic dysfunction–associated steatotic liver disease; NSBB, nonselective beta-blocker; PD-(L)1, programmed cell death protein 1/ligand 1; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitor.

Outcome of the whole cohort

The median follow-up from the start of immunotherapy and from the first CR (mRECIST) was 32.2 (95% CI: 29.9–34.4) months and 24.9 (95% CI: 20.6–29.2) months, respectively.

The median duration of ICI treatment was 22.6 (95% CI: 21.2–24.1) months, median time from immunotherapy start until the first CR (mRECIST) was 7.0 (95% CI: 5.6–8.3) months (Table 2), and median duration of response was 36.5 (95% CI: not evaluable–not evaluable [NE–NE]) months. One hundred twenty-eight

TABLE 2 Main outcome results

	All patients (n = 174)	CR-RECISTv1.1 (n = 97)	CR-mRECIST-only (n = 77)
Best overall response (RECISTv1.1), n (%)			
Complete response	97 (56)	97 (100)	—
Partial response	68 (39)	—	68 (88)
Stable disease	9 (5)	—	9 (12)
Curative conversion therapy performed, n (%)	13 (8)	2 (2)	11 (14)
Resection	5 (3)	—	5 (7)
Liver transplantation	4 (2)	2 (2)	2 (3)
Ablation	4 (2)	—	4 (5)
Pathological complete response, n (%)[a]	8 (89)	2 (100)	6 (86)
Death during FU, n (%)	23 (13)	12 (12)	11 (14)
Time to complete response, median (95% CI)	7.0 (5.6–8.3)	8.3 (6.4–10.3)	6.8 (5.3–8.4)
Overall survival (months), median (95% CI)	NE (NE–NE)	NE (NE–NE)	NE (NE–NE)
1-y OS rate (%)	98	100	96
2-y OS rate (%)	95	98	91
3-y OS rate (%)	86	87	86
4-y OS rate (%)	81	85	76
5-y OS rate (%)	77	78	76
Recurrence during FU, n (%)	59 (34)	37 (38)	22 (29)
Recurrence-free survival (mo), median (95% CI)	30.3 (21.5–39.1)	28.4 (18.3–38.4)	37.0 (NE–NE)
1-y RFS rate (%)	76	70	78
2-y RFS rate (%)	58	58	58
3-y RFS rate (%)	48	42	55
4-y RFS rate (%)	43	39	50
5-y RFS rate (%)	43	39	50

[a]Pathological complete response was assessed in patients who underwent surgical conversion therapy (n = 9) with either liver transplantation or resection, and percentages refer to this subgroup.
Abbreviations: CR-mRECIST, complete response according to modified Response Evaluation Criteria in Solid Tumors; CR-RECISTv1.1, complete response according to Response Evaluation Criteria in Solid Tumors version 1.1; FU, follow-up; NE–NE, not evaluable–not evaluable; OS, overall survival; RECISTv1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RFS, recurrence-free survival.

TABLE 3 Univariable and multivariable analyses of factors associated with recurrence-free survival

	Univariable		Multivariable first step		Multivariable last step	
	HR (95% CI)	*p*	aHR (95% CI)	*p*	aHR (95% CI)	*p*
Etiology						
Viral	1	—	1	—	1	—
Alcohol	1.8 (1.0–356)	0.068	1.5 (0.8–3.0)	0.208	1.6 (0.8–3.1)	0.164
MASLD	1.4 (0.7–2.9)	0.313	1.3 (0.6–2.7)	0.515	1.5 (0.7–3.0)	0.311
Other	2.4 (1.2–4.6)	0.012	2.6 (1.3–5.5)	0.008	2.7 (1.3–5.3)	0.005
ECOG PS, 1 vs. 0	1.1 (0.7–1.8)	0.691	1.1 (0.7–2.0)	0.648	—	—
Macrovascular invasion, yes vs. no	0.5 (0.3–0.9)	0.027	0.5 (0.3–0.9)	0.033	0.4 (0.2–0.7)	0.003
Extrahepatic metastases, yes vs. no	0.4 (0.2–0.7)	0.003	0.3 (0.2–0.6)	< 0.001	0.3 (0.2–0.6)	< 0.001
Alpha-fetoprotein, ≥ 1000 vs. < 1000 ng/ml	0.6 (0.3–1.1)	0.084	0.7 (0.4–1.4)	0.329	—	—
Any TRAE, yes vs. no	0.6 (0.4–1.0)	0.062	0.9 (0.5–1.6)	0.711	—	—
Immunosuppression for TRAE, yes vs. no	0.6 (0.4–1.0)	0.062	0.6 (0.3-1.4)	0.249	—	—
CR-RECISTv1.1, yes vs. no	1.3 (0.8–2.1)	0.373	1.0 (0.6–1.8)	0.869	—	—

Abbreviations: aHR, adjusted hazard ratio; CR-RECISTv1.1, complete response according to Response Evaluation Criteria in Solid Tumors version 1.1; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MASLD, metabolic dysfunction–associated steatotic liver disease; TRAE, treatment.

(74%) patients discontinued ICIs during follow-up due to recurrence (n = 21, 12%), adverse events (n = 22, 13%), ongoing CR (n = 57, 33%), curative conversion therapy (n = 9, 5%), or other reasons (n = 19, 11%).

At baseline, AFP levels were elevated (ie, ≥ 10 ng/mL) in 109 patients (63.4%). During treatment, median AFP levels declined from 39.8 (IQR, 4.7–1767.0) ng/mL at baseline (= ICI start) to 2.2 (IQR, 1.5–3.9) ng/mL at nadir (Supplemental Figure S2, http://links.lww.com/HEP/J634). AFP levels decreased to < 10 ng/mL during treatment in almost all patients (n = 92/109, 84%).

Median recurrence-free survival (RFS) from the first CR (mRECIST) was 30.3 (95% CI, 21.5–39.1) months, with a 1-, 2-, and 3-year RFS rate of 76%, 58%, and 48%, respectively (Table 2, Supplemental Figure S3A, http://links.lww.com/HEP/J634).

Fifty-nine (34%) patients experienced tumor recurrence after achieving CR, and 23 (13%) patients deceased during follow-up (Table 2). Median OS from immunotherapy start was not evaluable (95% CI: NE–NE), with a 1-, 2-, and 3-year OS rate of 98%, 95%, and 86%, respectively (Table 2, Supplemental Figure S3B, http://links.lww.com/HEP/J634). As antiangiogenic treatment is a concern when using mRECIST-criteria,[13] we repeated the main analysis in the subgroup of patients who received immunotherapy in combination with antiangiogenic treatment (ie, bevacizumab or TKI; n = 125). Again, OS and RFS were excellent in patients with CR-mRECIST-only and those who also had CR-RECISTv1.1 (Supplemental Table S1, http://links.lww.com/HEP/J634). Results were also comparable when analyzing patients with Child-Pugh class A liver function only (Supplemental Table S2, http://links.lww.com/HEP/J634) as well as first-line patients treated with an ICI regimen that had demonstrated efficacy in phase III trials (ie, atezolizumab+bevacizumab, durvalumab+tremelimumab, nivolumab+ipilimumab, and durvalumab monotherapy; Supplemental Table S3, http://links.lww.com/HEP/J634). Finally, we confirmed these results in patients who achieved CR to either systemic first-line or later-line systemic therapy (Supplemental Table S4, http://links.lww.com/HEP/J634).

In multivariable analysis, the presence of macrovascular invasion (aHR [95% CI], 0.4 [0.2–0.7]; $p = 0.003$) the and presence of extrahepatic metastasis (aHR [95% CI], 0.3 [0.2–0.6]; $p < 0.001$) were independently associated with improved RFS (Table 3).

Among those who discontinued ICI treatment for reasons other than recurrence (n = 107, 61%; Supplemental Table S5, http://links.lww.com/HEP/J634), recurrence rate was 28% (n = 30), and patients who received ICI treatment for ≥ 6 months after complete response (n = 56) had a longer RFS than those who discontinued ICI treatment earlier (n = 51) (median RFS [95% CI], not evaluable [not evaluable–not evaluable] vs. 37.0 [not evaluable–not evaluable]; $p = 0.008$), with 1-, 2-, and 3-year RFS rates of 92%, 78%, and 66% vs. 66%, 58%, and 58% (Figure 1A).

Similarly, in patients who discontinued ICI treatment because of ongoing complete response (n = 57, 33%), those who received ICI treatment for ≥ 6 months after complete response (n = 40) had a longer RFS than those who discontinued ICI treatment earlier (n = 17) (median RFS [95% CI], not evaluable [not evaluable–not evaluable] vs. 37.0 [not evaluable–not evaluable]; $p = 0.002$), with 1-, 2-, and 3-year RFS rates of 97%, 81%, and 81% vs. 79%, 55%, and 55% (Figure 1B).

Outcome of patients with CR-RECISTv1.1 and CR-mRECIST only

The median duration of ICI treatment was 22.2 (95% CI: 20.2–24.2) months for CR-RECISTv1.1 and 23.0 (95%

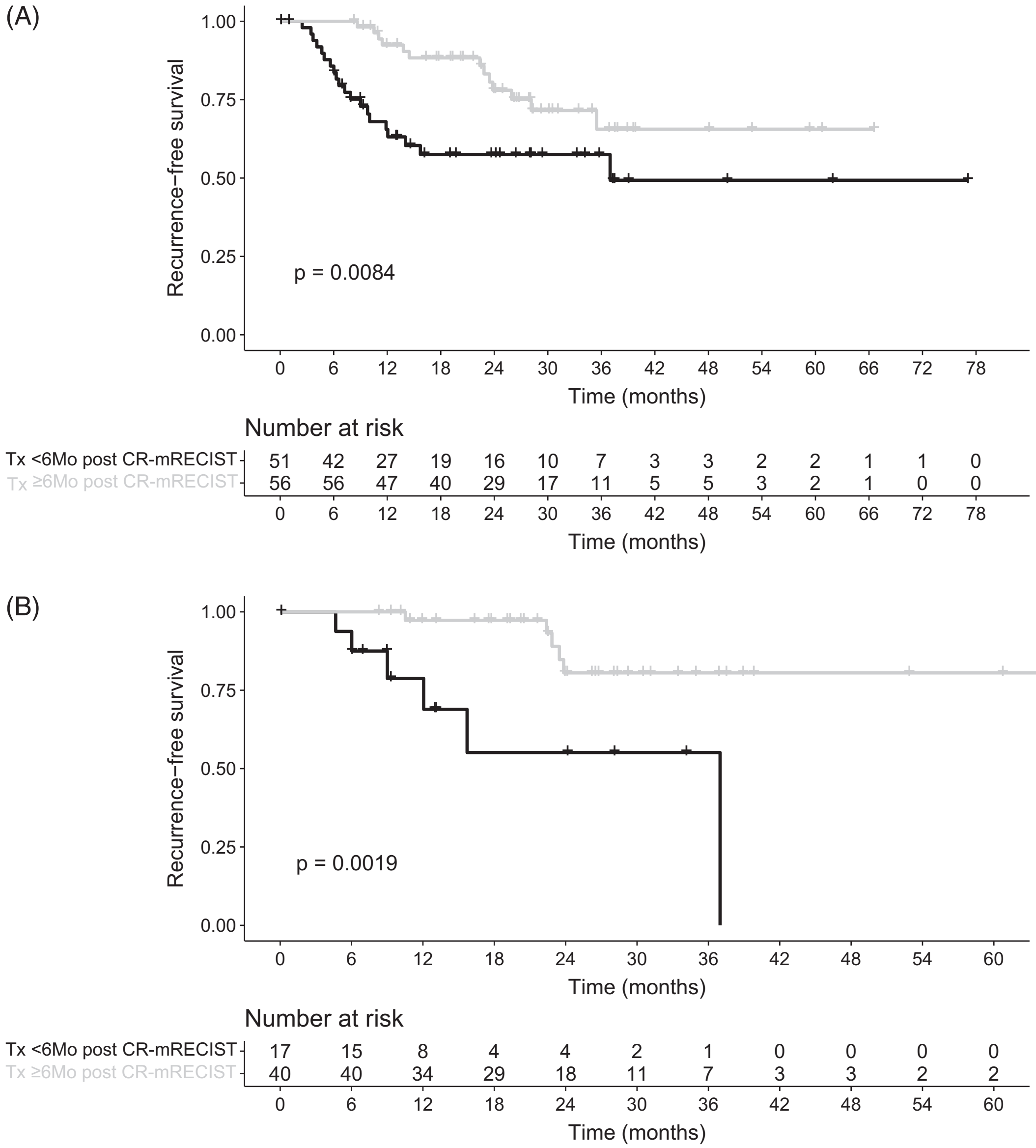

FIGURE 1 Comparison of recurrence-free survival between patients receiving ICI-based systemic treatment for $<$ vs. $\geq$6 months beyond complete response (according to mRECIST). (A) Patients who discontinued ICI treatment for reasons other than recurrence, and (B) patients who discontinued treatment due to ongoing complete response. Abbreviations: CR-mRECIST, complete response according to modified Response Evaluation Criteria in Solid Tumors; Mo, months; Tx, ICI-based systemic treatment.

CI: 20.7–25.2) months for CR-mRECIST only. Median time from immunotherapy start until first CR was 8.3 (95% CI: 6.4–10.3) months for CR-RECISTv1.1 (n = 97) and 6.8 (95% CI: 5.3–8.4) months for CR-mRECIST only (n = 77; Table 2).

Thirty-seven (38%; CR-RECISTv1.1) and 22 (29%; CR-mRECIST-only) patients experienced tumor recurrence after achieving CR. Twelve (12%; CR-RECISTv1.1) and 11 (14%; CR-mRECIST-only) patients deceased during follow-up (Table 2).

Median RFS from first CR was 28.4 (95% CI: 18.3–38.4) months, with a 1-, 2-, and 3-year RFS rate of 70%, 58%, and 42% for CR-RECISTv1.1 and 37.0 (95% CI: not evaluable–not evaluable) months, with a 1-, 2-, and 3-year RFS rate of 78%, 58%, and 55% for CR-mRECIST-only (Table 2, Figure 2A). Median OS from immunotherapy start was not evaluable (95% CI: not evaluable–not evaluable) months, with a 1-, 2-, and 3-year OS rate of 100%, 98%, and 87% for CR-RECISTv1.1 and not evaluable (95% CI: not evaluable–not evaluable) months, with a 1-, 2-, and 3-year OS rate of 96%, 91%, and 86% for CR-mRECIST-only (Table 2, Figure 2B).

Outcome of patients undergoing curative conversion therapy

Thirteen (7%) patients underwent curative conversion therapy after CR (liver transplantation, n = 4; resection,

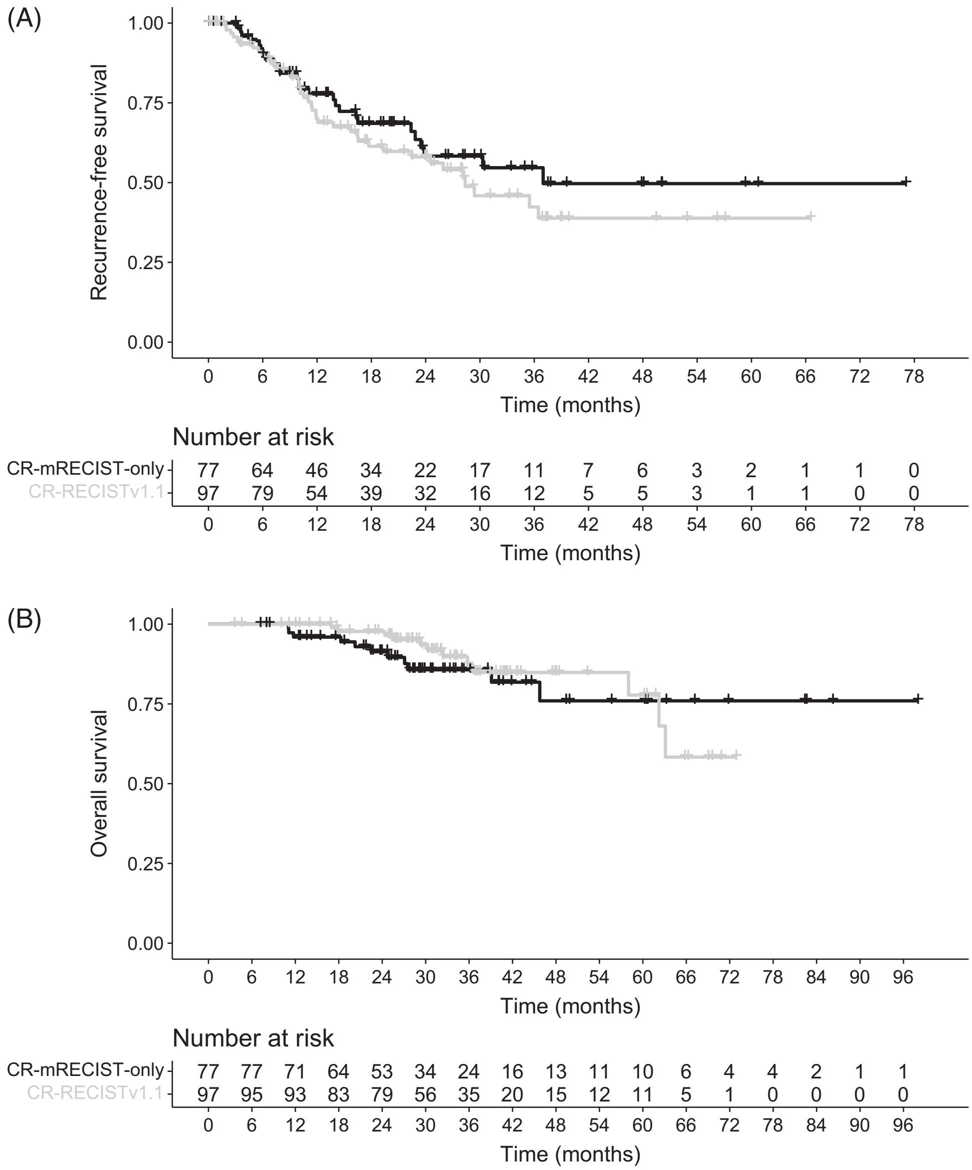

FIGURE 2 Kaplan-Meier survival curves of patients with CR-RECISTv1.1 and CR-mRECIST-only. (A) Recurrence-free survival (RFS) from the first complete response (according to RECISTv1.1 and mRECIST, respectively), and (B) overall survival from immunotherapy start. Abbreviations: CR-mRECIST, complete response according to modified Response Evaluation Criteria in Solid Tumors; CR-RECISTv1.1, complete response according to Response Evaluation Criteria in Solid Tumors version 1.1.

n = 5; ablation, n = 4) (Table 2, Supplemental Table S6, http://links.lww.com/HEP/J634). These patients received the following ICI-based therapies: PD-(L)1 monotherapy (n = 1), atezolizumab/bevacizumab (n = 9), durvalumab/tremelimumab (n = 1), and nivolumab/ipilimumab (n = 2).

Of patients who underwent resection or transplantation (n = 9), 8 had pathological complete response (CR-RECISTv1.1, n = 2/2; and CR-mRECIST-only, n = 6/7). Notably, of the subgroup of patients who had CR-mRECIST-only to immunotherapy combined with anti-angiogenic therapies (ie, bevacizumab) and underwent curative conversion treatment with resection or liver transplantation (n = 4), 3 patients (75%) had a pathological complete response.

Overall, 2 (15%) of all patients who underwent conversion therapy experienced recurrence, and 1 (8%) was deceased (1- and 3-year RFS: 75% and 75%; 1- and 3-year OS: 92% and 92%).

Treatment of recurrence

In total, 59 patients developed recurrence during follow-up. The most common radiological findings denoting the recurrence of disease were new hypervascularized liver lesions (n = 39, 66%), new extrahepatic lesions (n = 5, 9%), new hypervascularization of previously hypovascularized lesions (n = 4, 7%), new hypovascularized liver lesions (n = 3, 5%), and growth of hypovascularized liver lesions (n = 3, 5%). The remaining patients had mixed patterns of recurrence (Supplemental Table S7, http://links.lww.com/HEP/J634). The median AFP level at recurrence was 4.9 (range, 1.0–3159.0) ng/mL. The majority had Child-Pugh class A (n = 48, 81%). Fifty-five (93%) patients received at least 1 treatment for recurrence. The most common first therapies for recurrence included locoregional treatments (ie, transarterial chemoembolization, selective internal radiotherapy, radiotherapy) alone or combined with continuation of systemic therapy (n = 18, 33%), ablation (n = 14, 26%), other systemic therapies (n = 14, 26%), restart of the same ICI regimen (n = 6, 11%), and combination of locoregional plus other systemic therapies (n = 3, 6%).

Eight patients who developed recurrence after ICI was stopped were rechallenged with the same ICI regimen, including atezolizumab/bevacizumab (n = 5), durvalumab/tremelimumab (n = 1), nivolumab/regorafenib (n = 1), and pembrolizumab (n = 1). One additional patient treated with durvalumab beyond CR who developed recurrence was treated with another tremelimumab dose and continuation of durvalumab. Another patient who received atezolizumab/bevacizumab beyond CR and developed recurrence continued treatment with atezolizumab/bevacizumab. Rechallenge/continuation with the same regimen was administered as the first (n = 6), second (n = 3), or third (n = 1) line of treatment after HCC recurrence. According to RECISTv1.1, objective response rate (ORR) was 20% and DCR 70%; 1 patient (10%) had progressive disease, and 2 patients (20%) were not evaluable.

DISCUSSION

In this retrospective, international, multicenter study, we report the management and outcome of patients with HCC who achieved complete response to ICI-based systemic therapies. Several main conclusions can be drawn from our data that can inform clinical decision-making and patient counseling.

First, complete response to immunotherapy is a rare event, but those who achieve it have an excellent outcome. In our study, complete response occurred in less than 5% (mRECIST, 4.4%; RECISTv1.1, 2.5%) of patients with HCC treated with ICI-based systemic therapies in a noncurative setting. These numbers are comparable to those reported in phase III trials testing ICI monotherapy (RECISTv1.1, 1.5%–4%)[4,14] or ICI-based combinations (mRECIST, ~10%; RECISTv1.1, 2-5.5%;).[3,4,15] Patients with complete response had 1- and 3-year OS rates of 98% and 86%, and 1- and 3-year RFS rates of 76% and 48%, respectively. To put this into perspective, patients with HCC undergoing resection with curative intent have comparable 1- and 3-year RFS rates of around 80% and 55%, respectively.[16,17]

Notably, in our highly selected population with an exceptional response to immunotherapy, the presence of macrovascular invasion and extrahepatic metastasis were independently associated with improved RFS. This seems somewhat paradoxical at first glance. However, patients with more advanced tumors are less likely to achieve a complete remission with immunotherapy than those with earlier stage tumors,[3,18] and thus they probably require an even stronger immune activation. We therefore hypothesize that those few patients who achieve complete response despite having the most advanced tumors display the strongest and most profound immune response resulting in excellent long-term survival.

Second, the outcome of patients with complete responses according to mRECIST-only was excellent. Radiological complete response, according to RECISTv1.1, is defined by disappearance of all target and nontarget lesions,[11] but according to mRECIST, it only requires the disappearance of any intratumoral arterial enhancement in target and nontarget lesions.[10] The latter was developed to account for treatment-induced tumor necrosis. However, in the context of targeted therapies, the role of mRECIST has been questioned as antiangiogenic therapies can reduce arterial perfusion of HCC lesions, which may be misinterpreted as tumor necrosis.[13] Our study provides unique and important histological information, as 7 patients with CR-mRECIST-only underwent conversion therapy with resection or liver transplantation, and indeed, 6 of them had pathological complete responses. Moreover, recurrence rate, RFS, and OS were excellent in patients with CR-mRECIST-only. Even though the sample size is very limited, these data suggest that response to mRECIST in the context of immunotherapy may reflect necrosis rather than just changes in arterial perfusion of the tumor. Further studies in larger cohorts of patients who underwent liver resection or transplantation after CR to systemic therapies are required to confirm these findings.

Third, if discontinuation of immunotherapy is considered after achieving complete response, a longer duration of treatment beyond complete response may be associated with better outcomes. A retrospective analysis including different cancer types found that discontinuation within the first 12 months of anti-PD-(L)1 treatment was associated with a higher risk of recurrence.[19] European Society for Medical Oncology guidelines for metastatic melanoma recommend that patients with a confirmed complete response who have received immunotherapy for at least 6 months, can be considered for discontinuation of immunotherapy.[20] This recommendation was based on excellent disease-free survival rates of patients who stopped immunotherapy after a complete response.[21–23] However, recurrence of disease was more frequently observed in patients who received immunotherapy for less than 6 months.[23] Others proposed to consider ICI discontinuation in melanoma patients after a confirmed complete response for at least 6 months.[24] In our study, in patients who discontinued ICIs for reasons other than recurrence, those who received ICIs for at least 6 months beyond complete response had improved RFS. Similar results were observed in the subgroup that discontinued ICIs due to ongoing complete response. Based on these findings, it seems advisable to continue ICI treatment for at least 6 months after complete response in patients with HCC.

In this context, tools such as circulating tumor DNA (ctDNA) may aid in the decision to stop immunotherapy or not, as ctDNA-negativity may identify complete responders, while those with detectable ctDNA are likely to have residual disease.[25,26] However, ctDNA has not yet been used in routine clinical practice for HCC and requires further evaluation in clinical trials.

While in other tumor entities such as colorectal cancer with liver metastasis, resection of metastasis after neoadjuvant chemotherapy can be considered standard of care,[27] no recommendation on the use of locoregional therapies following responses to systemic therapy in HCC exists. Indeed, patients in our cohort had excellent long-term outcomes even though curative conversion was only performed in a very small subgroup of patients. However, the ultimate treatment aim is to achieve a disease-free but also treatment-free status, which might be achieved more rapidly and potentially in a larger proportion of patients with curative conversion treatment. Indeed, a very recent multicenter proof-of-concept study evaluated the use of curative conversion therapy following treatment with atezolizumab/bevacizumab in patients with intermediate-stage HCC. In this study, 23% of patients achieved drug-free status, and no recurrences were observed in this subgroup.[28] However, these patients did not have macrovascular invasion or extrahepatic metastases and the value of curative conversion treatment in patients with advanced HCC requires further evaluation.

Finally, we want to acknowledge some limitations. These include the retrospective nature of the study with all its potential confounders, the large time span of inclusion, the heterogeneous treatment regimens, and different lines of treatment. Moreover, the radiological evaluation of the complete response was based on investigators' assessment, but not on a central imaging review. While this must be acknowledged as a potential limitation, investigator-assessed tumor response was also used for key study end points in previous HCC trials.[4,5,29–31] Indeed, in phase III trials, complete response rates were often lower when assessed by investigators than when reviewed by an independent central facility.[3,15,30] Therefore, complete response rates in our study (mRECIST, 4.4%; RECISTv1.1, 2.5%) may reflect more conservative numbers, and we might have underestimated the proportion of patients with CR. However, all involved centers are tertiary referral centers and manage patients within a multidisciplinary tumor board. As everyday clinical decision-making is based on local tumor board evaluation, this approach better reflects the situation in a real-world setting, where interdisciplinary evaluation is used rather than a blinded review. Nevertheless, we cannot exclude that the concordance between central and local review might be worse in patients managed outside of clinical trials as previously suggested.[32] Furthermore, the retrospective design of the study prevented scheduled radiological assessment which might introduce some bias into RFS estimates. Finally, the limited follow-up time after CR of ~2 years might limit the robustness of 3-year RFS estimates.

In conclusion, only a small proportion of patients with advanced HCC achieve CR to noncurative immunotherapy-based systemic treatment, but these patients seem to have an excellent survival. OS and RFS rates were not only outstanding in those with CR-RECISTv1.1., but also in those with CR-mRECIST-only, and 6 of 7 patients with CR-mRECIST-only who underwent surgical conversion therapy had pathological complete response. Despite the outlined limitations, both of these findings underline the potential importance of mRECIST in the context of immunotherapy for clinical decision-making. When considering ICI discontinuation, treatment for at least 6 months beyond CR seems to be advisable as it was associated with improved RFS rates in our study.

DATA AVAILABILITY STATEMENT

Due to ethical considerations, individual patient data cannot be uploaded to a publicly available data repository. However, data is available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

Concept of the study (Bernhard Scheiner and Matthias Pinter), data collection (all authors), statistical analysis (Bernhard Scheiner and Matthias Pinter), drafting of the manuscript (Bernhard Scheiner and Matthias Pinter), revision for important intellectual content and approval of the final manuscript (all authors).

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CONFLICTS OF INTEREST

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49.
2. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022;76:681–93.
3. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382:1894–905.
4. Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evidence. 2022;1:EVIDoa2100070.
5. Sangro B, Chan SL, Kelley RK, Lau G, Kudo M, Sukeepaisarnjaroen W, et al. Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. Ann Oncol. 2024;35: 448–57.
6. Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2022;76:862–73.
7. Schmiderer A, Zoller H, Niederreiter M, Effenberger M, Oberhuber G, Krendl FJ, et al. Liver transplantation after successful downstaging of a locally advanced hepatocellular carcinoma with systemic therapy. Dig Dis. 2023;41:641–4.
8. Aby ES, Lake JR. Immune checkpoint inhibitor therapy before liver transplantation—Case and literature review. Transplant Direct. 2022;8:e1304.
9. Fukunaga A, Takata K, Itoh S, Yamauchi R, Tanaka T, Yokoyama K, et al. Complete tumor necrosis confirmed by conversion hepatectomy after atezolizumab-bevacizumab treatment for advanced-stage hepatocellular carcinoma with lung metastasis. Clin J Gastroenterol. 2023;16:224–8.
10. Lencioni R, Llovet J. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30:52–60.
11. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.
12. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. 1996;17:343–6.
13. Bruix J, Reig M, Rimola J, Forner A, Burrel M, Vilana R, et al. Clinical decision making and research in hepatocellular carcinoma: Pivotal role of imaging techniques. Hepatology. 2011;54: 2238–44.
14. Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): A randomised, multicentre, open-label, phase 3 trial. Lancet Oncol. 2022;23:77–90.
15. Llovet JM, Kudo M, Merle P, Meyer T, Qin S, Ikeda M, et al. Lenvatinib plus pembrolizumab versus lenvatinib plus placebo for advanced hepatocellular carcinoma (LEAP-002): A

randomised, double-blind, phase 3 trial. Lancet Oncol. 2023;24: 1399–410.
16. Shim JH, Jun MJ, Han S, Lee YJ, Lee SG, Kim KM, et al. Prognostic nomograms for prediction of recurrence and survival after curative liver resection for hepatocellular carcinoma. Ann Surg. 2015;261:939–46.
17. Li L, Zhang J, Liu X, Li X, Jiao B, Kang T. Clinical outcomes of radiofrequency ablation and surgical resection for small hepatocellular carcinoma: A meta-analysis. J Gastroenterol Hepatol. 2012;27:51–8.
18. Kudo M, Finn RS, Galle PR, Zhu AX, Ducreux M, Cheng AL, et al. IMbrave150: Efficacy and safety of atezolizumab plus bevacizumab versus sorafenib in patients with Barcelona Clinic liver cancer stage B unresectable hepatocellular carcinoma: An exploratory analysis of the phase III study. Liver Cancer. 2023;12:238–50.
19. Gauci ML, Lanoy E, Champiat S, Caramella C, Ammari S, Aspeslagh S, et al. Long-term survival in patients responding to anti-PD-1/PD-L1 therapy and disease outcome upon treatment discontinuation. Clin Cancer Res. 2019;25:946–56.
20. Keilholz U, Ascierto PA, Dummer R, Robert C, Lorigan P, van Akkooi A, et al. ESMO consensus conference recommendations on the management of metastatic melanoma: Under the auspices of the ESMO Guidelines Committee. Ann Oncol. 2020;31:1435–48.
21. Robert C, Ribas A, Hamid O, Daud A, Wolchok JD, Joshua AM, et al. Durable complete response after discontinuation of pembrolizumab in patients with metastatic melanoma. J Clin Oncol. 2018;36:1668–74.
22. Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): Post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol. 2019;20:1239–51.
23. Jansen YJL, Rozeman EA, Mason R, Goldinger SM, Geukes Foppen MH, Hoejberg L, et al. Discontinuation of anti-PD-1 antibody therapy in the absence of disease progression or treatment limiting toxicity: Clinical outcomes in advanced melanoma. Ann Oncol. 2019;30:1154–61.
24. Robert C, Marabelle A, Herrscher H, Caramella C, Rouby P, Fizazi K, et al. Immunotherapy discontinuation—How, and when? Data from melanoma as a paradigm. Nat Rev Clin Oncol. 2020;17:707–15.
25. Chehrazi-Raffle A, Muddasani R, Dizman N, Hsu J, Meza L, Zengin ZB, et al. Ultrasensitive circulating tumor DNA pilot study distinguishes complete response and partial response with immunotherapy in patients with metastatic renal cell carcinoma. JCO Precis Oncol. 2023;7:e2200543.
26. Chan KCA, Jiang P, Chan CWM, Sun K, Wong J, Hui EP, et al. Noninvasive detection of cancer-associated genome-wide hypomethylation and copy number aberrations by plasma DNA bisulfite sequencing. Proc Natl Acad Sci USA. 2013;110:18761–8.
27. Cervantes A, Adam R, Roselló S, Arnold D, Normanno N, Taïeb J, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34:10–32.
28. Kudo M, Aoki T, Ueshima K, Tsuchiya K, Morita M, Chishina H, et al. Achievement of complete response and drug-free status by atezolizumab plus bevacizumab combined with or without curative conversion in patients with transarterial chemoembolization-unsuitable, intermediate-stage hepatocellular carcinoma: A multicenter proof-of-concept study. Liver Cancer. 2023;12: 321–38.
29. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017; 389:2492–502.
30. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. Lancet. 2018;391:1163–73.
31. Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein concentrations (REACH-2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20: 282–96.
32. Rimola J, Díaz-González Á, Darnell A, Varela M, Pons F, Hernandez-Guerra M, et al. Complete response under sorafenib in patients with hepatocellular carcinoma: Relationship with dermatologic adverse events. Hepatology. 2018;67: 612–22.

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