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Hepatobiliary

The Role of Immunotherapy in Hepatocellular Carcinoma: A Systematic Review and Pooled Analysis of 2,402 Patients

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Immune checkpoint inhibitors • Immunotherapy • Hepatocellular carcinoma • PD-1 inhibitors • CTLA-4 inhibitors

Abstract

Background. Immune checkpoints inhibitors (ICIs) have emerged as a treatment option for several malignancies. Nivolumab, pembrolizumab, nivolumab plus ipilimumab, and atezolizumab plus bevacizumab have been approved for the management of advanced-stage hepatocellular carcinoma (HCC). We aimed to systematically review the literature and summarize the characteristics and outcomes of patients with HCC treated with ICIs.

Methods. A systematic literature search of PubMed, the Cochrane Library, and ClinicalTrials.gov was performed according to the PRISMA statement (end of search date: November 7, 2020). Quality of evidence assessment was also performed.

Results. Sixty-three articles including 2,402 patients were analyzed, 2,376 of whom received ICIs for unresectable HCC. Response to ICIs could be evaluated in 2,116 patients; the overall objective response rate (ORR) and disease control rate (DCR) were 22.7% and 60.7%, respectively, and the mean overall survival (OS) was 15.8 months. The ORR, DCR, and OS for nivolumab (n = 846) were 19.7%, 51.1%, and 18.7 months, respectively; for pembrolizumab (n = 435) they were 20.7%, 64.6% and 13.3 months, respectively. The combination of atezolizumab/bevacizumab (n = 460) demonstrated an ORR and DCR of 30% and 77%, respectively. The overall rate of treatment discontinuation because of adverse events was 14.9%. Fifteen patients received ICIs in the liver transplant (LT) setting (one pre-LT for bridging, 14 for post-LT recurrence); fatal graft rejection was reported in 40.0% (n = 6/15) and mortality in 80.0% (n = 12/15).

Conclusion. ICIs are safe and effective against unresectable HCC, but caution is warranted regarding their use in the LT setting because of the high graft rejection rate. ***The Oncologist*** 2021;26:e1036–e1049

Implications for Practice: This systematic review pooled the outcomes from studies reporting on the use of immune checkpoint inhibitors (ICIs) for the management of 2,402 patients with advanced-stage hepatocellular carcinoma (HCC), 2,376 of whom had unresectable HCC. The objective response rate and disease control rate were 22.7% and 60.7%, respectively, and the mean overall survival was 15.8 months. The overall rate of treatment discontinuation because of adverse events was 14.9%. Fifteen patients received ICIs in the liver transplant (LT) setting (one pre-LT for bridging, 14 for post-LT recurrence). Six of these patients experienced graft rejection (40.0%).

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Introduction

Hepatocellular carcinoma (HCC) constitutes the most frequent primary liver malignancy (85%–90%) and the fourth most common cause of cancer-related mortality in the world [1]. Resection, liver transplantation (LT), and ablation remain the mainstay of cure in the early stages, but recurrence rates are high, and most patients present with advanced-stage disease not amenable to these modalities [2]. Sorafenib, an antiangiogenic tyrosine kinase inhibitor, gained Food and Drug Administration (FDA) approval in 2007 and stood as the only FDA-approved therapy in HCC for a decade [3]. Starting in 2017, several other systemic agents have gained full approval for advanced HCC based on randomized phase III data, including lenvatinib and atezolizumab/bevacizumab in the first line [4] and regorafenib [5], cabozantinib [6], and ramucirumab [7] in refractory disease.

The emergence of immune checkpoints inhibitors (ICIs) in the management of multiple advanced malignancies [8, 9] led to the initiation of several trials aiming to evaluate the role of these agents in the treatment of HCC. The presence of tumor-infiltrating lymphocytes with increased programmed cell death protein-1 (PD-1) expression in HCC and their correlation with outcome provided evidence for a novel therapeutic target in HCC [10–12]. Nivolumab and pembrolizumab are humanized monoclonal antibodies that inhibit the interaction between PD-1 and programmed death-ligand 1 (PD-L1), thus inhibiting T-cell apoptosis and enhancing the cellular immune antitumor effects. These anti–PD-1 agents have recently gained accelerated approval as second-line treatments after sorafenib for patients with advanced HCC [13, 14]. Ipilimumab is a human monoclonal antibody exhibiting antitumor activity through an upregulation in T-cell activation; this is achieved via blockade of the inhibitory receptor cytotoxic T-lymphocyte associated protein 4 (CTLA-4), which is otherwise bound to the B7 molecule on the surface of antigen presenting cells [15]. Ipilimumab combined with nivolumab has also recently gained accelerated FDA approval for patients previously treated with sorafenib [16, 17]. The most recent ICI to show promise in advanced HCC is the PD-L1 inhibitor atezolizumab. In a randomized, phase III trial, the combination of atezolizumab and the antivascular endothelial growth factor antibody bevacizumab demonstrated a survival benefit over sorafenib, the first regimen to ever do so in advanced HCC, and thus gained full FDA approval in HCC [18].

The favorable initial survival outcomes of ICIs have led to their broader use on and off label as either first- or second-line options in patients with unresectable HCC [19]. Therefore, we aimed to summarize the available data on the demographic, clinical characteristics, and outcomes of patients with HCC treated with ICIs.

Materials and Methods

Study Design and Search Strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (supplemental online Table 1) [20] and in line with the protocol agreed by all authors. Eligible studies were restricted to clinical trials, cohort studies, case series, or case reports providing data on the safety and efficacy of PD-1, PD-L1, or CTLA-4 antibodies in patients with unresectable or metastatic HCC. Non-English studies and abstracts without full text were excluded, and no sample size restriction was applied. Studies were identified through search of the PubMed bibliographical database, Cochrane Library, and ClinicalTrials.gov (end of search date: November 7, 2020). The reference lists of studies included in the systematic review were also hand-searched for missed studies using the systematic "snowballing" procedure guidelines [21]. The literature search was conducted by four independent investigators (I.A.Z., A.P.E., D.G., M.H.H.), using the search strategy provided in supplemental online Table 2. All disagreements were resolved by consensus with the senior author (G.T.).

Data Extraction and Tabulation

Standardized, prepiloted forms were used for data extraction and tabulation as well as for quality assessment of eligible studies. Data extraction was performed independently by four investigators (I.A.Z., A.P.E., D.G., M.H.H.). The following data were extracted from the included studies: study characteristics (first author, year of publication, study design, study period if applicable, ICI used and setting of use, number of patients), age, sex, presence of risk factors (hepatitis B virus [HBV] and hepatitis C virus [HCV] infection, alcoholic liver disease, nonalcoholic steatohepatitis, cirrhosis), Eastern Cooperative Oncology Group (ECOG) performance status, Barcelona Clinic Liver Cancer (BCLC) stage, Child-Pugh (CP) classification, HCC disease extent, prior therapies implemented, adverse events, treatment response (complete response, partial response, stable disease, progressive disease, objective response rate [ORR], disease control rate [DCR]), and survival (progression-free survival [PFS], overall survival [OS], 6-month and 1-year survival rates). ORR was defined as the sum of all patients demonstrating complete or partial response divided by the total of evaluable patients, and DCR was defined as the sum of all patients demonstrating complete or partial response or stable disease divided by the total of evaluable patients.

Statistical Analysis

Continuous variables were summarized as means $\pm$ SD or median (interquartile range [IQR]), and categorical variables as frequencies and percentages accompanied by 95% confidence intervals (95% CIs). When continuous data were presented as medians and range, we applied the Hozo et al. [22] method to estimate the respective means and SDs. If the medians and IQR were reported within the included articles, we converted them to means and SDs according to Wan et al. [23]. All relative rates were estimated based on available data for each variable of interest, and available data were handled according to the principles stated in the Cochrane Handbook [24]. Data on outcomes of interest were tabulated and analyzed cumulatively. Data analyses

were performed with IBM SPSS Statistics 25 software (IBM Corp., Armonk, NY).

Quality of Evidence Assessment

For randomized controlled trials (RCTs), quality of evidence assessment was conducted with the modified Jadad scale, which includes randomization, blinding, withdrawals/dropouts, inclusion/exclusion criteria, adverse effects, and statistical analysis [25]. The score spans from 0 to 8, with a score of 4 to 8 indicating high quality and 0 to 3 indicating low quality.

For nonrandomized studies, quality of evidence assessment was performed using the Newcastle-Ottawa scale (NOS) [26], and studies were deemed of high (3 or 4 in selection domain AND 1 or 2 in comparability domain AND 2 or 3 in outcome domain), fair (2 in selection domain AND 1 or 2 in comparability domain AND 2 or 3 in outcome domain), and low quality (0 or 1 in selection domain OR 0 in comparability domain OR 0 or 1 in outcome domain), respectively.

The quality of the case series included in the present systematic review was assessed with a tool developed by the National Heart, Lung, and Blood Institute (NHLBI) [27]. The NHLBI scale ranges from 0 to 9, with a score 0 to 3 denoting low quality, 4 to 6 fair quality, and 7 to 9 high quality of studies.

The risk of bias of the eligible case reports was assessed with the Joanna Briggs Institute (JBI) scale [28]. This scale includes demographic characteristics, patient history, clinical condition, diagnostic tests, interventions, postintervention condition, adverse events/harms, and takeaway lessons. The range of the JBI scale is between 0 and 8, with a score of 0 to 3 denoting low quality and 4 to 8 denoting high quality.

Two reviewers (A.P.E., D.G.) rated the studies working independently, and final decision was reached by consensus with another author (I.A.Z.). A quality cutoff for exclusion of low-quality studies was set a priori according the scoring system of each individual scale as described above.

Results

Eligible Studies

Our systematic search of the literature yielded a total of 373 records, 63 of which were deemed eligible and were ultimately included in the present study [13, 14, 18, 29–88]. This included 11 clinical trials (4 randomized and 7 nonrandomized) and 8 cohort studies (Table 1), 12 case series, and 32 case reports (supplemental online Table 3). Fifty of the articles described the use of immunotherapy agents in the setting of unresectable HCC [13, 14, 18, 29–75], 3 in the neoadjuvant setting [76–78], and 10 in the setting of LT [79–88], and they reported on 2,402 patients in total (Fig. 1).

Quality of Evidence Assessment

The score of the modified Jadad scale for the RCTs [18, 54, 59, 63] was 6.5 $\pm$ 0.9 (supplemental online Table 4). The mean score of the NOS scale for the nonrandomized studies [13, 14, 30, 35, 36, 42, 45, 53, 56–58, 60, 66, 70, 73] was 7.4 $\pm$ 0.6 (supplemental online Table 5). The mean score of the NHBLI scale for the case series [31, 32, 37, 39, 40, 44, 51, 62, 67, 77, 80, 84] was 6.8 $\pm$ 0.9 (supplemental online Table 6). The mean score of the JBI scale for the case reports [29, 33, 34, 38, 41, 43, 46–50, 52, 55, 61, 64, 65, 68, 69, 71, 72, 74–76, 78, 79, 81–83, 85–88] was 7.2 $\pm$ 1.1 (supplemental online Table 7). These results highlight that the included studies were of high quality on average.

Unresectable Setting

A total of 2,376 patients received immunotherapy for the management of unresectable HCC. The mean age was 61.9 $\pm$ 10.8 years, and 82.0% were male (n = 1,948/2,376). The vast majority of patients had an ECOG performance status of 0 or 1 (94.2%, n = 1,988/2,110), CP class A liver disease (83.6%, n = 1,905/2,279), and BCLC stage C HCC (84.6%, n = 1,701/2,011). Macrovascular invasion was reported in 27.1% (n = 530/1,953) and extrahepatic disease in 64.3% (n = 1,473/2,292) of the patients. Prior localized therapies before ICI included liver resection in 28.0% (n = 332/1,187) of patients, transarterial chemoembolization in 43.3% (n = 386/891), radiofrequency or microwave ablation in 14.9% (n = 205/1,372), and yttrium-90 radioembolization in 48.4% (n = 44/91). Sorafenib preceded ICI therapy in 60.5% (n = 949/1,568) of patients. Details on patient demographics, disease extent, and prior treatments are presented in Table 2 and supplemental online Table 8.

Treatment response could be evaluated in 2,116 patients with HCC. The ORR and DCR were 22.7% (n = 481/2,116; 95% CI: 21.0%–24.6%) and 60.7% (n = 1,285/2,116; 95% CI: 58.6%–62.8%), respectively, in the overall population, and the mean time to treatment response was 4.8 months. The mean PFS was 6.0 months, and mean OS was 15.8 months. Six-month and 1-year overall survival rates were 71.6% (n = 1,434/2,002; 95% CI: 69.6%–73.6%) and 49.7% (n = 862/1,735; 95% CI: 47.3%–52.0%), respectively.

Efficacy data for nivolumab, pembrolizumab, atezolizumab/bevacizumab, and tremelimumab were individually analyzed. Treatment response to nivolumab could be evaluated in 846 patients with HCC. The ORR and DCR were 19.7% (n = 167/846; 95% CI: 17.2%–22.6%) and 51.1% (n = 432/846; 95% CI: 47.7%–54.4%), respectively, and the mean time to response was 5.4 months. The mean PFS was 7.3 months, and mean OS was 18.7 months. Six-month and 1-year overall survival rates were 63.1% (n = 539/854; 95% CI: 59.8%–66.3%) and 32.4% (n = 191/589; 95% CI: 28.8%–36.3%), respectively. Given that the published data on the outcomes after treatment with ipilimumab plus nivolumab in unresectable HCC were limited to 22 patients, these were excluded from the nivolumab-only analyses and demonstrated that ORR and DCR were 77.3% (n = 17/22; 95% CI: 56.2%–90.3%) and 95.5% (n = 21/22; 95% CI: 76.5% to >99.9%), respectively.

Treatment response to pembrolizumab could be evaluated in 435 patients with HCC. The ORR and DCR were 20.7% (n = 90/435; 95% CI: 17.1%–24.8%) and 64.6%

Table 1. Demographics of the clinical trials and cohort studies included in the systematic review

Year	First author	Country	Phase	Drug	Total patients, *n*	Patients with evaluable outcomes, *n*	ORR % (*n*/*n*)	Time to response, mean ± SD, months	DCR % (*n*/*n*)	PFS, mean ± SD, months	OS, mean ± SD, months
Clinical trials											
2020	Qin	China	II	Camrelizumab	217	195	16.4 (32/195)	2.4 ± 1.1	49.2 (96/195)	NA	13.8 ± 18.2
2020	Lee	International	Ib	Atezolizumab plus bevacizumab (non-randomized)	104	99	37.4 (37/99)	NA	74.7 (74/99)	7.3 ± 11.7	Median 17.1[a]
				Atezolizumab plus bevacizumab (randomized)	60	57	21.1 (12/57)	NA	70.2 (40/57)	5.6 ± 7.5	Not estimable
				Atezolizumab (randomized)	59	54	18.5 (10/54)	NA	53.7 (29/54)	3.4 ± 6.4	Not estimable
2020	Finn	International	III	Atezolizumab plus bevacizumab	336	304	27.3 (89/326)	NA	73.6 (240/326)	6.8 ± 12.2	Not estimable
2020	Bang	International	Ia/b	Ramucirumab plus durvalumab	28	26	10.7 (3/28)	7.9 ± 12.3	60.7 (17/28)	4.4 ± 5.1	10.7 ± 16.5
2020	Finn	International	III	Pembrolizumab vs. placebo	278	263	19.4 (51/263)	5.9 ± 2.6	65.8 (173/263)	3 ± 5.5	13.9 ± 4.7
2019	Agdashian	U.S.	I/II	Tremelimumab	39	34	23.5 (8/34)	NA	67.6 (23/34)	NA	10.9 ± 8.2
2019	Doi	Japan	I	Nivolumab plus mogamulizumab	15	15	26.7 (4/15)	NA	66.7 (10/15)	3.8 ± 5.8	11.3[a]
2019	Feun	U.S.	II	Pembrolizumab	29	28	32.1 (9/28)	NA	46.4 (13/28)	4.5 ± 6.6	13[a]
2018	Zhu	International	II	Pembrolizumab	104	98	18.4 (18/98)	2.8 ± 1.5	65.3 (64/98)	4.9 ± 9.9	12.9 ± 15.1
2017	El-Khoueiry	International	I/II	Nivolumab	262	250	19.6 (49/250)	4.0 ± 7.1	66.4 (166/250)	4.0 ± 9.3	15.0 ± 17.4
2013	Sangro	Spain	II	Tremelimumab	21	17	17.6 (3/17)	NA	76.5 (13/17)	6.5 ± 5.7	8.2 ± 18.3
Cohort studies											
2020	Sung	Korea	NA	Nivolumab	33	29	20.7 (6/29)	NA	34.5 (10/29)	NA	13.7 ± 9.7
2020	Choi	Korea	NA	Nivolumab	203	181	12.7 (23/181)	7.6 ± 11.9	39.8 (72/181)	6.9 ± 10.1	31.9 ± 48.8
2020	Fessas	International	NA	Nivolumab	233	218	22.4 (49/218)	NA	52.3 (114/218)	10.1 ± 30.6	12.2 ± 28.7
2020	Mahn	Germany	NA	Nivolumab (*n* = 10) or pembrolizumab (*n* = 4)	14	13	30.8 (4/13)	NA	76.9 (10/13)	6.2 ± 4.5	7.0 ± 4.9
2020	Kawaoka	Japan	NA	Pembrolizumab	82	2	NA	NA	NA	NA	NA
2019	Zhan	U.S.	NA	Nivolumab plus ipilimumab	23	22	77.3 (17/22)	NA	95.5 (21/22)	NA	NA
2019	Scheiner	Austria & Germany	NA	Nivolumab or pembrolizumab	65	54	14.8 (8/54)	5.4[a]	59.3 (32/54)	4.9 ± 8.5	9.9 ± 6.9
2019	Yu	Korea	NA	Nivolumab	76[a]	70	12.9 (9/70)	NA	22.9 (16/70)	NA	NA

[a]Not included in cumulative data because of the lack of data distribution measure.
Abbreviations: DCR, disease control rate; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

(*n* = 281/435; 95% CI: 60.0%–69.0%), respectively, and the mean time to treatment response was 5.1 months. The mean PFS was 3.9 months, and mean OS was 13.3 months. Six-month and 1-year overall survival rates were 75.2% (*n* = 318/423; 95% CI: 70.8%–79.1%) and 53.2% (*n* = 224/421; 95% CI: 48.4%–57.9%), respectively.

Treatment response to atezolizumab/bevacizumab could be evaluated in 460 patients with HCC. One subgroup of 54 evaluable patients receiving atezolizumab alone was excluded from these analyses to minimize heterogeneity. The ORR and DCR were 30.0% (*n* = 138/460; 95% CI: 26.0%–34.3%) and 77.0% (*n* = 354/460; 95% CI: 72.9%–80.6%),

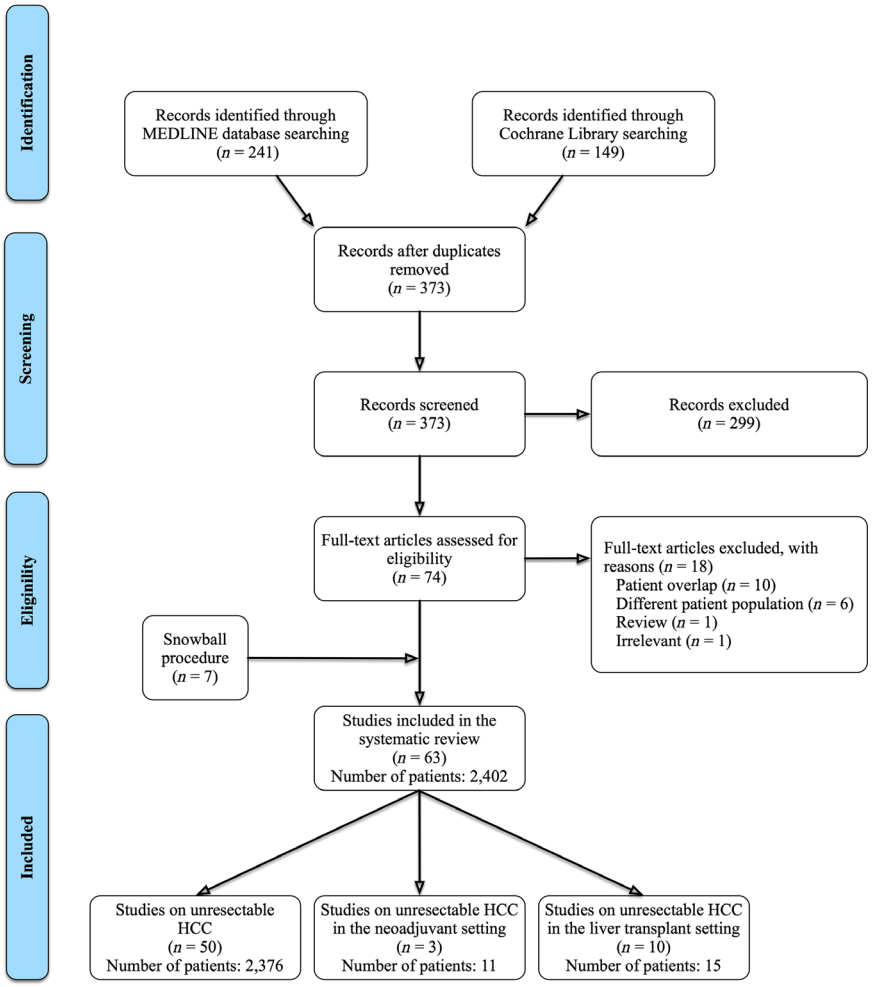

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the search strategy. Abbreviation: HCC, hepatocellular carcinoma.

respectively, whereas the mean time to treatment response was not available. The mean PFS was 6.8 months, and OS was not estimable. Six-month and 1-year overall survival rates were 84.1% (*n* = 370/440; 95% CI: 80.4%–87.2%) and 66.4% (*n* = 292/440; 95% CI: 61.8%–70.6%), respectively.

Treatment response to tremelimumab could be evaluated in 53 patients with HCC. The ORR and DCR were 22.6% (*n* = 12/53; 95% CI: 13.3%–35.7%) and 69.8% (*n* = 37/53; 95% CI: 56.4%–80.6%), respectively. The mean PFS was 6.5 months, and mean OS was 9.8 months. Six-month and 1-year overall survival rates were 69.8% (*n* = 37/53; 95% CI; 56.4%–80.6%) and 47.2% (*n* = 25/53; 95% CI; 34.4%–60.3%), respectively.

Neoadjuvant Setting

An additional 11 patients with a mean age of 51.5 ± 24.7 years received immunotherapy in the neoadjuvant setting for unresectable or potentially resectable HCC and were successfully bridged to liver resection. The etiology of their liver disease included HBV (*n* = 1/3) and HCV (*n* = 2/3) infection. Seven of 11 patients were treated with nivolumab monotherapy, and 4 patients were treated with combination of nivolumab plus ipilimumab. Data on outcomes were available for five (two with nivolumab and three with nivolumab plus ipilimumab) of the patients. The mean time to response was 1.6 months (range 1.5–2.0); ORR and DCR were 80% (*n* = 4/5; 95% CI: 36.0–98.0) and 100% (*n* = 5/5; 95% CI: 51.1–100.0), respectively; and the mean PFS and OS from the time of ICI administration were 2.0 and 4.0 (range 2.0–6.0) months, respectively.

Liver Transplant Setting

One patient with HCC received nivolumab as a bridge to LT and was successfully downstaged to within Milan criteria and was able to undergo LT; however, the patient experienced fatal graft rejection soon after LT.

Fourteen patients received ICIs (ten nivolumab, two pembrolizumab, and two ipilimumab) for the management of recurrent disease after LT for HCC. The mean age of patients was 50.8 ± 17.2 years [median (IQR) 56.4 (41.0–62.0) years], 71.4% (*n* = 10/14) were male, and the etiology of their liver disease included HBV (*n* = 1/7) and HCV (*n* = 5/7) infection. Seven patients had cirrhosis prior to LT,

Table 2. Demographic characteristics of the patients receiving immune checkpoint inhibitors in the unresectable setting

Year	First author	Age, years	Sex (M/F)	HBV	HCV	ECOG 0–1	ECOG > 1	BCLC A	BCLC B	BCLC C	BCLC D	CP A	CP B	CP C	Alcoholic	NASH	Cirrhosis
2020	Ando	64.0	1/0	0	1	NA	NA	NA	NA	NA	NA	0	1	0	NA	NA	NA
2020	Bang	60.0 ± 14.9	24/4	4	10	28	0	0	6	22	0	NA	NA	NA	8	NA	NA
2020	Choi	56.6 ± 10.6	171/32	168	8	180	23	0	8	195	0	132	71	0	NA	NA	NA
2020	Fessas	63.0 ± 9.7	184/49	83	95	143	11	4	23	204	2	158	75	0	29	24	NA
2020	Finn	63.6 ± 11.1	277/59	164	72	336	0	8	52	276	0	333	1	0	NA	NA	NA
2020	Lee[a]	57.3 ± 9.8	84/20	51	31	104	0	0	10	94	0	77	21	6	NA	NA	NA
2020	Lee[b]	56.0 ± 12.8	54/6	34	11	60	0	0	6	54	0	43	17	0	NA	NA	NA
2020	Lee[c]	58.5 ± 13.4	49/10	32	10	59	0	2	4	53	0	42	17	0	NA	NA	NA
2020	Mahn	64.6 ± 8.7	10/4	2	4	10	4	0	3	11	0	9	4	0	3	3	NA
2020	Meng	66.0 ± 6.6	4/0	4	0	NA	NA	0	2	2	0	4	0	0	NA	NA	4
2020	Nabrisky	60.0	1/0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	Oh	56.4 ± 11.6	3/2	3	1	NA	NA	NA	NA	NA	NA	4	1	0	0	1	NA
2020	Qin	49.7 ± 13.4	196/21	181	NA	217	0	0	11	206	0	213	4	0	NA	NA	NA
2020	Schulte	62.0	0/1	NA	NA	1	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	De Somer	83.0	1/0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	Sung	57.5 ± 10.1	25/8	29	1	NA	NA	0	4	29	0	26	7	0	NA	NA	NA
2020	Tan	62.0	1/0	0	1	NA	NA	NA	NA	NA	NA	0	1	0	0	0	0
2020	Yang	71.0	1/0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	Zhao	37.0	1/0	1	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	0	NA
2020	Kawaoka	67.8 ± 9.9	67/15	13	33	NA	NA	8	20	48	6	47	6	29	NA	NA	NA
2020	Kidampi	57.0	1/0	1	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2020	Finn	60.7 ± 12.2	226/52	72	43	278	0	0	56	222	0	277	1	0	159	NA	NA
2019	Adcock	NA	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	0	0
2019	Agdashian	59.9 ± 10.5	34/5	7	21	39	0	0	9	30	0	23	3	13	NA	NA	26
2019	Ang	66.4 ± 8.5	12/5	4	12	NA	NA	NA	NA	NA	NA	NA	NA	NA	6	1	
2019	Chakrabarti	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2019	Choi	70.0	1/0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2019	Dasanu	69.0	1/0	0	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	NA	1
2019	Doi	67.3 ± 11.5	14/1	NA	NA	15	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2019	Feun	62.6 ± 15.3	25/4	5	9	29	0	NA	NA	NA	NA	28	1	0	NA	NA	NA
2019	Kambhampati	61.0 ± 15.0	13/5	6	5	17	1	0	4	14	0	0	18	0	2	3	18
2019	Liu	63.0	1/0	1	0	NA	NA	0	0	1	0	0	1	0	NA	NA	1
2019	Petrioli	73.0	0/1	NA	NA	1	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2019	Qayyum	68.2 ± 7.1	6/3	1	4	NA	NA	NA	NA	NA	NA	9	0	0	0	4	9

(continued)

Table 2. (continued)

Year	First author	Age, years	Sex (M/F)	HBV	HCV	ECOG 0–1	ECOG > 1	BCLC A	BCLC B	BCLC C	BCLC D	CP A	CP B	CP C	Alcoholic	NASH	Cirrhosis
2019	Roderburg	77.0	0/1	0	1	NA	NA	0	0	1	0	NA	NA	NA	0	0	1
2019	Scheiner	65.2 ± 11.1	49/16	8	10	NA	NA	0	8	51	6	32	28	5	19	11	NA
2019	Tighe	66.0	1/0	0	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	1	1
2019	Wong	68.2 ± 5.6	6/0	4	0	NA	NA	NA	NA	NA	NA	4	0	0	0	2	6
2019	Yu	61.1 ± 10.8	65/11	56	6	73	3	0	4	69	3	59	14	3	6	NA	NA
2019	Zhan	NA	17/6	8	8	NA	NA	0	2	21	0	16	5	0	4	NA	NA
2018	Harsh	65.0	0/1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2018	Brown	61.0	1/0	0	1	NA	NA	NA	NA	NA	NA	0	1	0	NA	NA	1
2018	Grierson	82.0	1/0	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	0	0
2018	Joerger	68.0	1/0	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0
2018	Zhu	67.6 ± 8.3	86/18	22	26	104	0	0	25	79	0	98	6	0	80	NA	NA
2017	Saenz	57.0	0/1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2017	El-Khoueiry	63.1 ± 10.5	207/55	66	60	262	0	NA	NA	NA	NA	258	4	0	NA	NA	NA
2017	Chen	62.0	1/0	1	0	0	1	0	0	0	1	0	0	1	1	0	1
2017	Mamdani	79.0	1/0	0	0	NA	NA	NA	NA	NA	NA	1	0	0	NA	1	1
2017	Feng	55.4 ± 8.1	8/3	11	0	11	0	0	4	7	0	NA	NA	NA	NA	NA	NA
2016	Truong	75.0	1/0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2013	Sangro	65.2 ± 7.8	15/6	0	21	21	0	3	6	12	0	12	9	0	NA	NA	21
Total		61.9 ± 10.8	1,948/425	44.3% (1,042/2,350)	21.6% (508/2,350)	93.8% (1,988/2,110)	2.1% (43/2,110)	1.2% (25/2,011)	13.3% (267/2,011)	84.6% (1,701/2,011)	0.9% (18/2,011)	83.6% (1,905/2,279)	13.9% (317/2,279)	2.5% (57/2,279)	36.7% (314/856)	13.9% (55/396)	78.3% (267/341)

[a]Atezolizumab plus bevacizumab (nonrandomized).
[b]Atezolizumab plus bevacizumab (randomized).
[c]Atezolizumab alone (ramdomized).
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CP, Child-Pugh class; ECOG, Eastern Cooperative Oncology Group performance status; F, female; HBV, hepatitis B virus; HCV, hepatitis C virus; M, male; NA, not available; NASH, nonalcoholic steatohepatitis.

whereas CP class was not available for any patient. The mean ± SD and median (IQR) time from LT to HCC recurrence for these 14 patients was 38.6 ± 26.6 months and 34.2 (IQR: 14.4–62.0) months, respectively. Twelve of the 14 patients (85.7%) had received sorafenib for the management of HCC recurrence prior to ICI treatment. The mean ± SD and median (IQR) PFS on ICI treatment (n = 14) was 1.4 ± 0.8 months and 1.3 (IQR: 0.7–2.2) months, respectively. The mean ± SD and median (IQR) OS after starting ICI treatment (n = 14) was 1.8 ± 1.9 and 1.1 (1.0–1.3) months, respectively. Eleven of the 14 patients (78.6%) eventually died after HCC recurrence. Graft rejection was the cause of death in 45.4% (n = 5/11), and the mean ± SD and median (IQR) OS from time of ICI administration for these patients was 1.0 ± 0.1 and 1.0 (0.98–1.1) months, respectively. Disease progression or multiorgan failure were the causes of death in 54.5% (n = 6/11), and the mean ± SD and median (IQR) OS from time of ICI administration for these patients was 2.4 ± 2.2 and 1.3 (1.1–3.0) months, respectively. Three of the 14 patients (21.4%) were still alive with functional graft at 29, 20, and 10 months of follow-up after ICI initiation, respectively.

The characteristics of all 15 patients receiving ICIs in the setting of LT are summarized in Table 3.

Adverse Events

Adverse events leading to ICI discontinuation were documented in 14.9% of all the systematically reviewed patients (n = 327/2,201, 95% CI: 13.4%–16.4%). This included 7.0% of those who received nivolumab (n = 63/905, 95% CI: 5.5%–8.8%), 13.6% of those managed with pembrolizumab (n = 74/546, 95% CI: 10.9%–16.7%), 37.4% of those managed with atezolizumab/bevacizumab (n = 187/500, 95% CI: 33.3%–41.7%), and 3.2% of those managed with tremelimumab (n = 2/63, 95% CI: 0.2%–11.5). The overall rate of graft rejection in those that received ICIs in the setting of LT was 40.0% (n = 6/15, one patient receiving ICI pre-LT and five post-LT; 95% CI: 19.8–64.3). Fatigue was the most common adverse event in the total population (13.9%), followed by diarrhea (10.2%), rash (10.0%), pruritus (9.9%), and decreased appetite (8.5%). Additionally, the rate of hepatotoxicity in the total population, as defined by a significant increase in aspartate or alanine aminotransferase, bilirubin, or alkaline phosphatase levels, was 13.2% (n = 290/2,201, 95% CI: 11.8%–14.7%), 10.9% (n = 240/2,201, 95% CI: 9.7%–12.3%), 7.6% (n = 167/2,201; 95% CI: 6.6%–8.8%), and 2.6 (n = 57/2,201; 95% CI: 2.0%–3.4%), respectively. The clinical and laboratory treatment-related adverse events are summarized in Table 4 and supplemental online Table 9.

Ongoing Studies

The ongoing studies on the use of ICIs for the management of HCC are summarized in supplemental online Table 10.

Discussion

In the present systematic review assessing the use of ICIs in patients with HCC, we identified 63 eligible studies reporting on a total of 2,402 patients. Our findings highlight that approximately 23% of the patients receiving ICIs for the management of unresectable HCC demonstrated an objective response, whereas more than 61% achieved disease control. The mean PFS and OS were 6.0 and 15.8 months, respectively. Overall, ICIs were found to have manageable toxicity with fewer than 15% of the patients discontinuing therapy because of adverse events. These results highlight the promising and emerging role of ICIs in the armamentarium for the management of HCC.

Before the emergence of ICIs, patients with advanced-stage HCC relied mainly on sorafenib in the first line, which demonstrated a response rate of 2% and median OS of 10.7 months [3], and regorafenib in the second line, which exhibited a response rate of 11% and median OS of 10.6 months [5]. Our systematic review showed that the ORRs for nivolumab, pembrolizumab, and tremelimumab were 19.7%–22.6% and that the mean OS was 18.7, 13.3, and 9.8 months, respectively. The rate of patients that discontinued treatment is approximately 20% for sorafenib [89] and approximately 10% for regorafenib [5], whereas the rates for nivolumab, pembrolizumab, and tremelimumab were about 7%, 14%, and 3%, respectively. Because of the high heterogeneity among the studies included in our review, these results aim to synthesize all the available evidence and not perform head-to-head comparisons between ICIs and other systemic therapies.

The recent global, open-label, phase III IMBRAVE150 trial demonstrated the superiority of anti–PD-L1 inhibitor atezolizumab plus the antivascular endothelial growth factor receptor monoclonal antibody bevacizumab over sorafenib in both OS and PFS outcomes in patients with unresectable HCC and CP class A [18]. This study led to FDA approval of atezolizumab/bevacizumab for the frontline treatment of advanced HCC. Combining the results of this trial with the results of the GO30140 trial [59], we showed that the ORR for atezolizumab/bevacizumab was 30% and the PFS was 6.8 months, whereas about 37% of patients discontinued treatment because of adverse events. These findings may pave the way toward exploring the use of this combination in other settings. In addition, ongoing trials evaluating the role of ICIs combined with systemic therapies or locoregional modalities are ongoing and may affect the treatment algorithm for advanced HCC in the future.

Immune checkpoint inhibitor use for the management of recurrent disease after LT for HCC has been reported in 14 patients and as a bridge to LT in one patient. The high graft rejection rate of 40%, albeit in a limited number of cases, raises the question of the safety of ICIs in the management of HCC recurrence after LT. However, good tolerability and signs of significant anticancer efficacy were observed in some cases, so additional research into mechanisms of ICI-related graft rejection may provide insight to allow ICIs to be a viable salvage option for select LT recipients.

A growing body of evidence from non-HCC cancers suggests that certain biomarkers may predict response to

Table 3. Characteristics of the patients receiving ICIs in the liver transplant setting

Year	Author	ICI	Age/sex	ECOG	Transplant to ICI administration, years	Response	OS, months[a]	PFS, months[a]	Graft rejection	Transplant to graft failure, years	Prior sorafenib therapy	Immunosuppression	Last status
Pretransplant													
2019	Nordness	Nivolumab	65/M	NA	2[b]	Yes	0.3[c]	NA	Yes	NA	Yes	Tacrolimus, MMF	Death
Post-transplant													
2020	Anugwom	Ipilimumab	62/M	NA	5	No	NA	NA	Yes	NA	Yes	Tacrolimus	Death
2020	Pandey	Ipilimumab	65/F	NA	7.1	Yes	29	NA	No	NA	Yes	Everolimus, Tacrolimus	Alive
2019	Amjad	Nivolumab	62/F	NA	1.3	Yes	20	NA	No	NA	No	Tacrolimus, MMF	Alive
2018	DeLeon	Nivolumab	56.8/M	NA	2.7	No	1.2	2.2	No	NA	Yes	Tacrolimus	Death
		Nivolumab	55.9/M	1	7.8	No	1.1	0.7	No	NA	Yes	Sirolimus, MMF	Death
		Nivolumab	34.9/M	0	3.7	No	1.3	1.3	No	NA	Yes	Tacrolimus	Death
		Nivolumab	63.6/F	1	1.2	NA	0.3	NA	No	NA	Yes	Tacrolimus	Death
		Nivolumab	68/M	1	1.1	NA	0.9	NA	Yes	1.2	Yes	Sirolimus	Death
2018	Gassmann	Nivolumab	53/F	NA	2	No	1	NA	Yes	2.1	Yes	Everolimus, Tacrolimus	Death
2018	Rammohan	Pembrolizumab	57/M	NA	4.4	Yes	10	NA	No	NA	Yes	Tacrolimus	Alive
2017	De Toni	Nivolumab	41/M	NA	1	Yes	7	NA	No	NA	No	Tacrolimus	Death
2017	Friend	Nivolumab	20/M	NA	4	NA	1	NA	Yes	4.1	Yes	Sirolimus	Death
		Nivolumab	14/M	NA	3	NA	1	NA	Yes	3.1	Yes	Tacrolimus	Death
2017	Varkaris	Pembrolizumab	70/M	NA	8	No	3	NA	No	NA	Yes	Tacrolimus	Death

[a]From time of ICI administration.
[b]Time from ICI therapy initiation to transplant procedure (pretransplant setting); treated with nivolumab until 8 days pretransplant.
[c]Overall survival from liver transplantation.
Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; F, female; ICI, immune checkpoint inhibitor; M, male; MMF, mycophenolate mofetil; NA, not available; OS, overall survival; PFS, progression-free survival.

checkpoint inhibitors and thus can assist in the selection of patients who may benefit the most from treatment [90–94]. Specifically, in patients with advanced solid tumors, DNA mismatch repair and microsatellite instability (MSI) status can be predictive of response to ICI [92]. A second predictive biomarker is PD-L1 expression in tumor or immune cells, and ICIs have gained FDA approvals linked to PD-L1 positivity in multiple solid tumors [95]. In HCC, MSI is rarely seen, whereas PD-L1 expression is more common and seen in 17%–62% of the patients [13, 96, 97].

Two trials that notably evaluated the association of PD-L1 positivity with response to ICI in advanced HCC included the KEYNOTE-224 study [14] evaluating pembrolizumab and he CheckMate 040 study [13] evaluating nivolumab, after both progression on and intolerance to sorafenib. KEYNOTE-224 showed in a prespecified exploratory analysis that PD-L1 expression as assessed by the combined positive score was associated with response to therapy in a subset of patients with a combined positive score of at least 1, but the association with the tumor proportion score was not significant. CheckMate 040 showed that PD-L1 expression as assessed by the tumor proportion score was not significantly associated with response to therapy. However, because most studies in the present systematic review did not assess tumor positivity for PD-L1 and because of the high interstudy heterogeneity, results could not be cumulatively summarized for patients with PD-L1–positive and PD-L1–negative HCCs separately. Future research, in the form of RCTs investigating the outcomes of patients with HCC based on biomarker selection [98] could help identify subsets of patients with higher chances of benefit from ICI treatment in HCC; such studies may inform therapeutic decision-making, hence incarnating the concept of personalized medicine.

The present study has certain limitations. Firstly, the included studies comprised heterogeneous patient groups with various stages of disease that received several additional treatments for HCC; although we planned to perform subgroup analyses by disease stage, in most studies the outcomes were reported together for all

Table 4. Adverse events occurring in more than 5% of the patients

Clinical manifestation	Total[a]		Nivolumab		Pembrolizumab		Atezolizumab/ Bevacizumab		Tremelimumab	
	Frequency, % (*n*/*n*)	95% CI	Frequency, % (*n*/*n*)	95% CI	Frequency, % (*n*/*n*)	95% CI	Frequency, % (*n*/*n*)	95% CI	Frequency, % (*n*/*n*)	95% CI
Adverse events leading to ICI discontinuation	14.9 (327/2,201)	13.4–16.4	7.0 (63/905)	5.5–8.8	13.6 (74/546)	10.9–16.7	37.4 (187/500)	33.3–41.7	3.2 (2/63)	0.2–11.5
Grade 3 treatment-related adverse events	15.3 (336/2,201)	13.8–16.8	10.9 (99/905)	9.1–13.2	31.9 (174/546)	28.1–35.9	10.2 (51/500)	7.8–13.2	1.6 (1/63)	<0.01–9.3
Clinical treatment-related AEs										
Fatigue	13.9 (305/2,201)	12.5–15.4	11.2 (101/905)	9.3–13.4	15.9 (87/546)	13.1–19.3	18.2 (91/500)	15.1–21.8	11.1 (7/63)	5.2–21.5
Diarrhea	10.2 (224/2,201)	9.0–11.5	6.7 (61/905)	5.3–8.6	12.5 (68/546)	9.9–15.5	13.2 (66/500)	10.5–16.5	9.5 (6/63)	4.1–19.6
Rash	10.0 (220/2,201)	8.8–11.3	7.6 (69/905)	6.1–9.6	10.8 (59/546)	8.5–13.7	13.0 (65/500)	10.3–16.3	20.6 (13/63)	12.3–32.3
Pruritus	9.9 (217/2,201)	8.7–11.2	8.3 (75/905)	6.7–10.3	12.1 (66/546)	9.6–15.1	13.4 (67/500)	10.7–16.7	0.0 (0/63)	0.0–6.9
Decreased appetite	8.5 (187/2,201)	7.4–9.7	3.1 (28/905)	2.1–4.5	10.6 (58/546)	8.3–13.5	15.4 (77/500)	12.5–18.8	15.9 (10/63)	8.7–27.0
Proteinuria	7.6 (168/2,201)	6.6–8.8	0.0 (0/905)	0.0–0.5	0.0 (0/546)	0.0–0.8	22.8 (114/500)	19.3–26.7	0.0 (0/63)	0.0–6.9
Fever	6.1 (134/2,201)	5.2–7.2	0.3 (3/905)	0.1–1.0	5.7 (31/546)	4.0–8.0	17.8 (89/500)	14.7–21.4	0.0 (0/63)	0.0–6.9
Abdominal pain	5.8 (128/2,201)	4.9–6.9	0.2 (2/905)	<0.01–0.9	7.9 (43/546)	5.9–10.5	14.0 (70/500)	11.2–17.3	3.2 (2/63)	0.2–11.5
Nausea	5.8 (127/2,201)	4.9–6.8	3.9 (35/905)	2.8–5.4	8.1 (44/546)	6.0–10.7	7.8 (39/500)	5.7–10.5	0.0 (0/63)	0.0–6.9
Hypothyroidism	4.5 (100/2,201)	3.8–5.5	0.6 (5/905)	0.2–1.3	4.4 (24/546)	2.9–6.5	9.6 (48/500)	7.3–12.5	1.6 (1/63)	<0.01–9.3
Hepatitis	3.4 (76/2,201)	7–4.2.3	0.0 (0/905)	0.0–0.5	0.9 (5/546)	0.3–2.2	8.6 (43/500)	6.4–11.4	0.0 (0/63)	0.0–6.9
Dyspnea	3.4 (75/2,201)	7–4.2.3	0.1 (1/905)	<0.01–0.7	4.2 (23/546)	2.8–6.3	9.4 (47/500)	7.1–12.3	0.0 (0/63)	0.0–6.9
Anaphylactic reaction	3.3 (72/2,201)	2.6–4.1	0.6 (5/905)	0.2–1.3	1.7 (9/546)	0.8–3.2	7.2 (36/500)	5.2–9.8	1.6 (1/63)	<0.01–9.3
Weight loss	2.6 (58/2,201)	2.0–3.4	0.3 (3/905)	0.1–1.0	0.6 (3/546)	0.1–1.7	9.6 (48/500)	7.3–12.5	0.0 (0/63)	0.0–6.9
Arthralgia	2.6 (58/2,201)	2.0–3.4	0.1 (1/905)	<0.01–0.7	5.1 (28/546)	3.6–7.3	5.0 (25/500)	3.4–7.3	1.6 (1/63)	<0.01–9.3
Muscle weakness	2.6 (57/2,201)	2.0–3.4	0.0 (0/905)	0.0–0.5	5.5 (30/546)	3.9–7.8	5.0 (25/500)	3.4–7.3	0.0 (0/63)	0.0–6.9
Ascites	2.4 (53/2,201)	1.8–3.1	0.0 (0/905)	0.0–0.5	2.4 (13/546)	1.4–4.1	6.8 (34/500)	4.9–9.4	0.0 (0/63)	0.0–6.9
Myalgia	2.3 (51/2,201)	1.8–3.0	0.6 (5/905)	0.2–1.3	5.3 (29/546)	3.7–7.6	2.2 (11/500)	1.2–3.9	0.0 (0/63)	0.0–6.9
Abdominal distention	2.0 (44/2,201)	1.5–2.7	0.0 (0/905)	0.0–0.5	0.2 (1/546)	<0.01–1.1	7.2 (36/500)	5.2–9.8	0.0 (0/63)	0.0–6.9
Laboratory treatment-related AEs										
Increased AST	13.2 (290/2,201)	11.8–14.7	5.8 (52/905)	4.4–7.5	15.8 (86/546)	12.9–19.1	13.0 (65/500)	10.3–16.3	22.2 (14/63)	13.6–34.0
Increased ALT	10.9 (240/2,201)	9.7–12.3	5.2 (47/905)	3.9–6.9	12.6 (69/546)	10.1–15.7	9.8 (49/500)	7.5–12.7	11.1 (7/63)	5.2–21.5
Increased bilirubin	7.6 (167/2,201)	6.6–8.8	1.7 (15/905)	1.0–2.7	12.5 (68/546)	9.9–15.5	9.0 (45/500)	6.8–11.9	11.1 (7/63)	5.2–21.5
Anemia	5.0 (110/2,201)	4.2–6.0	1.1 (10/905)	0.6–2.1	6.2 (34/546)	4.5–8.6	9.2 (46/500)	7.0–12.1	1.6 (1/63)	<0.01–9.3

(continued)

Table 4. (continued)

Clinical manifestation	Total[a]		Nivolumab		Pembrolizumab		Atezolizumab/ Bevacizumab		Tremelimumab	
	Frequency, % (*n*/*n*)	95% CI	Frequency, % (*n*/*n*)	95% CI	Frequency, % (*n*/*n*)	95% CI	Frequency, % (*n*/*n*)	95% CI	Frequency, % (*n*/*n*)	95% CI
Thrombocytopenia	4.9 (108/2,201)	4.1–5.9	0.3 (3/905)	0.1–1.0	1.5 (8/546)	0.7–2.9	11.8 (59/500)	9.2–14.9	0.0 (0/63)	0.0–6.9
Increased ALP levels	2.6 (57/2,201)	2.0–3.4	0.7 (6/905)	0.3–1.5	1.5 (8/546)	0.7–2.9	6.6 (33/500)	4.7–9.2	0.0 (0/63)	0.0–6.9
Hyponatremia	2.0 (45/2,201)	1.5–2.7	0.3 (3/905)	0.1–1.0	0.9 (5/546)	0.3–2.2	4.8 (24/500)	3.2–7.1	20.6 (13/63)	12.3–32.3
Neutropenia	1.9 (41/2,201)	1.4–2.5	0.0 (0/905)	0.0–0.5	1.7 (9/546)	0.8–3.2	4.0 (20/500)	2.6–6.1	6.4 (4/63)	2.1–15.7

[a]The four drug columns do not add up to the total column because either the adverse events were attributed to ICIs other than those four or the drug that these events were attributed to was not specified.
Abbreviations: AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; ICI, immune checkpoint inhibitor.

stages, and thus subgroup analyses could not be conducted. Secondly, many of the eligible studies were retrospectively analyzed cohort studies, cases series, or case reports and thus impart a degree of selection bias; however, the average study quality according to our quality assessment was high. Thirdly, as with any systematic review, certain included articles did not report on all outcomes of interest; consequently, although this study had a systematic and detailed extraction of data, relative rates were estimated based on available data. Finally, we are aware of the "survival tail" commonly seen in patients treated with ICIs, which renders the use of median survival more relevant than mean survival; however, as in all systematic reviews and pooled analyses, the only way to cumulatively pool the outcomes is by converting the continuous variables from median and range/IQR to mean and SD, and thus our results are reported in means ± SD.

Conclusion

Over the past years, efforts have led to the development of new systemic agents for patients with HCC not amenable to resection. ICIs have proven to be effective in achieving deep and durable responses and an improvement in patient survival. Despite the wide range of adverse events associated with the use of ICIs, our findings suggest that they can be adequately tolerated as a treatment option in patients with HCC with only about 15% of the patients experiencing adverse events that lead to treatment discontinuation. However, caution is warranted regarding the use of ICIs in the setting of LT because of the high rate of graft loss, possibly related to dysregulated immune activation. The full texts of published abstracts and ongoing prospective comparative trials are awaited to provide additional data for more rigorous quantitative synthesis of evidence.

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Disclosures

Lipika Goyal: Debiopharm, H3 Biomedicine, Agios Pharmaceuticals, Taiho Pharmaceuticals, Klus Pharmaceuticals, QED, Pieris Pharmaceuticals, Alentis Therapeutics, Incyte Corporation, SIRTEX (SAB), Incyte, QED, H3Biomedicine, Alentis (C/A), Astra Zeneca (other—independent data monitoring committee). The other authors indicated no financial relationships.

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References

1. Fitzmaurice C, Abate D, Abbasi N et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: A systematic analysis for the Global Burden of Disease Study. JAMA Oncol 2019;5:1749–1768.

2. Ziogas IA, Tsoulfas G. Advances and challenges in laparoscopic surgery in the management of hepatocellular carcinoma. World J Gastrointest Surg 2017;9:233–245.

3. Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.

4. Kudo M, Finn RS, Qin S et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. Lancet 2018;391:1163–1173.

5. Bruix J, Qin S, Merle P et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;389:56–66.

6. Abou-Alfa GK, Meyer T, Cheng AL et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 2018;379:54–63.

7. Zhu AX, Kang YK, Yen CJ et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:282–296.

8. Motzer RJ, Escudier B, McDermott DF et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803–1813.

9. Weber JS, D'Angelo SP, Minor D et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): A randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015;16:375–384.

10. Shi F, Shi M, Zeng Z et al. PD-1 and PD-L1 upregulation promotes CD8(+) T-cell apoptosis and postoperative recurrence in hepatocellular carcinoma patients. Int J Cancer 2011;128:887–896.

11. Prieto J, Melero I, Sangro B. Immunological landscape and immunotherapy of hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 2015;12:681–700.

12. Flecken T, Schmidt N, Hild S et al. Immunodominance and functional alterations of tumor-associated antigen-specific CD8+ T-cell responses in hepatocellular carcinoma. Hepatology 2014;59:1415–1426.

13. El-Khoueiry AB, Sangro B, Yau T et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492–2502.

14. Zhu AX, Finn RS, Edeline J et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): A non-randomised, open-label phase 2 trial. Lancet Oncol 2018;19:940–952.

15. Buchbinder E, Hodi FS. Cytotoxic T lymphocyte antigen-4 and immune checkpoint blockade. J Clin Invest 2015;125:3377–3383.

16. He AR, Yau T, Hsu C et al. Nivolumab + ipilimumab combination therapy in patients with advanced hepatocellular carcinoma: Subgroup analysis from CheckMate 040. Presented at: 2020 Gastrointestinal Cancers Symposium; February 13–15, 2020; San Francisco, CA.

17. FDA approves nivolumab/ipilimumab for pretreated patients with hepatocellular carcinoma. News release. April 10, 2020. Accessed June 11, 2020. Available at www.ascopost.com/issues/april-10-2020/fda-approves-nivolumabipilimumab-for-pretreated-patients-with-hepatocellular-carcinoma/.

18. Finn RS, Qin S, Ikeda M et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894–1905.

19. Iñarrairaegui M, Melero I, Sangro B. Immunotherapy of hepatocellular carcinoma: Facts and hopes. Clin Cancer Res 2018;24:1518–1524.

20. Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ 2009;339:b2700.

21. Wohlin C. Guidelines for snowballing in systematic literature studies and a replication in software engineering. In: EASE '14: Proceedings of the 18th International Conference on Evaluation and Assessment in Software Engineering. New York, NY: Association for Computing Machinery; 2014:38:1–38:10.

22. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.

23. Wan X, Wang W, Liu J et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135.

24. Higgins J, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available at www.handbook.cochrane.org.

25. Oremus M, Wolfson C, Perrault A et al. Interrater reliability of the modified Jadad quality scale for systematic reviews of Alzheimer's disease drug trials. Dement Geriatr Cogn Disord 2001;12:232–236.

26. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–605.

27. National Heart Lung and Blood Institute. Quality assessment tool for case series studies. Accessed December 19, 2019. Available at https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

28. Joanna Briggs Institute Critical Appraisal tools. Checklist for Case Reports. Accessed January 15, 2020. Available at http://joannabriggs.org/research/critical-appraisal-tools.html.

29. Adcock CS, Puneky L V, Campbell GS. Favorable response of metastatic hepatocellular carcinoma to treatment with trans-arterial radioembolization followed by sorafenib and nivolumab. Cureus 2019;11:1–13.

30. Agdashian D, ElGindi M, Xie C et al. The effect of anti-CTLA4 treatment on peripheral and intra-tumoral T cells in patients with hepatocellular carcinoma. Cancer Immunol Immunother 2019;68:599–608.

31. Ang C, Klempner SJ, Ali SM et al. Prevalence of established and emerging biomarkers of immune checkpoint inhibitor response in advanced hepatocellular carcinoma. Oncotarget 2019;10:4018–4025.

32. Chakrabarti S, Tella SH, Kommalapati A et al. Clinicopathological features and outcomes of fibrolamellar hepatocellular carcinoma. J Gastrointest Oncol 2019;10:554–561.

33. Choi B, McBride A, Scott AJ. Treatment with pembrolizumab after hypersensitivity reaction to nivolumab in a patient with hepatocellular carcinoma. Am J Health Syst Pharm 2019;76:1749–1752.

34. Dasanu CA. Late-onset Stevens-Johnson syndrome due to nivolumab use for hepatocellular carcinoma. J Oncol Pharm Pract 2019;25:2052–2055.

35. Doi T, Muro K, Ishii H et al. A phase I study of the anti-CC chemokine receptor 4 antibody, mogamulizumab, in combination with nivolumab in patients with advanced or metastatic solid tumors. Clin Cancer Res 2019;25:6614–6622.

36. Feun LG, Li YY, Wu C et al. Phase 2 study of pembrolizumab and circulating biomarkers to predict anticancer response in advanced, unresectable hepatocellular carcinoma. Cancer 2019;125:3603–3614.

37. Kambhampati S, Bauer KE, Bracci PM et al. Nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh class B cirrhosis: Safety and clinical outcomes in a retrospective case series. Cancer 2019;125:3234–3241.

38. Liu Z, Li X, He X et al. Complete response to the combination of lenvatinib and pembrolizumab in an advanced hepatocellular carcinoma patient: A case report. BMC Cancer 2019;19:1062.

39. Petrioli R, Mazzei MA, Giorgi S et al. Hyperprogressive disease in advanced cancer patients treated with nivolumab: A case series study. Anticancer Drugs 2020;31:190–195.

40. Qayyum A, Hwang KP, Stafford J et al. Immunotherapy response evaluation with magnetic resonance elastography (MRE) in advanced HCC. J Immunother Cancer 2019;7:329.

41. Roderburg C, Berres ML, Wree A et al. Excellent response to anti-PD-1 therapy in a patient with hepatocellular carcinoma intolerant to sorafenib. Visc Med 2019;35:43–46.

42. Scheiner B, Kirstein MM, Hucke F et al. Programmed cell death protein-1 (PD-1)-targeted immunotherapy in advanced hepatocellular carcinoma: Efficacy and safety data from an international multicentre real-world cohort. Aliment Pharmacol Ther 2019;49:1323–1333.

43. Tighe SP, Iqbal U, Fernandes CT et al. Treatment of inoperable hepatocellular carcinoma with immunotherapy. BMJ Case Rep 2019;12:e229744.

44. Wong DJ, Lee J, Choo SP et al. Hyperprogressive disease in hepatocellular carcinoma

with immune checkpoint inhibitor use: A case series. Immunotherapy 2019;11:167–175.

45. Yu J Il, Lee SJ, Lee J et al. Clinical significance of radiotherapy before and/or during nivolumab treatment in hepatocellular carcinoma. Cancer Med 2019;8:6986–6994.

46. Brown ZJ, Heinrich B, Greten TF. Development of shellfish allergy after exposure to dual immune checkpoint blockade. Hepatic Oncol 2018;5:HEP02.

47. Grierson P, Crites D, Ruzinova MB et al. Distinct clinical and magnetic resonance features of metastatic hepatocellular carcinoma treated with pembrolizumab: A case report of late response after pseudoprogression. Hepatol Commun 2018;2:148–151.

48. Joerger M, Guller U, Bastian S et al. Prolonged tumor response associated with sequential immune checkpoint inhibitor combination treatment and regorafenib in a patient with advanced pretreated hepatocellular carcinoma. J Gastrointest Oncol 2019;10:373–378.

49. Chen SC, Chao Y, Yang MH. Complete response to the combination of pembrolizumab and sorafenib for metastatic hepatocellular carcinoma: A case report. Am J Gastroenterol 2017; 112:659–660.

50. Mamdani H, Wu H, O'Neil BH et al. Excellent response to Anti-PD-1 therapy in a patient with hepatocellular carcinoma: Case report and review of literature. Discov Med 2017;23: 331–336.

51. Feng D, Hui X, Shi-Chun L et al. Initial experience of anti-PD1 therapy with nivolumab in advanced hepatocellular carcinoma. Oncotarget 2017;8:96649–96655.

52. Truong P, Rahal A, Kallail KJ. Metastatic hepatocellular carcinoma responsive to pembrolizumab. Cureus 2016;8:e631.

53. Sangro B, Gomez-Martin C, De La Mata M et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. J Hepatol 2013;59:81–88.

54. Finn RS, Ryoo BY, Merle P et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: A randomized, double-blind, phase III trial. J Clin Oncol 2020;38:193–202.

55. Ando Y, Yamauchi M, Suehiro Y et al. Complete response to pembrolizumab in advanced hepatocellular carcinoma with microsatellite instability. Clin J Gastroenterol 2020;13:867–872.

56. Bang YJ, Golan T, Dahan L et al. Ramucirumab and durvalumab for previously treated, advanced non–small-cell lung cancer, gastric/gastro-oesophageal junction adenocarcinoma, or hepatocellular carcinoma: An open-label, phase Ia/b study (JVDJ). Eur J Cancer 2020; 137:272–284.

57. Choi WM, Lee D, Shim JH et al. Effectiveness and safety of nivolumab in Child–Pugh B patients with hepatocellular carcinoma: A real-world cohort study. Cancers (Basel) 2020; 12:1–14.

58. Fessas P, Kaseb A, Wang Y et al. Post-registration experience of nivolumab in advanced hepatocellular carcinoma: An international study. J Immunother Cancer 2020;8:e001033.

59. Lee MS, Ryoo BY, Hsu CH et al. Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): An open-label, multicentre, phase 1b study. Lancet Oncol 2020;21:808–820.

60. Mahn R, Vogt A, Kupczyk P et al. Programmed cell death protein 1 (PD-1)-inhibition in hepatocellular carcinoma (HCC): A single center experience. Scand J Gastroenterol 2020;55:1057–1062.

61. Nabrinsky E, James E. Highlighting survival with yttrium-90 radioembolization therapy in unresectable hepatocellular carcinoma. Cureus 2020;12:e8163.

62. Oh S, Park Y, Lee HJ,et al. A disintegrin and metalloproteinase 9 (ADAM9) in advanced hepatocellular carcinoma and their role as a biomarker during hepatocellular carcinoma immunotherapy. Cancers (Basel) 2020;12:745.

63. Qin S, Ren Z, Meng Z et al. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: A multicentre, open-label, parallel-group, randomised, phase 2 trial. Lancet Oncol 2020;21:571–580.

64. Sáenz de Santa María García M, Noguerado-Mellado B, Rojas-Pérez-Ezquerra P et al. First case of allergy to nivolumab. J Allergy Clin Immunol Pract 2017;5:1140–1141.

65. Schulte N, Li M, Zhan T et al. Response of advanced HCC to pembrolizumab and lenvatinib combination therapy despite monotherapy failure. Z Gastroenterol 2020;58:773–777.

66. Sung PS, Jang JW, Lee J et al. Real-world outcomes of nivolumab in patients with unresectable hepatocellular carcinoma in an endemic area of hepatitis B virus infection. Front Oncol 2020;10:1043.

67. Meng M, Li W, Yang X et al. Transarterial chemoembolization, ablation, tyrosine kinase inhibitors, and immunotherapy (TATI): A novel treatment for patients with advanced hepatocellular carcinoma. J Cancer Res Ther 2020;16: 327–334.

68. Tan NYL, Anavekar NS, Wiley BM. Concomitant myopericarditis and takotsubo syndrome following immune checkpoint inhibitor therapy. BMJ Case Rep 2020;13:e235265.

69. Yang X, Shi J, Chen X et al. Efficacy of cabozantinib and nivolumab in treating hepatocellular carcinoma with RET amplification, high tumor mutational burden, and PD-L1 expression. ***The Oncologist*** 2020;25:470–474.

70. Zhan C, Ruohoniemi D, Shanbhogue KP et al. Safety of combined yttrium-90 radioembolization and immune checkpoint inhibitor immunotherapy for hepatocellular carcinoma. J Vasc Interv Radiol 2020;31:25–34.

71. Zhao F, Zhou Y, Seesaha PK et al. Olaparib combined with immunotherapy for treating a patient with liver cancer carrying BRCA2 germline mutation: A case report. Medicine (Baltimore) 2020;99:e22312.

72. Harsch IA, Konturek PC. Acute-onset diabetes mellitus with ketoacidosis in a nivolumab-treated patient with hepatocellular carcinoma. Wiad Lek 2018;71:945–948.

73. Kawaoka T, Ando Y, Yamauchi M et al. Incidence of microsatellite instability-high hepatocellular carcinoma among Japanese patients and response to pembrolizumab. Hepatol Res 2020; 50:885–888.

74. Kidambi TD, Chu P, Lee JK et al. Immunotherapy-associated pseudomembranous colitis. Am J Gastroenterol 2019;114:1708.

75. De Somer T, Vanderstraeten E, Bouderez V et al. Resolution of a hepatoduodenal fistula after nivolumab treatment in a patient with hepatocellular carcinoma: Challenges in immunotherapy. Acta Clin Belg 2020 [Epub ahead of print].

76. Chen X, Zhang Y, Zhang N et al. Lenvatinib combined nivolumab injection followed by extended right hepatectomy is a feasible treatment for patients with massive hepatocellular carcinoma: A case report. Onco Targets Ther 2019;12:7355–7359.

77. Kaseb AO, Vence L, Blando J et al. Immunologic correlates of pathologic complete response to preoperative immunotherapy in hepatocellular carcinoma. Cancer Immunol Res 2019;7:1390–1395.

78. Wehrenberg-Klee E, Goyal L, Dugan M et al. Y-90 radioembolization combined with a PD-1 inhibitor for advanced hepatocellular carcinoma. Cardiovasc Intervent Radiol 2018;41:1799–1802.

79. Nordness MF, Hamel S, Godfrey CM et al. Fatal hepatic necrosis after nivolumab as a bridge to liver transplant for HCC: Are checkpoint inhibitors safe for the pretransplant patient? Am J Transplant 2020;20:879–883.

80. DeLeon TT, Salomao MA, Aqel BA et al. Pilot evaluation of PD-1 inhibition in metastatic cancer patients with a history of liver transplantation: The Mayo Clinic experience. J Gastrointest Oncol 2018;9:1054–1062.

81. Gassmann D, Weiler S, Mertens JC et al. Liver allograft failure after nivolumab treatment—A case report with systematic literature research. Transplant Direct 2018;4:1–7.

82. Rammohan A, Reddy MS, Farouk M et al. Pembrolizumab for metastatic hepatocellular carcinoma following live donor liver transplantation: The silver bullet? Hepatology 2018;67: 1166–1168.

83. De Toni EN, Gerbes AL. Tapering of immunosuppression and sustained treatment with nivolumab in a liver transplant recipient. Gastroenterology 2017;152:1631–1633.

84. Friend BD, Venick RS, McDiarmid SV et al. Fatal orthotopic liver transplant organ rejection induced by a checkpoint inhibitor in two patients with refractory, metastatic hepatocellular carcinoma. Pediatr Blood Cancer 2017;64: 26682.

85. Varkaris A, Lewis DW, Nugent FW. Preserved liver transplant after PD-1 pathway inhibitor for hepatocellular carcinoma. Am J Gastroenterol 2017;112:1895–1896.

86. Amjad W, Kotiah S, Gupta A et al. Successful treatment of disseminated hepatocellular carcinoma after liver transplantation with nivolumab. J Clin Exp Hepatol 2020;10:185–187.

87. Pandey A, Cohen DJ. Ipilumumab for hepatocellular cancer in a liver transplant recipient, with durable response, tolerance and without allograft rejection. Immunotherapy 2020;12: 287–292.

88. Anugwom C, Leventhal T. Nivolumab-induced autoimmune-like cholestatic hepatitis in a liver transplant recipient. ACG Case Rep J 2020;7: e00416.

89. Cheng AL, Kang YK, Chen Z et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A

phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25–34.

90. Garon EB, Rizvi NA, Hui R et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372: 2018–2028.

91. Carbognin L, Pilotto S, Milella M et al. Differential activity of nivolumab, pembrolizumab and MPDL3280A according to the tumor expression of programmed death-ligand-1 (PD-L1): Sensitivity analysis of trials in melanoma, lung and genitourinary cancers. PLoS One 2015;10: e0130142.

92. Le DT, Uram JN, Wang H et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509–2520.

93. Reck M, Rodriguez-Abreu D, Robinson AG et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:1823–1833.

94. Overman MJ, McDermott R, Leach JL et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): An open-label, multicentre, phase 2 study. Lancet Oncol 2017;18:1182–1191.

95. Davis AA, Patel VG. The role of PD-L1 expression as a predictive biomarker: An analysis of all US Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors. J Immunother Cancer 2019;7:278.

96. Calderaro J, Rousseau B, Amaddeo G et al. Programmed death ligand 1 expression in hepatocellular carcinoma: Relationship with clinical and pathological features. Hepatology 2016;64: 2038–2046.

97. Long J, Qu T, Pan XF et al. Expression of programmed death ligand-1 and programmed death 1 in hepatocellular carcinoma and its clinical significance. J Cancer Res Ther 2018;14 (suppl):S1188–S1192.

98. Harding JJ, Nandakumar S, Armenia J et al. Prospective genotyping of hepatocellular carcinoma: Clinical implications of next generation sequencing for matching patients to targeted and immune therapies. Clin Cancer Res 2019;25: 2116–2126.

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