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Systemic Treatment of Advanced Unresectable Hepatocellular Carcinoma after First-Line Therapy: Expert Recommendations from Hong Kong, Singapore, and Taiwan

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Keywords
Hepatocellular carcinoma · Liver cancer · Systemic treatment

Abstract

Background: Asia has a high burden of hepatocellular carcinoma (HCC) due to the high rates of chronic hepatitis B infection and accounts for 70% of HCC cases globally. In the past 20 years, the systemic treatment landscape of advanced HCC has evolved substantially – from tyrosine kinase inhibitors to immune-oncology agents plus anti-vascular endothelial growth factor agents. The appropriate sequence of therapies has become critical in optimizing patient outcomes given the increase in systemic therapeutic options. This article evaluates the evidence and provides expert recommendations for the use of systemic therapies after first-line treatment in patients with advanced HCC. ***Summary:*** Based on three virtual meetings held in early 2021, a team of 17 experts comprising oncologists, a hepatologist, and a hepatobiliary surgeon from Hong Kong, Singapore, and Taiwan reviewed available data about systemic treatments for HCC

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after first line and formulated 28 statements. These statements aimed to provide expert guidance on selecting first and subsequent lines of therapies as well as recommending therapies in special circumstances, such as poor liver function, posttransplantation, recent gastrointestinal bleeding, or autoimmune diseases. Data supporting the statements were drawn from clinical trials and real-world studies. The 28 statements were then evaluated anonymously using a 5-point Likert scale, and 24 reached consensus, predefined as achieving 75% agreement. Statements generated covered the selection of first-line systemic therapy, considerations and goals of second-line systemic therapies, treatment selection following first-line therapy, and treatment recommendations following first-line tyrosine kinase inhibitors, immune-oncology monotherapy, or immune-oncology combination therapy. The authors also shared expert opinion on the use of second-line systemic therapy in patients with liver dysfunction, liver transplantation, and recent gastrointestinal or autoimmune disease. ***Key Messages:*** These expert statements summarize the latest data and expert opinion on selecting systemic treatment following first-line therapy in patients with unresectable advanced or metastatic HCC.

Introduction

Asia has a high burden of hepatocellular carcinoma (HCC) due to high rates of chronic hepatitis B virus infection and accounts for >70% of incident cases globally [1]. Many patients with liver cancer are diagnosed late in the disease course [1], limiting their eligibility for surgical resection or locoregional therapies and thus leaving them reliant on systemic treatments.

Systemic treatment of advanced HCC has evolved considerably since the early 2000s, when doxorubicin chemotherapy or palliative supportive care were the main options. Over the past decade, clinical evidence has been accumulating for the use of tyrosine kinase inhibitors (TKIs) and immune-oncology (IO) agents, alone or in combination with antiangiogenic agents, in the first-line setting [2, 3]. However, data for systemic treatment in the second-line setting are limited after newer first-line systemic therapy options. As such, there is a need to collate clinical experience and provide guidance on the use of systemic therapy after first-line treatment in HCC. Herein, we evaluate existing evidence on the use of systemic therapies after first-line treatment, and document experience from a group of specialists from Hong Kong, Singapore, and Taiwan to provide expert opinion on treating HCC patients in Asia and beyond.

Table 1. Level of evidence [4]

Level	Type of evidence
1	Systematic review of randomized trials
2	Randomized trial
3	Non-randomized controlled cohort/follow-up studies
4	Case series, case control, or historically-controlled studies
5	Mechanism-based reasoning

Three online meetings of a group of experts from Hong Kong, Singapore, and Taiwan were held in February, March, and April 2021. As the discussion focused on systemic medical treatment, the expert members comprised mainly oncologists, with a hepatologist and a surgeon also attending. Because the selection of first-line therapy may influence subsequent treatment choices, pre-meeting surveys of the attendees were conducted to understand first-line treatment choices within the group and guidance statements were formulated on first-line therapy.

During the meetings, guidance statements and their supporting evidence were presented, and evaluated using a Likert scale (1 – accept completely; 2 – accept with some reservations; 3 – accept with major reservations; 4 – reject with reservations; 5 – reject completely). Voting was performed anonymously to encourage independent responses, and acceptance was defined as ≥75% of the group accepting a statement completely or with some but not major reservations. Where applicable, statements were evaluated using the Oxford Centre for Evidence-Based Medicine's 2011 Levels of Evidence (Table 1) [4]. A subjective "strength of recommendation" (weak, moderate, or strong) was also agreed by the group for each statement based on the level of evidence and agreement among the group. These statements were made assuming that treatment cost is not a concern because reimbursement situations vary between countries. Furthermore, although not specifically mentioned in the statements, enrollment into clinical trials may be an option to access drugs that are not locally approved.

A total of 24 statements were drafted, discussed, refined, and passed consensus approval (Table 2). They covered the selection of first and subsequent lines of therapies as well as recommendations for special patient populations.

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Table 2. Consensus statements

	Consensus statements	Level of evidence [4]	Level of agreement, %	Strength of recommendation
Selection of first-line systemic therapy				
1	Atezolizumab plus bevacizumab is the preferred first-line systemic treatment for medically-suitable patients who have good performance status (good liver function, ECOG PS 0–1, Child-Pugh A) with no contraindication or history of other liver disease	2	100	Strong
2	Oral TKI (lenvatinib or sorafenib) is the preferred first-line treatment in patients who prefer oral treatment or are contraindicated for IO	2	100	Moderate
3	Nivolumab may be considered for patients with contraindication for TKI or anti-VEGF agents, uncontrolled hypertension, recent cardiovascular conditions, or Child-Pugh B status for whom atezolizumab plus bevacizumab are contraindicated	3	94	Weak
Considerations and goals of second-line systemic therapies in HCC				
4	Patients who have good liver function reserve and performance status are eligible for second-line systemic therapy	2	100	Strong
5	The second-line treatment goals are to preserve liver function and extend survival; treatment tolerability is also a key consideration	5	100	Moderate
6	Timing of switching to second-line treatment should be made at the clinical judgment of the treating physician and led by clinical progression and not oligo-progression, minor enlargement of tumor or minor increase in tumor markers. Deterioration of liver function may also be an indicator for switching	5	94	Moderate
7	Where applicable, locoregional therapy can be considered prior to initiating second-line systemic therapy	5	100	Low
Treatment selection following first-line systemic therapy				
8	Choice of therapy in the second-line setting depends on the mode of action, safety, tolerability, efficacy and cost, as well as the response to first-line therapy, and the patient's liver function reserve, tumor burden, performance status, and quality of life	5	100	Moderate
9	Genomic sequencing is not considered useful in guiding treatment choice at this point	NA	100	Strong
Treatment recommendations following first-line TKI				
10	Regorafenib is a reasonable second-line treatment option in patients who received first-line sorafenib treatment if the patient tolerated sorafenib	2	82	Strong
11	Cabozantinib is a reasonable second-line treatment option after progression on other TKIs	2	100	Strong
12	Ramucirumab (in patients with AFP ≥400 ng/mL) is a second-line treatment option after first-line TKI if a VEGFR2-specific agent is preferred	2	100	Strong
13	An IO-based regimen may be considered as a second-line treatment option following first-line TKI because of its alternative mode of action	2	100	Weak
Treatment recommendations following first-line IO monotherapy				
14	Following IO therapy, cabozantinib, as well as other TKIs, are reasonable options in eligible patients	4	89	Low
Treatment recommendations following first-line IO combination therapy				
15	Lenvatinib or sorafenib may be considered in patients who progressed on first-line atezolizumab plus bevacizumab; cabozantinib, regorafenib, or ramucirumab may also be considered	3	94	Low
Patients with liver dysfunction				
16	For patients with Child-Pugh B7–8 status, sorafenib or nivolumab are preferred treatment options	3/4	88	Moderate
17	For patients with Child-Pugh B7–8 status, dose adjustments for sorafenib may be required	3	100	Moderate
Posttransplant patients				
18	IO agents should generally be avoided in patients who have had previous organ transplants because of the increased risk of graft rejection	4	100	Moderate
19	TKIs are more appropriate than IO agents in posttransplant patients	5	100	Moderate
Patients with recent gastrointestinal bleeding				
20	Patients who are to receive anti-VEGF therapy like bevacizumab or ramucirumab should be prescreened with an upper endoscopy to assess risk of variceal bleed	2	100	Strong
21	In patients with recent gastrointestinal bleeding, IO monotherapy may be considered instead of antiangiogenic therapy (including TKIs)	3	100	Moderate

Table 2 (continued)

	Consensus statements	Level of evidence [4]	Level of agreement, %	Strength of recommendation
Patients with autoimmune disease				
22	TKIs are preferred in patients with AID	4	100	Strong
23	IO therapy with close monitoring can be considered in patients with well controlled and non-life-threatening AID who are not on high-dose steroids	5	94	Moderate
24	Co-management with a specialist treating the underlying AID is needed	NA	94	Strong

AFP, alpha-fetoprotein; AID, autoimmune disease; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; IO, immuno-oncology; NA, not applicable; PS, performance status; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor-2.

Selecting First-Line Systemic Therapy

Statement 1: Atezolizumab plus bevacizumab is the preferred first-line systemic treatment for medically suitable patients who have good performance status (good liver function, Eastern Cooperative Oncology Group Performance Status [ECOG PS] 0–1, Child-Pugh A) with no contraindication or history of other liver disease (evidence: level 2; agreement: 100%; strength of recommendation: strong).

Statement 2: Oral TKI (lenvatinib or sorafenib) is the preferred first-line treatment in patients who prefer oral treatment or are contraindicated for IO (evidence: level 2; agreement: 100%; strength of recommendation: moderate).

Statement 3: Nivolumab may be considered for patients with contraindication for TKI or anti-vascular endothelial growth factor (VEGF) agents, uncontrolled hypertension, recent cardiovascular conditions, or Child-Pugh B status for whom atezolizumab plus bevacizumab are contraindicated (evidence: level 3; agreement: 94%; strength of recommendation: weak).

In 2008, the oral TKI sorafenib became the standard-of-care first-line treatment for HCC based on two randomized clinical trials (RCTs; ASIA-PACIFIC and SHARP), which showed overall survival (OS) benefit of sorafenib over placebo (ASIA-PACIFIC, median OS: 6.5 vs. 4.2 months; hazard ratio [HR], 0.68; $p = 0.014$; SHARP median OS 10.7 vs. 7.9 months; HR, 0.69; $p < 0.001$) [5, 6]. Subsequently, in the REFLECT study, lenvatinib met the primary endpoint of noninferiority to sorafenib for OS and showed improvement over sorafenib for progression-free survival (PFS), time to progression, and response rates [7]. In CHECKMATE 459, nivolumab, a programmed death 1 inhibitor, showed improvements over sorafenib in overall response rate (ORR), but primary endpoint of the study, OS, did not meet the predefined threshold of statistical significance [8]. Indeed, no agent demonstrated OS benefit over sorafenib until 2020 when the IMbrave150 trial found an improved OS (median: 19.2 vs. 13.4 months; HR, 0.66) and PFS (median: 6.9 vs. 4.3 months; HR, 0.65; $p < 0.001$) with atezolizumab plus bevacizumab over sorafenib, respectively – the highest in any phase 3 RCT in HCC to date [9–11]. Atezolizumab plus bevacizumab also demonstrated favorable ORR, disease control rate, and median duration of response over sorafenib [9, 10]. These results provide a rationale for positioning atezolizumab plus bevacizu-

mab as the new standard of care for first-line treatment of advanced HCC. As IMbrave150 only recruited patients with preserved liver function (Child-Pugh A5 or A6 status) [9], the experts have restricted this recommendation to patients with good liver function only.

Patients ineligible for atezolizumab plus bevacizumab may include those with Child-Pugh B or C liver function, poor performance status, coinfection with hepatitis B and C viruses due to the exclusion of such patients from the pivotal study, and uncontrolled hypertension because it was the most common grade 3/4 adverse effect with this combination [2, 9, 10]; in such circumstances, nivolumab may be considered [2]. Although nivolumab failed to show statistically significant improvement in OS over sorafenib in CHECKMATE 459 (primary endpoint; 16.4 vs. 14.7 months; $p = 0.0752$) [8], the expert group believes that nivolumab offers a clinically relevant OS benefit. Furthermore, the fact that nivolumab is generally better tolerated than sorafenib makes it a viable option for patients with contraindication or poor tolerability to TKI or VEGF agents [2]. Sorafenib, unlike many other agents, has data, albeit limited, supporting its use in patients with Child-Pugh B status and thus may be considered in patients who are ineligible for an IO-based therapy due to compromised liver function [2, 12].

A proposed statement – *Cautious use of atezolizumab plus bevacizumab can be considered for patients with Child-Pugh B status where liver dysfunction is driven by cancer-related factors rather than decompensated cirrhosis* – failed to gain consensus during discussions due to a lack of evidence. Expert opinion was that while patients with Child-Pugh B status due to cirrhosis are ineligible for atezolizumab plus bevacizumab, patients whose liver dysfunction is driven by cancer-related factors might become eligible for this combination if the reduced tumor burden improves liver function and Child-Pugh status. However, a consensus could not be formed because of a lack of data to support this phenomenon.

Notably, the first-line management of advanced unresectable HCC continues to evolve with emerging data from studies of novel combinations. Preliminary data from the phase 2/3 ORIENT-32 trial found a significantly longer OS with sintilimab plus bevacizumab biosimilar (IBI305) than sorafenib (median: not reached vs. 10.4 months; $p < 0.0001$) in Chinese patients with unresectable, hepatitis B virus-associated advanced HCC [13]. Durvalumab plus a single priming dose of tremelimumab conferred a significantly prolonged OS versus sorafenib in the phase 3 HIMALAYA trial in treatment-naïve unresectable HCC (data not shown) [14]. The results of the COSMIC-312 study showed that cabozantinib plus atezolizumab met the coprimary endpoint of improved PFS versus sorafenib (median PFS 6.8 vs. 4.2 months, respectively; $p = 0.0012$), but the interim analysis of OS did not show a statistically significant benefit for cabozantinib plus atezolizumab [15]. Further results from these and other ongoing studies will help refine the treatment strategy in the first-line setting.

Considerations and Goals of Second-Line Systemic Therapies in HCC

Statement 4: Patients who have good liver function reserve and performance status are eligible for second-line systemic therapy (evidence: level 2; agreement: 100%; strength of recommendation: strong).

Statement 5: The second-line treatment goals are to preserve liver function and extend survival; treatment tolerability is also a key consideration (evidence: level 5; agreement: 100%; strength of recommendation: moderate).

Statement 6: Timing of switching to second-line treatment should be made at the clinical judgment of the treating physician and led by clinical progression and not oligo-progression, minor enlargement of tumor, or minor increase in tumor markers. Deterioration of liver function may also be an indicator for switching (evidence: level 5; agreement: 94%; strength of recommendation: moderate).

Statement 7: Where applicable, locoregional therapy can be considered prior to initiating second-line systemic therapy (evidence: level 5; agreement: 100%; strength of recommendation: low).

The goal of first-line systemic therapy is to prolong survival while preserving liver function [16]; while these remain important, as HCC progresses tolerability becomes an increasingly important consideration. Many patients have a worse Karnofsky Performance Status after first-line treatment; therefore, safety and tolerability become a higher concern in the second-line relative to the first-line setting. As many systemic therapies have a moderate toxicity profile, eligibility for second or subsequent lines of treatment relies on good liver function, and ECOG PS. Poor liver function reserve, rapid progression of tumors, and nonresolving severe adverse events (AEs) from first-line therapy may all constitute reasons to exclude second-line therapy.

In general, symptomatic progression or decline in liver function should prompt a switch to second-line therapy. An exception to this general rule can be found in the ASIA-PACIFIC and SHARP studies, where patients were allowed to stay on sorafenib (or placebo) after progression [5, 6], due to the lack of options a decade ago when those studies were conducted. However, anticancer treatment should be discontinued in case of drug-related liver function decline. Although some patients may derive benefit from continuing treatment despite radiological progression, with the current array of treatment options, disease progression should prompt a switch. Pseudoprogression, an initial transient increase in tumor size upon starting IO therapy followed by a decrease in tumor burden, has been observed in IO-treated patients with various solid tumors, including liver cancer [17, 18]. If patients are treated with first-line IO therapy, the switch to second-line should only occur once progression, rather than pseudoprogression, has been confirmed. In such patients, the addition of locoregional therapy to IO may be an option if the disease is generally stable, but some focal oligo-progression has occurred. In patients with a good response to first-line therapy, reductions in lesion size may make them eligible for locoregional options (e.g., radio-frequency ablation, transcatheter arterial chemoembolization, or radioembolization). However, in the authors' clinical experience, most patients develop progressive disease that cannot be locally treated after first-line.

Treatment Selection following First-Line Systemic Therapy

Statement 8: Choice of therapy in the second-line setting depends on the mode of action, safety, tolerability, efficacy, and cost, as well as the response to first-line therapy, and the patient's liver function reserve, tumor burden, performance status, and quality of life (evidence: level 5; agreement: 100%; strength of recommendation: moderate).

Statement 9: Genomic sequencing is not considered useful in guiding treatment choice at this point (agreement: 100%; strength of recommendation: strong).

Although not necessarily based on clinical evidence, the expert panel believes that it is preferable that the second-line therapy has a different mechanism of action to the first-line therapy. In addition to mechanism of action, the duration and quality of response to first-line therapy should also be considered when selecting a second-line therapy. Currently, there is insufficient evidence to support the use of genomic data to guide second-line treatment choice in HCC [19].

Treatment Recommendations following First-Line TKI

Statement 10: Regorafenib is a reasonable second-line treatment option in patients who received first-line sorafenib treatment if the patient tolerated sorafenib well (evidence: level 2; agreement: 82%; strength of recommendation: strong).

Statement 11: Cabozantinib is a reasonable second-line treatment option after progression on other TKIs (evidence: level 2; agreement: 100%; strength of recommendation: strong).

Statement 12: Ramucirumab (in patients with alpha-fetoprotein [AFP] ≥400 ng/mL) is a second-line treatment option after first-line TKI if a VEGFR2-specific agent is preferred (evidence: level 2; agreement: 100%; strength of recommendation: strong).

Statement 13: An IO-based regimen may be considered as a second-line treatment option following first-line TKI because of its alternative mode of action (evidence: level 2; agreement: 100%; strength of recommendation: weak).

Most data that guide treatment selection after progression on first-line TKIs are in patients who received sorafenib in the first-line setting; evidence to guide decision making after other first-line therapies is scarce. Another notable limitation is that all phase 3 trials were conducted in Child-Pugh A patients with only very few patients with Child-Pugh B included [5–7]. Given that until recently, the standard first-line therapy was predominantly a TKI; there are more data supporting treatment after progression from first-line TKI.

In patients treated with sorafenib at first line, complete datasets from phase 3, placebo-controlled trials are available for second-line use of regorafenib, cabozantinib, ramucirumab, and pembrolizumab [20–23]. All of these agents are associated with a survival advantage compared with placebo (Table 3 [20–27]).

Regorafenib was the first drug approved by the US Food and Drug Administration (FDA) in sorafenib-treated patients with HCC based on the results of the phase 3 RESORCE study in a population with Child-Pugh A status and disease progression on sorafenib [21, 28]. Regorafenib was the first systemic agent to demonstrate a survival benefit (vs. placebo) in this setting and in addi-

Table 3. OS outcomes in clinical trials of second-line therapies in patients with progression on sorafenib [20–27]

Study	Design	Phase	Comparators, *n*	Median OS, months	HR
RESORCE [21]	Randomized, double-blind	3	Regorafenib ($n = 374$) versus placebo ($n = 193$)	10.6 versus 7.8	0.63
CELESTIAL [20]	Randomized, double-blind	3	Cabozantinib ($n = 470$) versus placebo ($n = 237$)	10.2 versus 8.0	0.76
REACH-2 [23]	Randomized, double-blind	3	Ramucirumab ($n = 197$) versus placebo ($n = 95$)	8.5 versus 7.3	0.71
KEYNOTE-224 [25]	Non-randomized, open-label	2	Pembrolizumab ($n = 104$)	12.9	NA
KEYNOTE-240 [22]	Randomized, double-blind	3	Pembrolizumab ($n = 278$) versus placebo ($n = 135$)	13.9 versus 10.6	0.78
KEYNOTE-394 [27]	Randomized, double-blind	3	Pembrolizumab ($n = 453$) versus placebo ($n = 153$)	14.6 versus 13.0	0.79
CHECKMATE 040* (nivolumab plus ipilimumab cohorts) [24]	Randomized, open-label	1/2	Nivolumab plus ipilimumab Arm A ($n = 50$) Arm B ($n = 49$) Arm C ($n = 49$)	 22.8 12.5 12.7	 NA NA NA
CHECKMATE 040 (nivolumab only cohort) [26]	Non-randomized, open-label	1/2	Nivolumab ($n = 145$)	15.6	NA

Data from different studies have varying designs and may not be directly comparable. HR, hazard ratio; NA, not available; OS, overall survival; QXW, every X weeks.
* Arm A: nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, Q3W (4 doses), followed by nivolumab 240 mg Q2W; Arm B: nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, Q3W (4 doses) followed by nivolumab 240 mg Q2W; Arm C: nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W.

tion to an OS advantage, the RESORCE study reported improvements over placebo in PFS (median: 3.1 vs. 1.5 months; $p < 0.0001$), time to progression (median: 3.2 vs. 1.5 months), disease control (65% vs. 36%; $p < 0.0001$), and ORR (11% vs. 4%; $p = 0.0047$) [21].

Cabozantinib, a third-generation TKI, was approved by the FDA in 2019 based on results from the phase 3 CELESTIAL trial which enrolled patients with HCC with prior sorafenib and up to two previous systemic treatments [20, 28]. Cabozantinib demonstrated improvements over placebo in OS (medians: 10.2 vs. 8.0 months; $p = 0.005$), PFS (medians: 5.2 vs. 1.9 months; $p < 0.001$), and ORR (4% vs. 1%; $p = 0.009$) [20], and although cabozantinib-treated patients reported high-grade AEs at approximately twice the rate of placebo-treated patients (68% vs. 36%, respectively), few AEs led to discontinuation (16% vs. 3%, respectively), and they could generally be managed with dose-reductions and supportive care [20].

Ramucirumab was approved by the FDA in 2019 following the results of the phase 3 REACH-2 trial, a study that enrolled a biomarker-selected (AFP ≥400 ng/mL) post-sorafenib HCC population [23, 29]. Ramucirumab-treated patients showed improved OS compared with placebo-treated patients (median: 8.5 vs. 7.3 months; $p = 0.0199$) and an acceptable tolerability and safety profile [23]. It has been suggested that high AFP levels may be associated with different disease biology than normal AFP levels, thus ramucirumab may be a viable option in these biomarker-selected patients [23, 30].

Although data are limited, the expert panel preferred switching patients who progress on TKI to agents with a different mode of action, and hence preferred using an IO-based therapy after first-line TKI. Data supporting the use of IO post TKI are available for pembrolizumab and nivolumab [22, 24, 25, 27].

Pembrolizumab was given accelerated approval in 2018 based on preliminary data from the KEYNOTE-224 study, a single-arm phase 2 study that enrolled 169 patients with advanced HCC and Child-Pugh A status who had progression or intolerance to sorafenib [25, 31]. The primary outcome, ORR, was 17% and median OS and PFS (12.9 and 4.9 months, respectively) indicated that pembrolizumab was efficacious in this setting [25]. Further data on efficacy and safety are available from the placebo-controlled phase 3 KEYNOTE-240 study, which also enrolled patients with Child-Pugh A status and disease progression or intolerance to sorafenib [22]. Although pembrolizumab did not meet the prespecified significance thresholds for OS and PFS improvements compared with placebo in KEYNOTE-240, improve-

ments in OS (median: 13.9 vs. 10.6 months; $p = 0.024$), PFS (median: 3.0 vs. 2.8 months; $p = 0.0022$), ORR (18.3% vs. 4.4%; $p < 0.001$), and duration of response (13.8 months vs. not reached) were observed [22]. The recommendation for pembrolizumab in this setting is weak due to the failure to meet the primary endpoint of the KEYNOTE-240 study. Additional data supporting pembrolizumab in this setting are the results of the KEYNOTE-394 trial, a placebo-controlled phase 3 study that enrolled 453 Asian patients with HCC previously treated with sorafenib [27]. The study achieved its primary endpoint of statistically significant improvement of OS versus placebo (median: 14.6 vs. 13.0 months; $p = 0.018$), and also met key secondary endpoints of statistically significant improvements over placebo in PFS (HR, 0.74; $p = 0.0032$) and ORR (estimated difference, 11.4%; $p = 0.00004$) [27].

Use of nivolumab, with or without ipilimumab, in post-sorafenib patients with HCC was assessed in cohorts of the phase 1/2 CHECKMATE 040 study, which enrolled patients with Child-Pugh A status after failure or intolerance to sorafenib (and approximately 25% of patients having two or more prior therapies) [24, 26]. Combination therapy with nivolumab following progression with sorafenib was granted accelerated approval by the FDA in 2020 based on CHECKMATE 040 data [32]. However, in April 2021, the FDA's Oncologic Drugs Advisory Committee voted not to maintain the accelerated approval of nivolumab monotherapy in the second-line setting because nivolumab failed to achieve statistical significance for the primary endpoint (OS) in CHECKMATE 459, and Bristol Myers Squibb voluntarily withdrew this indication [33].

There are no phase 3 data to guide selection of post-lenvatinib therapies, and a proposed statement on this topic, *Addition of an IO therapy may be considered in patients who had first-line lenvatinib treatment and had minimal disease progression* – failed to gain consensus among the experts. A post hoc analysis of the REFLECT study shows only 33% of patients treated with first-line lenvatinib and received second-line anticancer medication [34], but this may reflect the lack of treatment options at the time. This analysis found that lenvatinib responders who received subsequent sorafenib treatment ($n = 35$) had a median OS of 26.2 months [34], suggesting sorafenib is an acceptable option after first-line lenvatinib. Smaller studies from Japan have reported data on second-line therapies following lenvatinib, but there are not enough data to inform treatment [35, 36].

The statements formulated by the experts are generally in line with existing guidelines from the American Association for the Study of Liver Diseases and International Liver Cancer Association (ILCA) where regorafenib, cabozantinib, and ramucirumab (or sorafenib for lenvatinib-treated patients) are recommended for use after first-line sorafenib or lenvatinib [28, 37].

Treatment Recommendations following First-Line IO Monotherapy

Statement 14: Following IO monotherapy, cabozantinib, as well as other TKIs, are reasonable options in eligible patients (evidence: level 4; agreement: 89%; strength of recommendation: low).

There are few data to guide selection of second-line therapy in patients who progress on first-line IO monotherapy, and existing guidelines are based largely on expert opinion. Furthermore, IO monotherapy is not recommended as a preferred first-line treatment option [2]. Referencing the management of renal cell carcinoma, in patients with an intermediate or poor-risk profile, after the failure of the standard combination IO therapy, TKI or anti-VEGF therapies are considered [38]. Notably, hyperprogression – a flare of tumor growth upon IO treatment – has also been identified in patients who received nivolumab as first- or second-line treatment (after sorafenib) [39, 40], and, as this phenomenon can limit subsequent treatment options, tumor growth should be carefully assessed in patients receiving IO agents.

Post-IO monotherapy data are available for cabozantinib only. The CELESTIAL study assessed cabozantinib in 707 patients treated with up to two prior agents including sorafenib, including 14 patients who had been treated with IO therapy [41]. Patients with prior IO therapy had similar OS and PFS to the overall study population, and cabozantinib had a similar safety profile in patients with or without prior IO treatment [41]. Real-world use of cabozantinib as second- or later-line therapy in advanced HCC has been summarized in a cohort study of 42 patients from Hong Kong [42]. Most patients received cabozantinib as second- or third-line treatment; almost all had received prior TKI, and patients who progressed on IO therapy received cabozantinib either as single agent or as an add-on therapy [42]. Patients receiving cabozantinib monotherapy had shorter OS than those with cabozantinib-IO combinations (median, 8.3 [$n = 27$] vs. 15.1 [$n = 15$] months, respectively) [42]. Although no data exist, the experts also believe other TKIs may be suitable options following IO monotherapy based on their mechanism of action.

Pembrolizumab or nivolumab plus ipilimumab were evaluated in a cohort study of patients who progressed on prior IO agents (68% were Child-Pugh A status) [43].

Median survival was 10.9 months and OS rate was 21.6% at 3 years; improved outcomes were observed in patients with Child-Pugh A status or albumin-bilirubin Grade 1. Most AEs were skin-related (32%) or endocrinological (20%); hepatitis was rare [43]. A statement – *In patients who have good liver function and do not have primary resistance towards IO, pembrolizumab or nivolumab plus ipilimumab are options following progression from IO* – did not gain consensus among the experts due to a lack of evidence.

Treatment Recommendations following First-Line IO Combination Therapy

Statement 15: Lenvatinib or sorafenib may be considered in patients who progressed on first-line atezolizumab plus bevacizumab; cabozantinib, regorafenib, or ramucirumab may also be considered (evidence: level 3; agreement 94%; strength of recommendation: low).

Although there are few data to guide second-line selection following first-line atezolizumab plus bevacizumab, the National Comprehensive Cancer Network (NCCN) guidelines recommend regorafenib, cabozantinib, ramucirumab, or reexposure to first-line TKIs (lenvatinib/sorafenib) [2]. The recently updated European Society for Medical Oncology (ESMO) guidelines also recommends sorafenib, lenvatinib, cabozantinib, regorafenib, or ramucirumab after progression on first-line atezolizumab plus bevacizumab [19]. The American Society of Clinical Oncology (ASCO) guidelines advocate the use of TKIs (preferably sorafenib or lenvatinib) as second-line therapy if progression occurs on atezolizumab plus bevacizumab [44], and similar recommendations are found in the French Intergroup Clinical Practice Guidelines [45]. The ILCA guidelines note that there are no data to support one TKI over another in this patient subgroup [37].

Lenvatinib and low-dose sorafenib have favorable effects on the immune microenvironment and, due to their inhibition of multiple target kinases, are thought to have a higher antitumor activity than bevacizumab, which only inhibits VEGF [46]. The use of lenvatinib following PD-1/PD-L1 blockade is supported by a real-world study of 36 patients in Japan that showed a median OS (from lenvatinib initiation) of 15.8 months and a median PFS of 10 months [47]. A real-world study in 49 patients with HCC in Hong Kong, Korea, and Singapore previously treated with atezolizumab plus bevacizumab found no significant difference in OS between patients receiving lenvatinib or sorafenib (median, 16.6 vs. 11.2 months), but a statistically significant increase in PFS for lenvatinib (median, 6.1 vs. 2.5 months; $p = 0.004$) was reported [48].

Recommendations on Treatment for Special Populations

Patients with HCC and Liver Dysfunction

Statement 16: For patients with Child-Pugh B7–8 status, sorafenib or nivolumab are preferred treatment options (evidence: level 3/4; agreement: 88%; strength of recommendation: moderate).

Statement 17: For patients with Child-Pugh B7–8 status, dose adjustments for sorafenib may be required (evidence: level 3; agreement: 100%; strength of recommendation: moderate).

The GIDEON registry study of patients with HCC demonstrated that sorafenib can be safely used in patients with Child-Pugh B status in the real world, with 21% (n = 666) of the safety population having Child-Pugh B status [12, 49]. Types and incidence of AEs were similar between the Child-Pugh A and Child-Pugh B subgroups, but longer median OS was reported in the Child-Pugh A subgroup than the Child-Pugh B subgroup (intent-to-treat population; median: 13.6 months vs. 5.2 months) [12]. The reduced benefit observed for sorafenib may be due to the progression of cirrhosis in patients with more advanced disease [12]. Similar data were seen in a case series that included 234 Child-Pugh A and 63 Child-Pugh B patients, noting reduced OS and PFS benefits in the latter group (10.3 vs. 3.8 months and 4.3 vs. 2.1 months, respectively) [50]. Nonetheless, the observational nature of these data and the lack of comparator make it difficult to provide a definitive recommendation on the use of sorafenib in patients with Child-Pugh B status.

The CHECKMATE 040 cohort 5 study of nivolumab is the only prospective study in advanced HCC that included a Child-Pugh B cohort, most of whom were Child-Pugh B7–8 status [51]. Median OS was 7.6 months among the Child-Pugh B cohort, and longer median OS was observed in sorafenib-naïve patients (sorafenib-naïve, 9.8 months; sorafenib-treated, 7.4 months); toxicity profile, including hepatic AEs was similar between the Child-Pugh A (n = 262) and Child-Pugh B (n = 49) cohorts [51]. A real-world cohort study also assessed the effectiveness and safety of nivolumab from Korea; in this study, median OS was 42.9, 11.3, 15.3, and 7.4 weeks for patients with Child-Pugh A, B, B7, and B8/9 status, respectively [52]. Real-world reports from both Japan and Korea also suggested that lenvatinib had reduced efficacy in Child-Pugh B compared with Child-Pugh A patients [53, 54]. Furthermore, another real-world study from Korea

reported a decline in liver function shortly after starting lenvatinib, with 22.6% of patients with Child-Pugh A status at initiation deteriorating to Child-Pugh B status after 4 weeks [55]. The authors thus concluded lenvatinib is best used only in patients with good liver function. Because of these data, a proposed statement – *Lenvatinib should be used judiciously in patients with Child-Pugh B7–8 status* – failed to gain consensus approval from the experts. In line with other expert groups, we suggest immunotherapy can be used with caution in patients with Child-Pugh B status [56, 57], but we cannot recommend a systemic therapy for those with Child-Pugh C status due to a lack of evidence.

Posttransplant Patients

Statement 18: IO agents should generally be avoided in patients who have had previous organ transplants because of the increased risk of graft rejection (evidence: level 4; agreement: 100%; strength of recommendation: moderate).

Statement 19: TKIs are more appropriate than IO agents in posttransplant patients (evidence: level 5; agreement: 100%; strength of recommendation: moderate).

Use of IO agents in liver transplant recipients has been evaluated in a small case series ($n = 14$), with graft rejection reported in 4 patients [58]. Similar results were found in a small series of solid organ transplant recipients ($n = 7$) treated with PD-L1 inhibitors for various metastatic cancers; 2 patients experienced graft rejection [59]. A literature review found a graft loss rate of 36% (4/11) in liver transplant patients treated with IO agents for a variety of cancer types (predominantly, melanoma or HCC) [60]. In general, available data suggest that IO be avoided in patients with solid organ transplants due to the high risk of graft loss [56]. A review of IO use in patients posttransplant noted that the decision to use IO should consider tumor growth rate, available alternatives to IO, and consequences of graft rejection [61]. The consequence of graft rejection in kidney versus liver transplant recipients is notable, as dialysis offers an alternative if the graft is rejected in the former, whereas no such alternative exists for liver transplant patients [61, 62]. Based on these risks, the authors preferred TKIs to IO agents in this subpopulation.

Patients with Recent Gastrointestinal Bleeding

Statement 20: Patients who are to receive anti-VEGF therapy like bevacizumab or ramucirumab should be prescreened with an upper endoscopy to assess risk of variceal bleed (evidence: level 2; agreement: 100%; strength of recommendation: strong).

Statement 21: In patients with recent gastrointestinal bleeding, IO monotherapy may be considered instead of antiangiogenic therapy (including TKIs) (evidence: level 3; agreement: 100%; strength of recommendation: moderate).

Gastrointestinal bleeding is a common complication in patients with cirrhosis [63], and patients should be carefully screened prior to receiving anti-VEGF therapy. In the IMbrave150 study of atezolizumab plus bevacizumab, patients with untreated/incompletely treated gastrointestinal varices (assessed by upper endoscopy and treated according to local practice) were excluded [9]. During the study, 2.4% of patients treated with atezolizumab plus bevacizumab had any variceal bleeding versus less than 1% in the sorafenib arm [9]. Any-grade bleeding or hemorrhage was reported in 30% of patients in the atezolizumab plus bevacizumab arm and 18% of patients in the sorafenib arm, but rates of grade 3–4 bleeding were similar (9% and 6%, respectively) [10]. Although upper endoscopy and primary prophylaxis were requested less than 6 months prior to starting treatment, fatal bleeding events or perforated ulcers occurred in 6 patients (1.8%) and in 1 patient (<1%) assigned to atezolizumab plus bevacizumab or sorafenib, respectively [9, 10].

A pooled analysis of randomized trials in HCC concluded that a statistically significant risk of any-grade bleeding with sorafenib did exist (~6.6% with sorafenib vs. 3.4% in control arms; $p = 0.04$), but it did not differ substantially from renal cancer trials [64]. In the REFLECT study, patients treated with first-line lenvatinib had a rate of grade 3–5 hemorrhagic events of 5% [65].

Patients with Autoimmune Disease

Statement 22: TKIs are preferred in patients with autoimmune disease (AID) (evidence: level 4; agreement: 100%; strength of recommendation: strong).

Statement 23: IO therapy with close monitoring can be considered in patients with well-controlled and non-life-threatening AID who are not on high-dose steroids (evidence: level 5; agreement: 94%; strength of recommendation: moderate).

Statement 24: Comanagement with a specialist treating the underlying AID is needed (agreement: 94%; strength of recommendation: strong).

AIDs such as autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis are risk factors for HCC [66], and data on the safety of IO agents in this population are limited [56]. A review of several case series found that a "flare" of AIDs occurred in 5–15% of patients following IO initiation, leading to some discontinuations [61]. The authors recommended that IO agents be avoided in patients with neurological or neuromuscular disorders or whenever AID reactivation may be life threatening. Use of IO agents should also be avoided in patients with poorly controlled AID or on high doses of immunosuppression. The authors concluded that the first choice of therapy in this population should be TKIs. The European League Against Rheumatism (EULAR) published consensus recommendations on managing the risk of medium- to high-dose steroid therapy in rheumatic diseases [67], and these recommendations are also suitable for patients with HCC receiving high-dose steroid therapy for AID. Adhering to the EULAR recommendations, notably those on selecting and monitoring steroid doses and those for steroid-sparing therapies, may potentially improve eligibility of patients for IO therapy.

A risk-prevention strategy for IO treatment of patients with AIDs recommended that, in patients with various cancer types, nonselective immunosuppressants should be replaced with selective immunosuppressants before starting IO agents as they are less likely to impact IO efficacy [68]. Owing to the complexity of managing HCC in patients with AID, the authors unanimously approved a recommendation that such patients be managed by a multidisciplinary team including oncologists, hepatologists, and immunologists/rheumatologists.

Conclusions

These statements are limited by the lack of evidence in many topics, especially for treatment options after first-line treatments other than sorafenib. However, the increasing number of first-line treatment options, and the benefits they are bringing patients with HCC necessitates more clarity on the use of systemic therapy in the second-line setting. Although evidence is scarce, we offer these statements as expert opinions to guide clinicians in different real-life scenarios.

As the first-line treatment options continue to evolve, with atezolizumab plus bevacizumab becoming the standard of care, along with emerging data from various IO combinations (such as the HIMALAYA, COSMIC-312, and ORIENT-32 studies [13–15]), the use of subsequent therapies is likely to change. Therefore, efforts to capture high-quality real-world data, such as patient registries, will play an important role as a source of evidence to further refine guidance of second-line treatments for HCC.

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Statement of Ethics

This publication was written in compliance with Good Publication Practice 3 ethical guidelines [69]. This manuscript is a review of published studies and no new research activities involving human or animal subjects were performed. Therefore, an institutional or ethical review was not considered necessary by the authors.

Conflict of Interest Statement

Dr. Chan has received consulting fees from AstraZeneca, Merck Sharp & Dohme, Eisai, and Ipsen and research funding from Bayer, Eisai, Ipsen, Sirtex, and Merck Sharp & Dohme. Dr. Chan is also an Editorial Board Member of *Liver Cancer*. Dr. Chen has received grants from GlaxoSmithKline, Merck Serono, OBI Pharma, Pfizer, Polaris, Ministry of Science and Technology, and the Ministry of Health and Welfare; personal fees from Bristol Myers Squibb, Eli Lilly, Five Prime, Merck Sharp & Dohme, Merrimack Pharmaceuticals, Ono Pharmaceutical, PharmaEngine, and Shire; grants and nonfinancial support from Celgene; and grants, personal fees, and nonfinancial support from Novartis, Syncore, and TTY Biopharm. Dr. Cheng has received travel support from Bayer Yakuhin, Ltd., Eisai, Roche/Genentech, Chugai Pharmaceutical, and IQVIA; honoraria for speakers bureau from Bayer Yakuhin, Ltd., Novartis, Eisai, Ono Pharmaceutical, and Amgen Taiwan; and consulting fee from AstraZeneca, Bristol Myers Squibb, Eisai, Merck Serono, Novartis, Ono Pharmaceutical, Exelixis, IPSEN Innovation, Bayer Healthcare, Merck Sharp & Dohme, Roche/Genentech, BeiGene, F. Hoffmann-La Roche, and IQVIA. Dr. Cheng is an Associate Editor of *Liver Cancer*. Dr. Choo owns stock/shares of Bristol Myers Squibb and has received honoraria and consulting fee from Bristol Myers Squibb, Bayer, Roche, AstraZeneca, Merck Sharp & Dohme, and Ipsen; she has also received honoraria from Eisai. Dr. Hsu has received honoraria from AstraZeneca, Bayer, Bristol Myers Squibb/Ono Pharmaceuticals, Eisai, Ipsen, Merck Sharpe & Dohme, and Roche; and grants or

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Author Contributions

The manuscript was conceived and designed by Stephen Lam Chan, Li-Tzong Chen, Ann-Lii Cheng, Tan To Cheung, Su Pin Choo, Chiun Hsu, Yi-Hsiang Huang, David Tai, and Thomas Yau. Data acquisition was performed by Stephen Lam Chan, Li-Tzong Chen, Ann-Lii Cheng, Tan To Cheung, Tracy Shum, David Tai, Thomas Yau, Cynthia S. Y. Yeung, and Wei Peng Yong. Data were analyzed and interpreted by Stephen Lam Chan, Li-Tzong Chen, Ann-Lii Cheng, Tan To Cheung, Su Pin Choo, Yi-Hsiang Huang, Ada Lai Yau Law, Thomas Leung, Shi-Ming Lin, Anna Yin-Ping Tai, David Tai, and Thomas Yau. The manuscript was drafted by Su Pin Choo, Tan To Cheung, David Tai, and Thomas Yau. All the authors revised the manuscript for important intellectual content, and all the authors approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this article are available in PubMed at https://pubmed.ncbi.nlm.nih.gov/ or as described in the reference list.

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