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Hepatobiliary

Immune-Checkpoint Inhibitors for Advanced Hepatocellular Carcinoma: A Synopsis of Response Rates

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

Key Words. Hepatocellular carcinoma • Nivolumab • Pembrolizumab • Ipilimumab • Atezolizumab • Sorafenib • Lenvatinib

Abstract

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death worldwide. A first-line standard of care, sorafenib results in median overall survival of 12 months in patients with Child-Pugh class A disease and 6 months in patients with Child-Pugh class B disease with objective response rates (ORRs) not exceeding 19%. These low efficacy rates have driven research on alternative therapeutic options, particularly immune-checkpoint inhibitors (ICIs). We reviewed the response rates (estimated by RECIST 1.1 criteria) across patients with advanced HCC treated with ICIs in phase I–IV clinical trials published between December 2012 to December 2020; 17 reports were identified as eligible and included in the quantitative analysis. Within the selected studies, pembrolizumab + lenvatinib reached the highest absolute ORR (36%), with first-line atezolizumab + bevacizumab showing the second highest ORR (27.3%). With regard to second-line therapy, nivolumab + ipilimumab reached an ORR of 32%, and pembrolizumab alone resulted in an ORR of 17% among sorafenib-experienced patients with advanced HCC. In summary, current studies show high response rates of ICIs in patients with advanced HCC. Nonetheless, further studies are required in the second-line setting to further evaluate ICI therapeutic superiority. Finally, it is of particular interest to examine the therapeutic potential of ICIs for patients with decompensated liver disease (Child-Pugh class C), currently not eligible for any systemic therapy. ***The Oncologist*** 2021;26:e1216–e1225

Implications for Practice: Immune-checkpoint inhibitors (ICIs) can provide high objective response rates (ORR, estimated with RECIST 1.1. criteria) when used as first-line treatment in advanced hepatocellular carcinoma, particularly pembrolizumab + lenvatinib (ORR 36%) or atezolizumab + bevacizumab (ORR 27.3%). In sorafenib-experienced patients, nivolumab + ipilimumab (ORR 32%) provided the highest ORR among ICI-based regimens. These findings emphasize high therapeutic potential of ICI-based therapies in patients with advanced hepatocellular carcinoma, although further studies are required to further validate and define their role in this context.

Introduction

Hepatocellular carcinoma (HCC) is currently the fifth most commonly diagnosed cancer in men (554,000 new cases every year) and ninth among women (228,000 new cases every year) [1]. Multikinase inhibitors (MKIs) have been the standard of care (SoC) for advanced HCC; in particular sorafenib, which targets vascular endothelial growth factor receptor (VEGFR) 1, VEGFR2, VEGFR3, Raf proteins (BRAF, c-CRAF), platelet-derived growth factor receptor-beta, and other cell surface kinases such as KIT, FLT-3, RET/PTC, has shown improved efficacy when compared with placebo, with an extension of overall survival (OS) from 7.9 to 10.7 months [2]. An alternative first-line MKI is lenvatinib, targeting VEGFR1–3 with a median of OS of 13.6 months [3] (Fig. 1). Recommended second-line drugs are the MKIs

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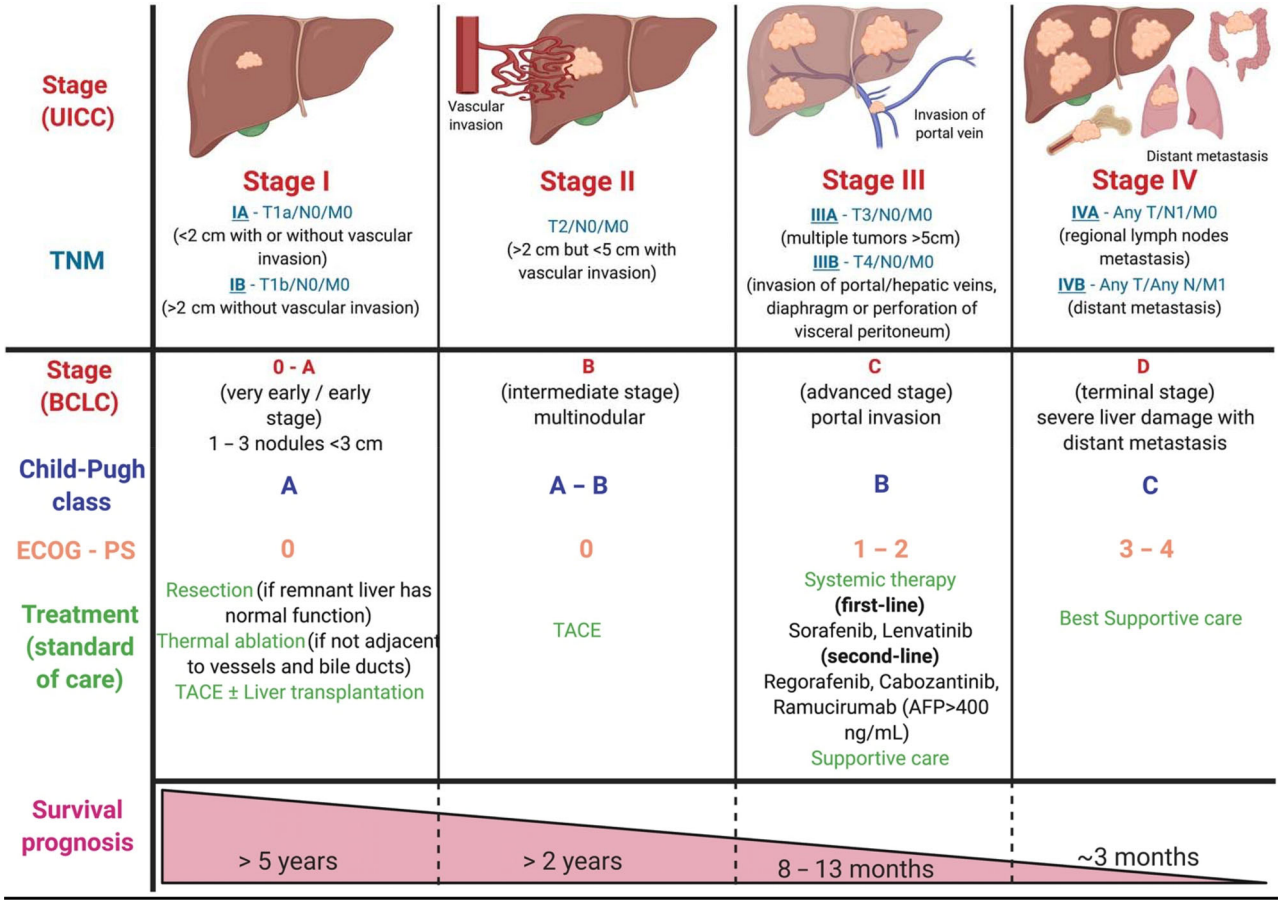

Figure 1. Staging of hepatocellular carcinoma and therapeutic options: Overview.
Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; TACE, transarterial chemoembolization; UICC, Union for International Cancer Control.

regorafenib [4] and cabozantinib [5] and the monoclonal antibody (mAb) ramucirumab targeting VEGFR2; the latter is most effective in patients with alpha-fetoprotein (AFP) >400 ng/mL [6].

The discovery and implementation of immune-checkpoint inhibitors (ICIs) has heralded a new era in the treatment of cancer [7]. ICIs are human IgG mAbs that block immune checkpoint molecules such as cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death-1 ligand-1 (PD-L1) (Fig. 2) [8]. These proteins are expressed on malignant cells and antigen-presenting cells and are responsible for limiting CD8+ T-cell activation and thus contribute to immunosurveillance escape [7]. The first ICI approved by the U.S. Food and Drug Administration (FDA) was ipilimumab (anti–CTLA-4 ICI) in 2011 for the treatment of metastatic melanoma [7]. Since then, several other ICIs targeting PD-1 (nivolumab, pembrolizumab) and PD-L1 (atezolizumab, avelumab, durvalumab) were granted FDA approval and have been successfully introduced into clinical practice [7]. To date, ICIs have already replaced previous SoCs for patients with advanced metastatic melanoma, head and neck squamous cell carcinoma, non-small cell lung carcinoma, and urothelial carcinoma [9]. Of note, HCCs are known to induce CTLA-4 expression on CD4+ T cells [10]. Moreover, biopsies obtained from patients with HCC commonly overexpress another inhibitory immune checkpoint, PD-L1, also responsible for inactivating cytotoxic T cells [11]. Thus, there is a biological rationale for ICI clinical testing in patients with advanced HCC [12].

A critical milestone for HCC treatment was achieved in 2020 with the approval of atezolizumab + bevacizumab as a new first-line therapeutic option for HCC [13]. With more than 600 clinical trials currently underway across the globe for the purpose of elucidating ICI clinical outcomes in patients with HCC, it is critical to comprehensively summarize existing data.

Materials and Methods

This review is reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines [14].

Literature Search

Two authors (D.S., G.A.) independently searched the electronic databases Scopus, MEDLINE, Embase, Web of Science, and Cochrane Library from December 31, 2012, to December 31, 2020, using keywords (ipilimumab, tremelimumab, avelumab, durvalumab, atezolizumab, nivolumab,

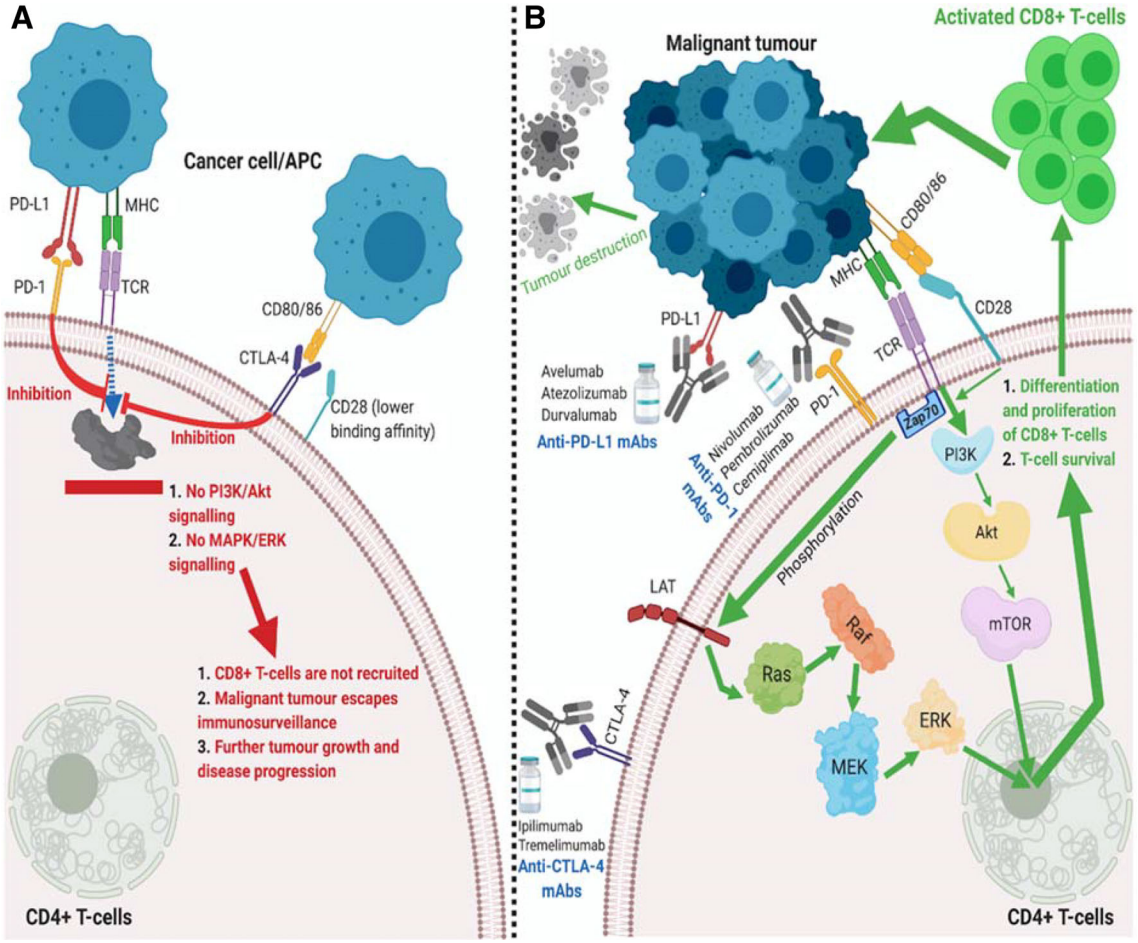

Figure 2. Molecular mechanisms of immune-checkpoint inhibitors. **(A):** Activation of immune checkpoints (PD-1 and CTLA-4) result in downregulation of the cytotoxic T-cell response. Binding of PD-1 with its ligand PD-L1 expressed by cancer cells or antigen-presenting cells limits the activation of T cells. CTLA-4 modulates the same activity via binding to CD80/86 ligands on APCs/cancer cells. **(B):** In contrast, activation of CD8+ T cells occurs in the presence of immune-checkpoint inhibitor therapy. Blocking CTLA-4, PD-1 with its ligands stimulates activation of PI3K/Akt and MAPK/ERK pathways, stimulating CD8+ T-cell activation, proliferation, and increased T-cell survival.

Abbreviations: Akt, protein kinase B; APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte–associated antigen-4; ERK, extracellular signal-regulated kinase; LAT, linker for activation of T cells; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MHC, major histocompatibility complex; mTOR, mammalian target of rapamycin; PD-1, programmed cell death-1; PD-L1, programmed cell death-1 ligand 1; PI3K, phosphoinositide 3-kinase; TCR, T-cell receptor.

pembrolizumab, hepatocellular carcinoma, liver cancer, immune-checkpoint inhibitors) linked by operators AND and OR. Abstracts presented at annual meetings of the American Society of Clinical Oncology and European Society for Medical Oncology were also examined. Abstracts were considered eligible if the study was published for the first time and matched eligibility criteria established for the purposes of this study. In addition, we searched through bibliographies of selected articles and clinical trial registries (www.clinicaltrials.gov) using said keywords.

The records found through primary search were initially screened by title and abstract. The full text of potentially eligible studies was reviewed, and if eligible the study was included into the analysis. Selected studies were reviewed by all authors, and all discrepancies were solved by consensus. If one study was reported multiple times, the study with the most comprehensive and up-to-date data was included.

Study Endpoints

The primary aim of this review was to determine the objective response rate (ORR) of patients with advanced HCC treated with ICIs. ORR is a clinical endpoint representing the proportion of patients with complete response (disappearance of all target lesions) or partial response (at least a 30% decrease in the sum of diameters of target lesions) measured radiologically and evaluated by RECIST 1.1 [15, 16]. Secondary endpoints focused on summarizing safety outcomes, if published across examined trials.

Eligibility Criteria

Reports of clinical trials evaluating therapeutic outcomes of ICIs in patients with advanced HCC were considered as eligible if they met following criteria: (a) phase I–IV randomized clinical trial or prospective clinical study, (b) the experimental arm consisted of ICI treatment, (c) ORR was evaluated and reported according to RECIST 1.1 criteria, and

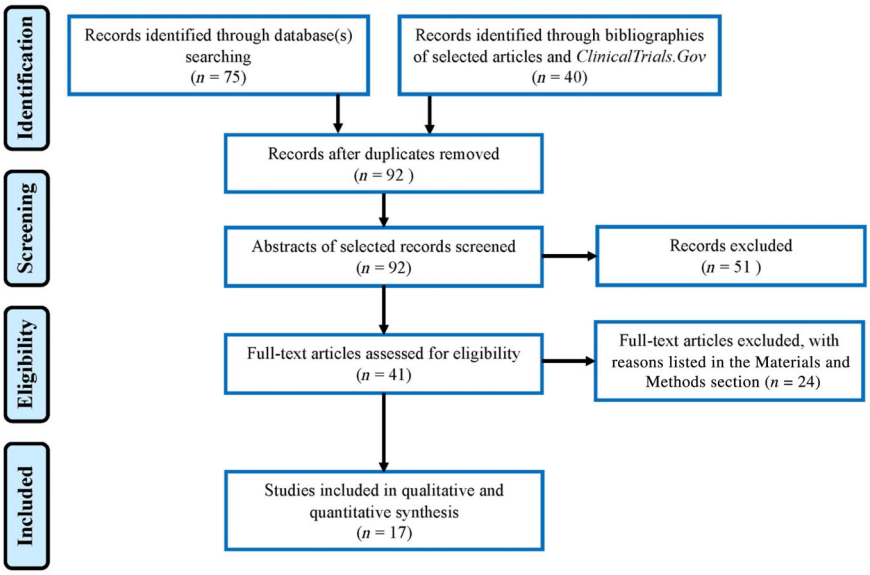

Figure 3. PRISMA (Preferred Reported Items for Systematic Reviews and Meta-Analysis) flowchart of literature search.

(d) English was the publication language. Exclusion criteria were the following: (a) ICIs used in combination with transarterial chemoembolization, (b) case reports, (c) reports published not in the English language, and (d) systematic reviews and meta-analysis.

Data Synthesis

Results were structured based on the therapeutic line of ICI usage. Data synthesis was performed using Stata version 16 (StataCorp, College Station, TX) software. ORR was visualized using forest plot.

Results

We identified 115 potentially relevant studies during the literature search, of which 17 were eligible for further analysis (Fig. 3). Twelve phase I/II clinical trials, three clinical phase III trials, and two pilot prospective cohort studies were identified as eligible. The number of patients in selected eligible studies varied from 10 to 371 (Table 1).

First-Line Treatment

Pembrolizumab + Lenvatinib

Our review established the highest ORR in patients treated with the combination of pembrolizumab (PEMBRO) and lenvatinib (LEN) [17]. This was an open-label phase Ib study comprising patients with Child-Pugh class A disease (n = 100) with Eastern Cooperation Oncology Group performance status (ECOG PS) 0–1 and Barcelona Clinic Liver Cancer (BCLC) stage B (n = 29) and C (n = 71). ORR was 36% (1 patient reached a complete response [CR]; 35 reached partial response [PR]) [17]. In addition, median progression-free survival (PFS) was 8.6 months (95% confidence interval [CI], 7.1–9.7 months), and median OS was 22 months (95% CI, 20.4 to not reached) [17]. Grade 3–4 treatment-related adverse events (TRAEs) were reported in 67% (n = 67) of patients. Further validation of this regimen is ongoing in the phase III LEAP-002 randomized clinical trial (NCT03713593).

Atezolizumab + Bevacizumab

The second highest response rate was seen in a study of the combination of atezolizumab and bevacizumab. The phase Ib trial NCT02715531 reported an ORR of 34% (n = 23; CR in 1, PR in 22) with median PFS of 14.9 months (95% CI, 8.1 to not reached) in sorafenib-naïve patients [18]. Grade 3–4 TRAEs were reported in 25% (n = 17) of patients.

The randomized clinical trial NCT03434379 (IMbrave 150) evaluated efficacy and safety of atezolizumab with bevacizumab as a first-line treatment in patients with advanced HCC that commenced in 2018 [19]. By the 30th of January 2019, the investigators had enrolled 501 patients across 17 countries and distributed them at a 2:1 ratio in the atezolizumab + bevacizumab arm (experimental; n = 336) and the sorafenib arm (control; n = 165) [13]. ORR was reported as 27.3% (CR was reached by 5.5% [n = 18]; PR by 21.8% [n = 71]) and 11.9% (CR was reached by 0%; PR by 11.9% [n = 19]) in the experimental and control arms, respectively (p < .001) [13]. Moreover, 12-month OS was greater (p < .001) in the experimental arm compared with the control arm: 67.2% (95% CI, 61.3–73.1) and 54.6% (95% CI, 45.2–64), respectively [13]. Finally, the median PFS was 6.8 months (95% CI, 5.7–8.3) versus 4.3 months (95% CI, 4–5.6) in the experimental and control arms, respectively (p < .001) [13]. With regard to safety outcomes, incidence of grade 3–5 TRAEs was more frequent in the experimental arm compared with the control group: 38% (n = 125) versus 30.8% (n = 48), respectively, although significance was not reported [13]. Treatment discontinuation due to adverse events was required for 7% (n = 23) and 10.3% (n = 16) in the experimental and control arms, respectively [13]. In conclusion, atezolizumab and bevacizumab provided significantly higher ORR, OS, and PFS as a first-line treatment compared with sorafenib. The FDA has recently approved this therapeutic regimen for patients with unresectable HCC as a new first-line alternative [20].

Table 1. Summary of selected clinical trials

Author (year)	Phase; NCT	ICI-based therapeutic regimen	Number of patients (*n*)	Sponsor
Sangro et al. (2013)	Pilot study NCT01008358	2L tremelimumab 15 mg/kg on day 1 of 90-day cycle	*n* = 21	Universidad de Navarra
El-Khoueiry et al. (2017)	Phase I/II NCT01658878	Dose-escalation phase [A] 1L/2L nivolumab 0.1–10 mg/kg Q2W Dose-expansion phase [B] 1L/2L nivolumab 3 mg/kg Q2W	[A] *n* = 48 0.1 mg/kg (*n* = 6) 0.3 mg/kg (*n* = 9) 1 mg/kg (*n* = 10) 3 mg/kg (*n* = 10) 10 mg/kg (*n* = 13) [B] *n* = 214	Bristol-Myers Squibb
Yen et al. (2017)	Phase Ia/Ib NCT02407990	2L BGB-A317 (tislelizumab) 5 mg/kg Q3W	*n* = 11	BeiGene
Wainberg et al. (2017)	Phase I/II NCT01693562	2L durvalumab 10 mg/kg Q2W	*n* = 40	MedImmune LLC
Kelley et al. (2017)	Phase I/II NCT02519348	2L durvalumab 20 mg/kg + tremelimumab 1 mg/kg Q4W (four doses) Followed by durvalumab 20 mg/kg Q4W	*n* = 40	MedImmune LLC
Pishvaian et al. (2018)	Phase Ib NCT02715531	1L atezolizumab 1,200 mg + bevacizumab 15 mg/kg Q3W	*n* = 68	Hoffmann-La Roche
Zhu et al. (2018)	Phase II NCT02702414	2L pembrolizumab 200 mg Q3W	*n* = 104	MSD
Finn et al. (2019)	Phase III NCT02702401	2L pembrolizumab 200 mg Q3W + BSC	*n* = 278	MSD
Floudas et al. (2019)	Pilot study; NCT02821754	2L tremelimumab 75 mg + durvalumab 1,500 mg (four doses) Followed by durvalumab 1,500 mg	*n* = 10	National Cancer Institute
Kudo et al. (2019a)	Phase I/II NCT01658878	1L/2L nivolumab 240 mg Q2W	*n* = 49	Bristol-Myers Squibb
Kudo et al. (2019b)	Phase Ib NCT03289533	1L avelumab 10 mg/kg Q2W + axitinib 5 mg BID	*n* = 22	Pfizer
Yau et al. (2019a)	Phase I/II NCT01658878	Arm [A]: 2L nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W (four doses) Arm [B]: 2L nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (four doses) Arm [C]: 2L nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W	[A] *n* = 50 [B] *n* = 49 [C] *n* = 49	Bristol-Myers Squibb
Yau et al. (2019b)	Phase III NCT02576509	1L nivolumab 240 mg Q2W	*n* = 371	Bristol-Myers Squibb
Finn et al. (2020)	Phase III NCT03434379	1L atezolizumab 1,200 mg + bevacizumab 15 mg/kg Q3W	*n* = 336	Hoffmann-La Roche
Yau et al. (2020)	Phase I/II NCT01658878	Arm [A]: 1L/2L nivolumab 240 mg Q2W + cabozantinib 40 mg daily Arm [B]: 1L/2L nivolumab 3 mg/kg Q2W + cabozantinib 40 mg daily + ipilimumab 1 mg/kg Q6W	[A] *n* = 36 [B] *n* = 35	Bristol-Myers Squibb
Finn et al. (2020)	Phase Ib NCT03006926	1L lenvatinib daily + pembrolizumab 200 mg Q3W	*n* = 100	Eisai Co. Ltd.
Qin et al. (2020)	Phase II NCT02989922	[A] 2L camrelizumab 3 mg/kg Q2W [B] 2L camrelizumab 3 mg/kg Q3W	[A] *n* = 109 [B] *n* = 108	Jiangsu Hengrui

Abbreviations: 1L, first-line treatment (sorafenib-naïve); 2L, second-line treatment (sorafenib-experienced); BID, twice a day; BSC, best supportive care; ICI, immune-checkpoint inhibitor; MSD, Merck Sharp & Dohme; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks.

Avelumab + Axitinib

Not all therapeutic strategies using ICIs show as impressive clinical outcomes as the aforementioned two. For example, the NCT03289533 open-label phase Ib trial studied avelumab in combination with axitinib as a first-line treatment for advanced HCC (*n* = 22) [21]. Preliminary results indicated an ORR of 13.6% (*n* = 3) and median PFS of 5.5 months (95% CI, 1.9–7.3) with 77.2% (*n* = 17) of patients experiencing grade 3–4 TRAEs [21]. Further study of this regimen was therefore halted.

Nivolumab

In 2012, Bristol-Myers Squibb established the CheckMate 040 trial (NCT01658878) in order to determine the efficacy and safety of nivolumab (NIVO) in patients with advanced HCC. Prior treatment with sorafenib was allowed. Phase I of

this study was divided into dose-escalation (n = 48) and dose-expansion (n = 214) stages. The dose-escalation stage established the NIVO dosage of 3 mg/kg as the most tolerable among patients with advanced HCC [22]. The dose-expansion stage reported an ORR of 20% (n = 42). Detailed analysis demonstrated that sorafenib-naïve (n = 56) patients had ORR of 23% (n = 13; 0 patients had CR; 13 patients had PR) compared with 21% (n = 12; 2 patients had CR; 10 had PR) in sorafenib-experienced (n = 57) patients. Grade 3–4 TRAEs were reported in 25% (n = 12) and 19% (n = 40) in dose-escalation and dose-expansion stages, respectively [22].

Phase II of NCT01658878 reported that NIVO resulted in a median OS of 9.8 months with ORR 10.2% among sorafenib-naïve patients with Child-Pugh class B, advanced HCC [23]. Of note, median OS in similar sorafenib-treated patients does not exceed 5 months [24, 25]. These data support a higher therapeutic efficacy of NIVO in patients with Child-Pugh class B HCC, although further validation is required.

The phase III CheckMate 459 trial (NCT02576509) evaluated the efficacy of nivolumab (n = 371) as a first-line treatment compared with sorafenib (n = 372) [26]. NIVO reached a median OS of 16.4 months compared with 14.7 months for sorafenib (p = .0752). ORR among NIVO-treated patients was 15%, with 4% (n = 14) reaching CR, compared with 7% in sorafenib-treated patients, with 1% (n = 5) reaching CR (p > .05) [26]. Grade 3–4 TRAEs were more common (p = .00001) among patients treated with sorafenib (49%, n = 179) compared with the NIVO arm (22%, n = 81) [26].

In summary, current clinical data are insufficient to support NIVO alone as first-line treatment. However, its efficacy in patients with Child-Pugh class B, advanced HCC is of particular interest and is currently further investigated in NCT01658878 trial, which has finished enrolment; final results are anticipated by April 2022.

Second-Line Treatment

Nivolumab + Ipilimumab

The nonrandomized phase II CheckMate 040 trial (NCT01658878) elucidated outcomes of combination NIVO with CTLA-4 inhibitor ipilimumab (IPI) for sorafenib-experienced patients [27]. It was established that NIVO 1 mg/kg + IPI 3 mg/kg every 3 weeks (Q3W) resulted in a median OS of 23 months (95% CI, 9 to not reached; data cutoff was at 24 months) and ORR of 32% (n = 16) among which 8% (n = 4) reached CR [27]. Thus, NIVO with IPI reached clinically meaningful outcomes as a second-line treatment in patients with advanced HCC previously treated with sorafenib. According to the authors, the treatment was well tolerated; however, grade 3–4 TRAEs were detected in 37% (n = 55) of patients, of whom 5% had to permanently discontinue ICI treatment [27]. The NIVO with IPI regimen has been recently granted accelerated FDA approval as a second-line therapeutic alternative for patients with unresectable HCC [28].

In addition, Yau et al. assessed efficacy of NIVO + MKI cabozantinib (CABO) and NIVO + IPI + CABO [29]. Interim analysis showed ORR 17% (PR reached by six patients) and 26% (PR reached by nine patients) among patients treated with NIVO + CABO and NIVO + IPI + CABO, respectively [29]. Grade 3–4 TRAEs were reported by 42% (n = 15) and 71% (n = 25) of patients in the NIVO + CABO arm and the NIVO + IPI + CABO arm, respectively [29]. Although both therapeutic combinations reached clinically meaningful outcomes, the triple regimen resulted in a higher rate of grade 3–4 TRAEs.

Pembrolizumab

The phase II KEYNOTE-224 trial (NCT02702414), a nonrandomized open-label trial, examined PEMBRO efficacy (200 mg intravenously Q3W) in sorafenib-experienced patients with ECOG PS 0–1 and Child-Pugh class A (n = 104). Interim analysis reported ORR of 17% (n = 18; one patient with CR, 17 with PR), median overall survival of 12.9 months (95% CI, 9.7–15.5), and median PFS of 4.9 months (95% CI, 3.4–7.2) [30]. Grade 3–4 TRAEs were detected in 4% (n = 4) of patients [30]. Final results are anticipated by May 2021.

Evaluation of PEMBRO efficacy in advanced HCC was also undertaken in the phase III KEYNOTE-240 (NCT02702401) randomized clinical trial. Patients were divided into two cohorts: PEMBRO with best supportive care (BSC) and placebo with BSC. All patients were sorafenib-experienced, had Child-Pugh class A disease, were uninfected with hepatitis B or C virus, and were ECOG PS 0–1 [31]. The authors reported that ORR was 16.9% (n = 47) and 2.2% (n = 3) in the PEMBRO + BSC and placebo + BSC cohorts, respectively (p = .00001); however, survival and safety endpoints were not reported [31]. Final results of the trial are anticipated by June 2021.

Durvalumab/Tremelimumab

In 2013, the phase II nonrandomized trial NCT01008358 evaluated tremelimumab in patients with advanced HCC [32]. It was reported that no patients achieved CR and that three reached PR [32]. Moreover, median OS was 8.2 months (95% CI, 4.6–21.3) with 45% of patients developing grade 3–4 TRAEs [32]. Despite the lack of therapeutic efficacy, this was the first clinical trial testing an anti–CTLA-4 mAb in patients with advanced HCC.

The NCT01693562 nonrandomized clinical trial evaluated durvalumab efficacy in patients with various solid tumor malignancies [33]. With regard to their HCC cohort, no therapeutic benefit of durvalumab as a second-line treatment for Child-Pugh class A and sorafenib-progressed patients was established [33]. ORR was 10.3% with median OS of 13.2 months (95% CI, 6.3–21.1) [33]. TRAEs occurred in 80% (n = 32) of patients, with 20% (n = 8) developing grade 3–4 [33]. Preliminary data did not support durvalumab as a second-line treatment for advanced HCC.

Phase II of the nonrandomized NCT02519348 trial evaluated the therapeutic activity of combination durvalumab with tremelimumab in patients with advanced HCC progressed on sorafenib (n = 40) [34]. ORR was reached by 15% (n = 6; zero patients with C; six patients with PR) with grade 3–4 TRAEs met by 20% (n = 8) of patients [34]. The trial has finished enrolment, and final results are anticipated by March 2021. However, preliminary results do not support

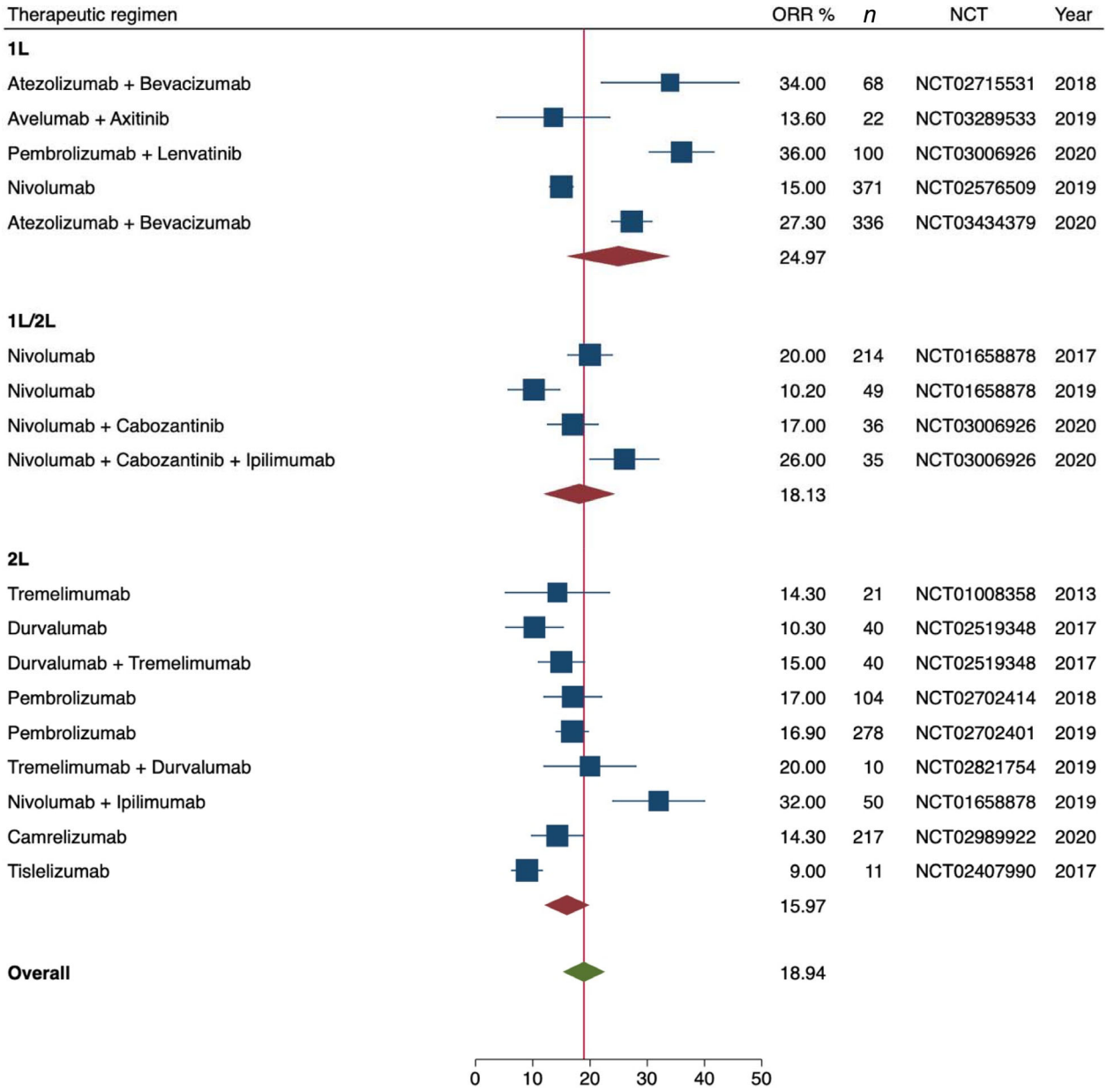

Figure 4. Overall response rate among patients with advanced hepatocellular carcinoma treated with immune-checkpoint inhibitors. Forest plot visualization of ORR among studies included in this review. Studies are separated by the therapeutic line.
Abbreviations: 1L, first line; 2L, second line; 1L/2L, studies where immune-checkpoint inhibitors were used in a mixed cohort of patients; NCT, National Clinical Trial number; ORR, objective response rate.

this regimen as a second-line therapeutic option for patients with advanced HCC.

Tislelizumab/Camrelizumab

The open-label phase Ia/Ib NCT02407990 studied efficacy of a novel anti–PD-1 mAb BGB-A317 (Tislelizumab) in solid tumors [35]: The interim analysis of patients with sorafenib-refractory advanced HCC (n = 11) showed 9% (n = 1) PR with grade 3–4 TRAEs detected in 18% (n = 2) [35]. Investigators concluded that BGB-A317 was tolerable, and further exploration is conducted in the NCT02407990 trial.

Finally, Qin et al. (NCT02989922) analyzed efficacy of anti–PD-1 mAb camrelizumab in previously treated patients with advanced HCC [36]. It was reported that ORR reached 11.9% (n = 13) and 17.6% (n = 19) in patients treated with camrelizumab 3 mg/kg every 2 weeks (n = 109) and 3 mg/kg Q3W (n = 108), respectively [36]. Median OS reached 14.2 and 13.2 months in said groups, respectively [36]. Grade 3–4 TRAEs were reported in 22% (n = 47) of a total cohort of patients (n = 217) [36]. Investigators hypothesized that camrelizumab may become a new second-line therapeutic alternative for advanced HCC [36].

Discussion

ICIs are considered a promising addition to the oncologist's therapeutic arsenal. Their therapeutic success in the treatment of metastatic lung cancer and melanoma has encouraged further studies aimed at determining their potential in

other solid organ malignancies [9]. Here we summarize existing data regarding ICI efficacy and safety in patients with advanced HCC with a specific focus on response rates (Fig. 4).

To date, sorafenib and LEN are major first-line treatment options for patients with advanced HCC [2]. Kudo et al. established that the median ORR among sorafenib-treated patients was 6.5% (95% CI, 4.3–8.7), whereas the alternative multikinase inhibitor LEN provided an ORR of 18.8% (95% CI, 15.3–22.3) (p = .0001) [3]. Relatively low survival rates [37], poor response rates [38], and high frequency of grade 3–4 TRAEs [39] have motivated researchers to examine other therapies, particularly ICIs.

Our analysis has shown that PEMBRO in combination with LEN resulted in an ORR of 36% in sorafenib-naïve patients with Child-Pugh class A, advanced HCC [40]. In addition, a recent case report demonstrated that a patient with Child-Pugh class B disease (AFP = 14,429.3 ng/mL) developed CR after 9 months of PEMBRO (2 mg/kg Q3W) + LEN (8 mg once daily) with a current OS of 22 months [41]. Together these data suggest that PEMBRO + LEN has a promising therapeutic potential as a first-line therapeutic approach.

The second highest ORR in our analysis was reached by combination of anti–PD-L1 mAb atezolizumab with anti–vascular endothelial growth factor mAb bevacizumab. It resulted in significantly higher OS and PFS compared with the control arm (sorafenib). The regimen has been recently approved by the FDA as the first-line therapeutic option for patients with advanced HCC [20]. Despite the fact that bevacizumab itself may interfere with cancer progression by limiting tumor angiogenesis [42], it should be noted that the results of the phase II NCT00867321 trial reported that SOR with bevacizumab alone in patients with advanced HCC had poor responses and excessive toxicity, which led to study discontinuation [43]. It further emphasizes the clinical significance of ICIs, particularly atezolizumab, for the treatment of advanced HCC.

With regard to first-line ICI monotherapy, NIVO has shown encouraging preliminary results in CheckMate 459 and 040. NIVO resulted in slightly higher ORR and lower rates of grade 3–4 TRAEs compared with sorafenib in patients with Child-Pugh class A, advanced HCC, albeit not reaching statistical significance [26]. Interestingly, NIVO resulted in median OS of 9.8 months in sorafenib-naïve patients with Child-Pugh class B, advanced HCC [23]. In comparison, a recent meta-analysis has shown that patients with Child-Pugh class B HCC treated with sorafenib reached a median OS of 4.6 months [44] suggesting the superior therapeutic efficacy of NIVO in these patients.

Currently approved second-line treatments for patients with advanced HCC, including regorafenib, cabozantinib, and ramucirumab, have a median OS of 10.6, 10.2, and 8.5 months, respectively, with low response rates [45]. With regard to second-line ICIs, we established that the combination of NIVO 1 mg/kg + IPI 3 mg/kg Q3W was highly effective and resulted in a median OS of 23 months and ORR of 32% [27]. Moreover, we established that PEMBRO 200 mg Q3W was the second most effective second-line therapeutic approach with a median OS of 12.9 months and ORR of 17% [30]. Thus, ICIs can provide higher survival and response rates in sorafenib-progressed patients. Finally, the FDA has recently granted an accelerated approval for NIVO + IPI combination as a second-line treatment alternative [28], although final results are to be reported in 2021.

To summarize, our study evaluated ICI response rate as well as other reported efficacy and safety outcomes in patients with advanced HCC. Based on the current data, ICI-based therapeutic strategies can provide a superior alternative as a first- or second-line treatment for patients with advanced HCC compared with current SoC.

Strength and Limitations

To our knowledge, this is the first systematic review that comprehensively summarizes response rates and safety outcomes of ICIs in patients with advanced HCC. However, this study has several limitations. Firstly, despite our attempt to comprehensively and systematically search the literature, it is possible that some relevant studies may have not been identified. Secondly, 13 of 17 trials have reported only preliminary findings in abstract form, which limits understanding as to whether the trial cohort was initially powered for establishing superiority of ICIs compared with SoC.

Conclusion

ICIs have revolutionized clinical oncology. Their clinical use is rapidly expanding, and recent approval of atezolizumab + bevacizumab as first-line treatment for metastatic HCC provides a new treatment option for patients. However, ICIs' therapeutic utility for all patients with HCC remains uncertain. Questions remain about whether ICIs can provide therapeutic benefit for patients with severe HCC progression, particularly those with BCLC stage D and Child-Pugh class C who are currently ineligible for any therapy. Understanding the role of ICIs in this context will provide new knowledge regarding liver cancer treatment and markedly improve the prognosis of these patients.

Furthermore, the role of ICIs in earlier stages of disease is unclear. There are ongoing randomized clinical trials determining the role of adjuvant ICIs for HCC: NCT03847428 (durvalumab + bevacizumab) and NCT03383458 (nivolumab); preliminary results are anticipated by 2022. The potential of ICI as an adjuvant treatment will become another significant milestone for HCC immunotherapy.

Treatment guidelines for advanced HCC will continue to evolve as ICIs become more widely available for this disease. Critical questions about appropriate sequencing and combination of ICIs and ICIs and MKIs are being explored. Our systematic review has shown that PEMBRO + LEN and atezolizumab + bevacizumab result in high ORR as a first-line treatment. With regard to second-line treatment, high ORR was seen in patients treated with NIVO + IPI. Furthermore, NIVO increased median OS for patients with Child-Pugh class B. Results of ongoing studies exploring the use of ICIs in early stages of HCC progression as well as in patients with Child-Pugh classes B and C are eagerly anticipated.

Acknowledgments

This project was supported by the Ainsworth Bequest to the School of Medicine of Western Sydney University and the Robert W. Storr Bequest to the Sydney Medical Foundation of the University of Sydney. Data can be obtained from the corresponding author on a reasonable request via e-mail (Golo.Ahlenstiel@health.nsw.gov.au).

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Disclosures

The authors indicated no financial relationships.

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