Hepatology International
https://doi.org/10.1007/s12072-024-10732-z

GUIDELINES

APASL clinical practice guidelines on systemic therapy for hepatocellular carcinoma-2024

George Lau[1] · Shuntaro Obi[2] · Jian Zhou[3] · Ryosuke Tateishi[4] · Shukui Qin[5] · Haitao Zhao[6] · Motoyuki Otsuka[7] · Sadahisa Ogasawara[8] · Jacob George[9] · Pierce K. H. Chow[10] · Jianqiang Cai[11] · Shuichiro Shiina[12] · Naoya Kato[13] · Osamu Yokosuka[14] · Kyoko Oura[15] · Thomas Yau[16] · Stephen L. Chan[17] · Ming Kuang[18] · Yoshiyuki Ueno[19] · Minshan Chen[20] · Ann-Lii Cheng[21] · Gregory Cheng[22,58] · Wan-Long Chuang[23] · Oidov Baatarkhuu[24] · Feng Bi[25] · Yock Young Dan[26] · Rino A. Gani[27] · Atsushi Tanaka[28] · Wasim Jafri[29] · Ji-Dong Jia[30] · Jia-Horng Kao[31] · Kiyoshi Hasegawa[32] · Patrick Lau[33] · Jeong Min Lee[34] · Jun Liang[35] · Zhenwen Liu[36] · Yinying Lu[37] · Hongming Pan[38] · Diana A. Payawal[39] · Salimur Rahman[40] · Jinsil Seong[41] · Feng Shen[42] · Gamal Shiha[43,59,60,61] · Tianqiang Song[44] · Hui-Chuan Sun[45] · Tsutomu Masaki[15] · Ekaphop Sirachainan[46] · Lai Wei[47] · Jin Mo Yang[48] · Jose D. Sallano[49] · Yanqiao Zhang[50] · Tawesak Tanwandee[51] · AKadir Dokmeci[52] · Shu-sen Zheng[53] · Jia fan[54] · Sheung-Tat Fan[55] · Shiv Kumar Sarin[56] · Masao Omata[57]

Received: 11 July 2024 / Accepted: 16 September 2024

Abstract
In Asia–Pacific region, hepatocellular carcinoma is a serious health threat attributing to over 600,000 deaths each year and account for over 70% of global cases. Clinically, the major unmet needs are recurrence after curative-intent surgery, liver transplantation or local ablation and disease progression in those with hepatocellular carcinoma not eligible for resection or failed locoregional therapy. In the recent few years, new targeted therapy and immune-checkpoint inhibitors have been registered as systemic therapy to address these issues. Notably, new forms of systemic therapy, either as first-line or second-line therapy for unresectable hepatocellular or those not eligible for locoregional therapy, are now available. New data is also emerging with the use of systemic therapy to prevent hepatocellular carcinoma recurrence after curative-intent resection or local ablation therapy and to retard disease progression after locoregional therapy. In the future, further implementation of immune-checkpoint inhibitors and other forms of immunotherapy are expected to bring a new paradigm to the management of hepatocellular carcinoma. New insight related to immune-related adverse events with the use of immunotherapy has allso enabled optimization of the therapeutic approach to patients with hepatocellular carcinoma. The purpose of this clinical practice guideline is to provide an up-to-date recommendation based on clinical evidence and experience from expert Asia–Pacific key opinion leaders in the field of hepatocellular carcinoma. Three key questions will be addressed, namely: (1) Which patients with hepatocellular carcinoma should be considered for systemic therapy? (2) Which systemic therapy should be used? (3) How should a patient planned for immune checkpoint-based systemic therapy be managed and monitored?

Keywords Hepatocellular carcinoma · Systemic therapy · Guidelines · The Asian Pacific Association for the study of the liver

Introduction

Since the inception of the first Asian–Pacific Association for the study of liver (APASL) hepatocellular carcinoma (HCC) working party in 2007 and the publication of its first guidelines in 2010]1] (revised in 2017) [2], major advances in systemic therapy for HCC have been made [3–6]. To date, despite the availability of effective HCC surveillance and preventive measures, most of the HCC still present at advanced stage as reflected by the high mortality–incidence ratio across the Asia–Pacific region [7], [8]. Most of these patients diagnosed with HCC are therefore beyond curative measures such as surgical resection, local ablation or liver transplantation [9]. This is further compounded by the scarcity of living donors and organs in the Asia–Pacific region

Extended author information available on the last page of the article

which precludes patients with HCC eligible for liver transplantation as a curative measure [10].

Even for those patients who received curative-intent surgery, liver transplantation or local ablation in accordance to various HCC treatment guidelines, recurrence is still a very common clinical problem [11, 12]. The major etiology of HCC in Asia–Pacific region is chronic hepatitis B (CHB) and C (CHC) infection [13–15], compounded by the recent rise of metabolic dysfunction-associated fatty liver diseases (MAFLD) [16]. In countries like China which accounts for nearly half of the global annual cases of HCC, CHB is the major etiology of HCC [7, 8]. In Japan, Egypt, and Mongolia, CHC plays a major role in causing HCC [13–15]. In the recent few years, new targeted therapy and immune-checkpoint inhibitors (ICIs) have been registered as first-line or second-line therapy for HCC that is unresectable or not eligible for locoregional therapy [17–30]. There are also emerging data to support the use of ICIs-based therapy to prolong progression-free survival after locoregional therapy and recurrence-free survival after local ablation or curative-intent surgical therapy for patients with HCC [31, 32]. The gravity of CHB and CHC as etiology of HCC in the Asia–Pacific region is of great relevance, as the response to ICIs has been suggested to be much higher, as compared to targeted therapy [33]. The purpose of this clinical practice guideline is to provide an up-to-date recommendation based on clinical evidence and experience from expert Asia–Pacific key opinion leaders in HCC.

Development process for the guideline

In 2023, the steering committee of the Asian Pacific Association for the Study of the Liver (APASL) initiated the working party on the use of systemic therapy for HCC. To this end, a panel of experts from different disciplines in the Asia–Pacific region with diverse and vast experiences in the management of HCC was assembled. Hepatologists, oncologists (medical and radiation), surgeons (hepatobiliary and transplant), radiologists (diagnostic and interventional), immunologists, pathologists, oncologists and palliative care nurses from different administrative regions/countries in the Asia–Pacific region were invited to form a working party which formulated this clinical practice guidance for the use of systemic therapy for HCC. All panel members were required to disclose their relationships with industry during the guideline formulation until accepted for publication by Hepatology International (official journal of APASL). The Chairs were responsible for writing up the guidelines with the support of all panel members. All recommendations were categorized as strong recommendation (Grade 1) or weak recommendation (Grade 2) according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Table 1) [34]. The guidelines were also presented at the 33rd APASL annual conference held at Kyoto, Japan (26th to 31st April, 2024). Further comments were incorporated into the guidelines according to open discussion (Fig. 1).

Clinical management by MDT

With the evolving complexity in the management of HCC due to rapidly renewed understanding of the complex pathophysiologic and biological nature of HCC, expanded use of surgical resection and liver transplantation, and the continuous emergence and evolution of locoregional and ICIs-based systemic treatment, it is increasingly recognized that the multidisciplinary team (MDT) plays a crucial role in the comprehensive management of HCC. MDT should comprise specialists in multiple fields including hepatology, radiology, surgery, transplant surgery, interventional radiology, medical oncology, radiation oncology and palliative care. MDT could enable comprehensive discussions with collective expertise of the team in interpreting imaging, pathology results, formulating diagnoses and devising management strategies [35–38]. This is supported by the cumulating evidence that MDT can offer significant benefits in patient

Table 1 Grading of Recommendations Assessment, Development and Evaluation (GRADE) system

Grading of evidence	
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case control analytical studies
II-3	Multiple time series, dramatic uncontrolled studies
III	Expert opinion, descriptive epidemiology
Grading of recommendation	
1	Strong recommendation: factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes and cost
2	Weaker recommendation: variability in preferences and value, or more uncertainty Recommendation is made with less certainty: higher cost or resource consumption

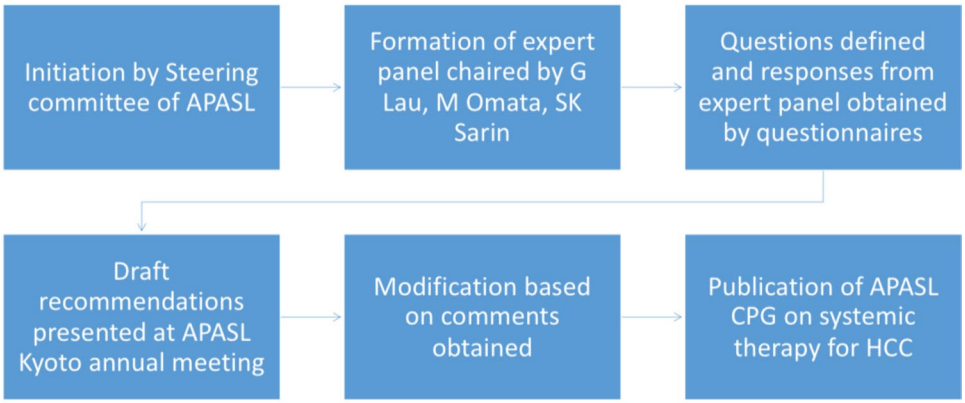


Fig. 1 Workflow of APASL systemic therapy for the HCC working party

diagnosis, treatment planning and overall survival outcomes [39–43]. Based on a recent systematic review and meta-analysis, MDT was also found to be associated with increase rate of early-stage HCC detection suggesting possible referral bias contributing to improved overall survival [44].

Recommendation 1

Consider assembling a multidisciplinary team with experienced hepatologists, oncologists, radiologists (diagnostic and interventional), oncology nurse, surgeon (transplant and hepatobiliary), pathologist, molecular biologists and palliative care specialists, for the management of HCC.

[Grading: Evidence_II-2__ Recommendation__1__].

*Unresectable HCC (***Fig. 2** *and* **Table 2***)*

Surgical resection and local ablation remain as the mainstay of curative strategy for HCC, with a 5-year survival rate of 60% and higher for patients within the Milan criteria [45] The decision to proceed with surgical resection or local ablation requires careful consideration of tumor biology, including the number of tumor nodules, tumor size, and presence of vascular involvement, as well as underlying liver dysfunction and overall patient performance status [46]. The definition of surgical resectability or feasibility of local ablation varies in different centers and treatment guidelines (Table 1) [2, 15, 47–51]. The ultimate decision depends on the experience of the surgeon involved. However, due to the delay in diagnosis, HCC often present at an advanced stage when resection or local ablation is no longer feasible. For cirrhotic patients with early-stage, surgically uHCC, liver transplantation (LT) is an ideal treatment. While the Milan criteria remains the accepted selection criteria for LT candidates with HCC, multiple other expanded criteria such as the Up-to-7-criteria, total tumor volume, extended Toronto criteria, and Kyoto criteria, have been proposed. However, due to the scarcity of organ and living donors in the Asia–Pacific region, many such patients cannot obtain timely liver transplantation as a curative measure [10, 52–54].

Recommendation 2

Staging follows APASL 2017 version (Fig. 2) and resectability of HCC defined as patients without extrahepatic spread, without diffuse, infiltrative, extensive bilobar liver involvement, have well-defined nodules with preserved portal flow, but can vary with the experience of the hepatobiliary surgical team involved. Liver transplant should be considered for cirrhotic patients with early-stage surgically uHCC, within accepted selection criteria.

[Grading: Evidence_III__ Recommendation__2__].

*First-line systemic therapy (***Table 3***)*

Until 2018, sorafenib (Nexavar) was the only available systemic therapy for unresectable HCC (uHCC) [55, 56]. Then three global phase 3 clinical studies (REFLECT, IMbrave 150 and HIMALAYA) made lenvatinib, atezolizumab–bevacizumab and dual ICIs therapy with tremelimumab–durvalumab as Single Tremelimumab Regular Interval Durvalumab (STRIDE) therapy approved worldwide, as first-line therapy for uHCC [17, 19, 20, 24]. Recently, the use of dual ICIs therapy with anti-CTLA4 and PD-1/PD-L1 is further supported by the phase 3 CheckMate 9DW trial which showed that treatment with first-line nivolumab in combination with ipilimumab resulted in a statistically significant and clinically meaningful improvement in overall survival (OS) compared with investigator's choice of sorafenib or lenvatinib in patients with advanced HCC [25]. In mainland China, there were four additional phase 2–3 clinical trials (ZGDH3, ORIENT-32, CARES-310 and Rationale-301) which led to the approval of donafenib, sintilimab plus bevacizumab biosimilar IBI305, camrelizumab plus rivoceranib and tislelizumab for uHCC, by the National Medical Products Administration (NMPA), China (Table 3) [18, 21–23].

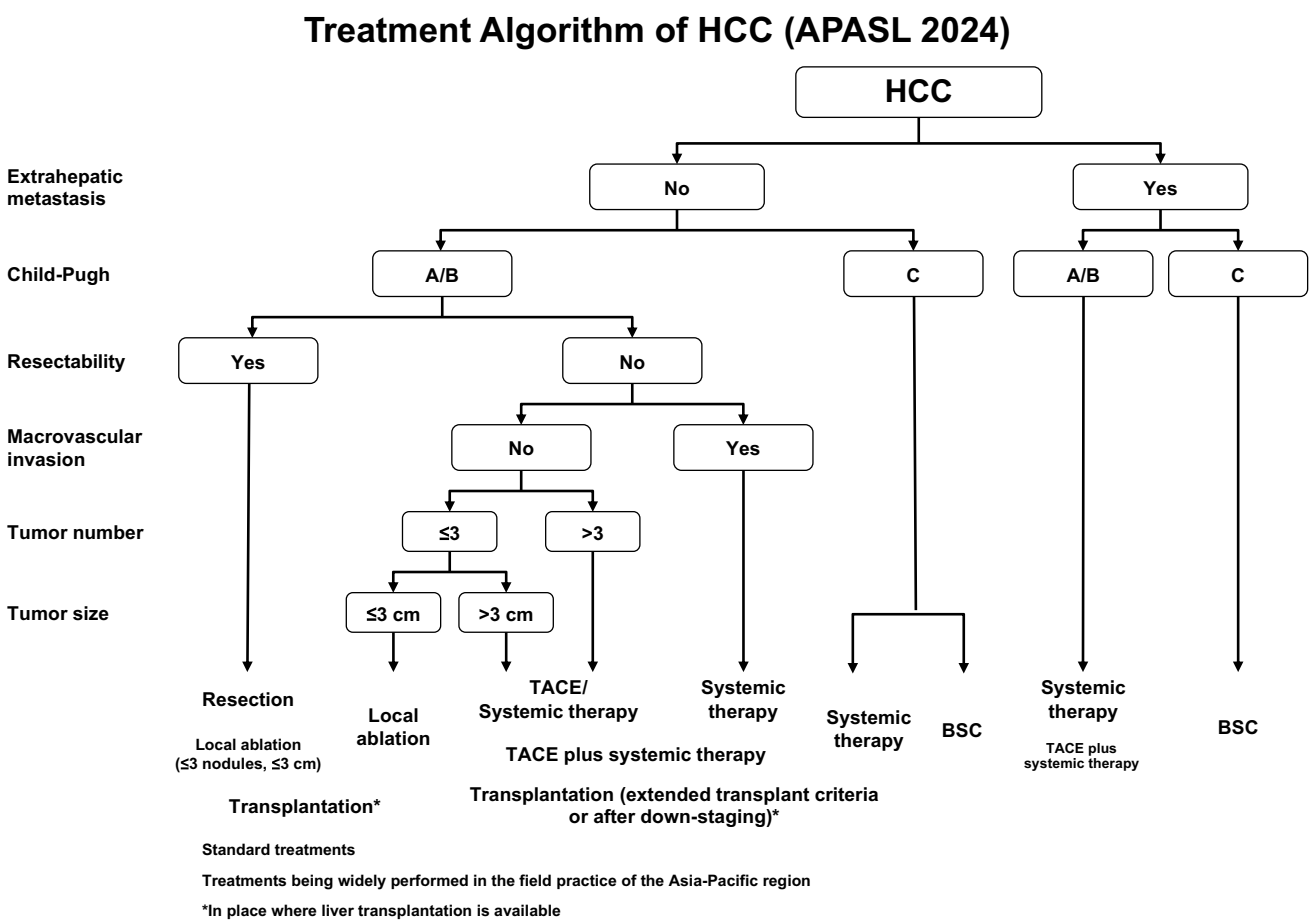


Fig. 2 HCC staging and treatment algorithm

Table 2 Definition of resectability

Guideline	Definition of resectability
Barcelona Clinic Liver Cancer (BCLC) (2022 version) [47]	Among patients with single BCLC-A HCC, resection is favored over ablation owing to lower recurrence especially treating tumors > 2 cm. Among individuals with multifocal BCLC-A HCC (three or more nodules, each ≤ 3 cm), the 2022 BCLC updated guidelines do not recommend resection; rather, these patients are recommended to undergo ablation for non-LT candidates, while LT is suggested for acceptable LT candidates
China liver cancer (CNLC) (2022 version) [15]	• Surgical resection may be considered even in patients with tumors localized to the same liver segment or the ipsilateral hemi-liver • Patients with multinodular tumors (> 3 nodules, > 3 cm) not considered for resection by BCLC are also eligible for resection if confined to the same segment or lobe and the main portal trunk is not invaded
EASL, Clinical Practice Guidelines: Management of hepatocellular carcinoma (2018) [48]	Liver resection is recommended for single HCC of any size and in particular for tumors > 2 cm, when hepatic function is preserved, and sufficient remnant liver volume is maintained
Japan Society of Heptatology (JSH) guideline (2021 version) [49]	Similar to BCLC recommendation (1–3 nodules), except that patients with nodule > 3 cm may also be considered for resection
Korean Liver Cancer Study Group (KLCSG)-National Cancer Center (NCC) Korea practice guidelines (2022 version) 50	Similar to BCLC recommendation (1–3 nodules) without specifying tumor size (> 3 cm or not)
Indian National Association for Study of the Liver Consensus (2023 version) [51]	Similar to BCLC recommendation
APASL (2017 version) [2]	Similar to BCLC recommendation

Table 3 Positive phase 3 studies in uHCC: first-line therapy

Study	REFLECT [17]	ZGDH3 [18]	IMbrave150 [19, 20]	ORIENT-32 [21]	CARES-310 [22]	RATIONALE-301 [23]	HIMALAYA [24]	CheckMate-9DW [25]
Drug	Lenvatinib vs sorafenib	Donafenib vs sorafenib	Atezolizumab + bevacizumab vs sorafenib	Sintilimab + IBI305 vs sorafenib	Camrelizumab + rivoceranib vs sorafenib	Tislelizumab vs sorafenib	Tremelimumab + durvalumab vs sorafenib	Nivolumab + ipilimumab vs sorafenib or lenvatinib
Geographical area	Global (154 centers in 20 countries)	China (37 centers in China)	Global (111 centers in 17 countries and regions)	China (50 centers in China)	Global (95 centers in 13 countries and regions)	Global (117 centers in 11 countries and regions)	Global (181 centres in 16 countries and regions)	Global (147 centres in 24 countries and regions)
N	478 vs 476	334 vs 334	336 vs 165	380 vs 191	272 vs 271	342 vs 332	393 vs 389	335 vs 333
mOS(m)	13.6 vs 12.3	12.1 vs 10.3	19.2 vs 13.4	Not reached vs 10.4	22.1 vs 15.2	15.9 vs 14.1	16.4 vs 13.8	23.7 vs 20.6
PFS(m)	7.3 vs 3.6	3.7 vs 3.6	6.9 vs 4.3	4.6 vs 2.8	5.6 vs 3.7	2.1 vs 3.4	3.8 vs 4.1	9.1 vs 9.2
Absolute survival gain								
OS(m)	1.3	1.8	5.8	N.A	6.9	1.8	2.6	3.1
PFS(m)	3.7	0.1	2.6	1.8	2.9	−1.3	−0.3	−0.1
HR (95% CI)								
OS	0.92 (0.79–1.06) NI	0.83 (0.70–0.99) $P=0.0245$	0.66 (0.52–0.85) $P=0.0009$	0.57 (0.43–0.75) $P<0.0001$	0.62 (0.49–0.80) $P<0.0001$	0.85 (0.71–1.02) $P=0.04$	0.78 (0.65–0.93) $P=0.0035$	0.79 (0.65–0.96) $P=0.018$
PFS	0.66 (0.57–0.77) $P<0.001$	0.91 (0.76–1.08) $P=0.1029$	0.65 (0.53–0.81) $P=0.0001$	0.56 (0.46–0.70) $P<0.0001$	0.52 (0.41–0.65) $P<0.0001$	1.11 (0.92–1.33) N.A	0.90 (0.77–1.05) N.A	0.87 (0.72–1.06) N.A

In REFLECT, lenvatinib (an inhibitor of VEGF receptors 1–3, FGF receptors 1–4, PDGF receptor α, RET and KIT) was compared to sorafenib in noninferiority design for uHCC. Lenvatinib at a dose of 12 mg/day for body weight ≥ 60 kg or 8 mg/day for body weight < 60 kg was compared to sorafenib 400 mg twice daily in 28-day cycles in patients with uHCC. The median OS for lenvatinib (13.6 months; 95% CI 12.1–14.9) was noninferior to sorafenib (12.3 months, 10.4–13.9; hazard ratio [HR] 0.92, 95% CI 0.79–1.06). The most common any-grade adverse events (AEs) for lenvatinib were hypertension (42%), diarrhea (39%), decreased appetite (34%) and decreased weight (31%) [17].

In IMbrave 150, treatment with 1200 mg of atezolizumab (anti-PDL1) plus 15 mg per kilogram of body weight of bevacizumab (anti-VEGF) intravenously every 3 weeks was compared to 400 mg sorafenib orally twice daily. By month 12, atezolizumab–bevacizumab treated patients had a significantly longer OS than those treated with sorafenib (67.2% Vs 54.6%) and the HR was 0.58 (95% confidence interval [CI], 0.42 to 0.79; $p < 0.001$). Median progression-free survival (PFS) was 6.8 months (95% CI 5.7 to 8.3) and 4.3 months (95% C, 4.0 to 5.6) in the respective groups (HR for disease progression or death, 0.59; 95% CI 0.47 to 0.76; $p < 0.001$) [19]. Updated analysis 12 months after the primary analysis showed the median OS was 5.8 months longer with atezolizumab–bevacizumab than sorafenib. Serious AEs occurred more frequently in the atezolizumab–bevacizumab treatment arm (49%) than in the sorafenib arm (33%) and were mainly gastrointestinal hemorrhage (2.4% versus 1.9%), esophageal variceal hemorrhage (2.4% versus 0.6%), and pyrexia (2.1% vs 1.3%) [20].

In the HIMALAYA study, a single, high priming dose of 300 mg tremelimumab (anti-CTLA4) plus 1500 mg durvalumab (anti–PDL1) every 4 weeks, an infusion regimen termed STRIDE (Single Tremelimumab Regular Interval Durvalumab) was compared to 1500 mg durvalumab every 4 weeks and oral sorafenib 400 mg twice daily. STRIDE demonstrated a statistically significant and clinically meaningful improvement in overall survival compared to sorafenib (stratified HR of 0.78 [95% CI 0.66, 0.92],

two-sided p value = 0.0035); median OS was 16.4 months (95% CI 14.2, 19.6) versus 13.8 months (95% CI 12.3, 16.1). The overall survival with durvalumab monotherapy was noninferior to that with sorafenib (HR 0.86; 95.67% CI 0.73 to 1.03; noninferiority margin, 1.08). Grade 3/4 treatment-emergent AEs occurred for 50.5% of patients with STRIDE, 37.1% with durvalumab, and 52.4% with sorafenib. Recent update of 4-year OS rate with STRIDE (n = 393) was 25.2% compared to 15.1% with sorafenib (n = 389; HR, 0.78; 95% CI 0.67–0.92; 2-sided p = 0.0037), showing similar magnitude of benefit from the 3-year landmark analysis, which revealed an OS rate of 30.7% with the STRIDE and 19.8% with sorafenib alone [24]. The Asian subpopulation analysis (including Hong Kong, India, South Korea, Taiwan, Thailand and Vietnam, but not Japan) (n = 479) revealed that median OS times for the STRIDE regimen (16.5 months; 95% CI 12.6–22.1; HR 0.68) and for durvalumab (16.6 months; 95% CI 12.2–19.2; HR 0.83) were longer for sorafenib (11.8 months; 95% CI 9.4–14.7) and the corresponding median OS times in the overall population (n = 1,171) were 16.4 months (95% CI 14.2–19.6; HR 0.78) for STRIDE, 16.6 months (95% CI 14.1–19.1; HR 0.86) for durvalumab and 13.8 months (95% CI 12.3–16.1) for sorafenib. Also, results from an additional subpopulation analysis of patients from Hong Kong/Taiwan (n = 141) were generally consistent with the overall Asian subpopulation analysis, with median OS of 29.4 months (HR 0.44) for STRIDE, 23.6 months (HR 0.64) for durvalumab and 19.1 months for sorafenib [57]. Recent data showed that STRIDE significantly improved OS versus sorafenib and demonstrated durable long-term survival (OS rate 25.2% vs 15.1%) in the 4-year and OS rate (19.6% vs 9.4%) in the 5-year follow-up analysis, with a manageable safety profile [58, 59]. OS benefit with STRIDE was enhanced in participants experiencing disease control per RECIST v1.1 and the OS rate ratios for STRIDE versus sorafenib increasing over time [59].

In CheckMate 9DW, 668 patients were randomized to nivolumab 1 mg/kg IV and ipilimumab 3 mg/kg IV every 3 weeks (up to 4 cycles), then nivolumab 480 mg every 4 weeks (n = 335) or lentivinab at a dose of 12 mg/day for body weight ≥ 60 kg or 8 mg/day for body weight < 60 kg or sorafenib 400 mg twice daily (n = 333). The median OS was 23.7 months with nivolumab + ipilimumab versus 20.6 months with lentivinab or sorafenib (HR 0.79; 95% CI 0.65–0.96; p = 0.0180), with respective 24-month OS rates of 49% versus 39%. Objective response rate was higher with nivolumab + ipilimumab (36%) vs lentivinab or sorafenib (13%; p < 0.0001) and complete response was observed in 7% of patients treated with nivolumab + ipilimumab but only 2% in patients treated with lentivinab or sorafenib. The safety profile for the combination of nivolumab + ipilimumab remained consistent with previously reported data and was manageable with established protocols. Treatment-related AEs of any grade were reported in 84% of patients with nivolumab + ipilimumab and 91% in patients with lenvatinib or sorafenib. Grade 3/4 treatment-related AEs occurred in 41% and 42% of patients, respectively [25]. The FDA has accepted a supplemental biologics license application (sBLA) for first-line nivolumab (Opdivo) plus ipilimumab (Yervoy) in adults with uHCC.

In the multicenter, randomized, controlled phase II-III trial ZGDH3 conducted in mainland China, donafenib (a novel multikinase inhibitor and a deuterated sorafenib derivative) was compared to sorafenib in patients with uHCC. The median OS was significantly longer with donafenib than sorafenib treatment (HR 0.831; 95% CI 0.699 to 0.988; p = 0.0245), though the median progression-free survival (PFS) was 3.7 versus 3.6 months (p = 0.0570). Drug-related grade ≥ 3 AEs occurred in significantly fewer patients receiving donafenib than sorafenib (125 [38%] versus 165 [50%]; p = 0.0018). With these data, donafenib was approved by China NMPA for uHCC in 2021 [18].

In the phase 2–3 ORIENT-32 study, sintilimab (humanized IgG4 monoclonal anti-PD-1) plus IBI305 (a bevacizumab biosimilar) group showed a significant improvement in OS (HR 0·57, 95% CI 0·43–0·75; p < 0·0001) and PFS (4·6 months [95% CI 4·1–5·7]) than did patients in the sorafenib group (2·8 months [2·7–3·2]; stratified HR 0·56, 95% CI 0·46–0·70; p < 0·0001) [21]. In CARES-310, 543 patients with uHCC were randomly assigned to receive either camrelizumab (humanized IgG4 monoclonal anti-PD-1) 200 mg intravenously every 2 weeks plus rivoceranib (also known as apatinib, a highly selective VEGFR2-targeted TKI) 250 mg orally once daily or sorafenib 400 mg orally twice daily. Median PFS was significantly improved with camrelizumab–rivoceranib versus sorafenib (5·6 months [95% CI 5·5–6·3] vs 3·7 months [2·8–3·7]; HR 0·52 [95% CI 0·41–0·65]; one-sided p < 0·0001) and median OS was significantly extended with camrelizumab–rivoceranib versus sorafenib (22·1 months [95% CI 19·1–27·2] vs 15·2 months [13·0–18·5]; HR 0·62 [95% CI 0·49–0·80]; one-sided p < 0·0001). Treatment-related serious AEs were reported in 66 (24%) patients in the camrelizumab–rivoceranib group and 16 (6%) in the sorafenib group [22]. In RATIONALE-301, 674 patients with uHCC were randomized 1:1 to receive tislelizumab (anti-PD1), 200 mg intravenously every 3 weeks, or sorafenib tosylate, 400 mg orally twice daily. The primary end point of OS noninferiority of tislelizumab versus sorafenib was met in the intention-to-treat population and the median OS was 15.9 (95%CI, 13.2–19.7) months versus 14.1 (95%CI, 12.6–17.4) months, respectively (HR 0.85 [95.003%CI, 0.71–1.02]). However, the superiority of tislelizumab versus sorafenib was not met and the median PFS was 2.1 (95%CI, 2.1–3.5) months versus 3.4 (95%CI, 2.2–4.1) months with tislelizumab (HR 1.11 [95%CI, 0.92–1.33]). The incidence of treatment-emergent

AEs was 96.2% (325 of 338 patients) for tislelizumab and 100% ($n=324$) for sorafenib. Grade 3 or greater treatment-related AEs were reported in 75 patients (22.2%) receiving tislelizumab and 173 (53.4%) receiving sorafenib. There was a lower incidence of treatment-related AEs leading to drug discontinuation (21[6.2%] vs 33 [10.2%]) and drug modification (68 [20.1%] vs 187 [57.7%]) with tislelizumab vs sorafenib [23] (Table 4).

Patients with impaired liver function test

In the real world, a substantial number of patients with advanced HCC have impaired liver function. Despite this, most pivotal randomized controlled trials have excluded patients with moderate liver dysfunction (Child–Pugh–Turcotte B, CPT-B) [60]. Among HCC patients treated with sorafenib, OS was significantly lower in patients with CPT-B vs CPT-A liver function, suggesting treatment should be individualized for patients with CPT-B cirrhosis [61]. However, the efficacy and tolerability of ICIs for CPT-B patients with advanced HCC remain unclear. In a recent systematic review and meta-analysis which included 22 studies with 699 CPT-B patients and 2114 CPT-A patients with advanced HCC, ICIs therapy in the CPT-B group appeared to be safe and showed a significant number of radiologic responses, but survival outcomes were inferior compared with the CPT-A group [62]. Notably, further subgroup analyses did not reveal any significant differences in radiologic response, survival, or incidence of AEs between patients with CTP-B with 7 and 8/9 scores. However, due to the limited sample size (fewer than 100 cases with CTP-B with 8/9 scores across 6 studies, further multicenter prospective cohort studies are needed to evaluate the association of CTP-B score with the efficacy and tolerability of ICI treatment in these patients [63–68].

Recommendation 3a (Fig. 3a)

Patients with uHCC not eligible for locoregional therapy with ECOG PS 0–1 and CPT- A and B, including those with portal vein tumor thrombus, should be offered systemic therapy.

[Grading: Evidence_I__ Recommendation__1__].

The first choice of systemic therapy should be anti-VEGF + anti-PD-1/anti-PD-L1*

(in those without risk of bleeding) or dual ICIs with anti-CTLA-4 and anti-PD1/anti-PDL1 or anti-PD-1[#]/anti-PD-L1[##]. For those patients with limited resources or have contraindications to immunotherapy, lentivinab or sorafenib should be considered.

*Atezolizumab + bevacizumab or sintilimab + IBI305 or camrelizumab + rivoceranib (apatinib).

[#] anti-PD-1 in mainland China; [##] anti-PD-L1 in Japan.

[Grading: Evidence_I__ Recommendation__1__].

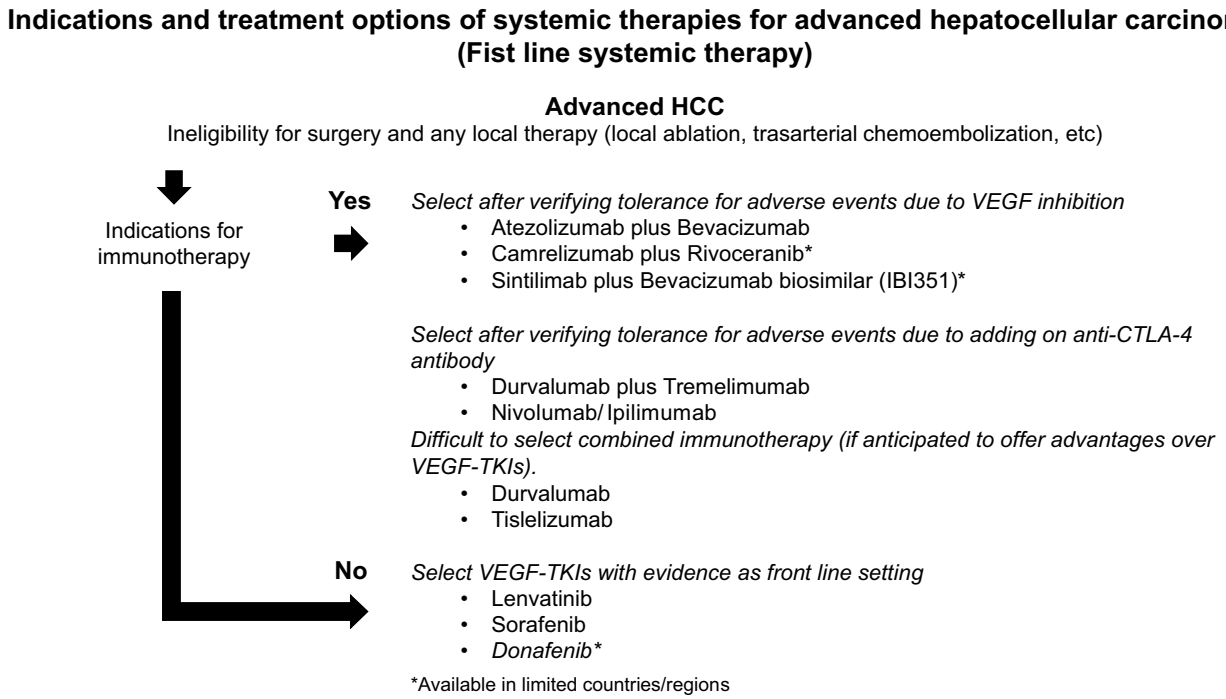
Second-line therapy for unresectable HCC (Table 4)

For those patients with uHCC who failed to respond or have disease progression with sorafenib, regorafenib, cabozantinib and ramucirumab (at α-fetoprotein concentrations of 400 ng/mL or higher), pembrolizumab and apatinib (in mainland China) have become the treatment options based on positive phase 3 clinical trials results (Table 4) [26–30].

Table 4 Positive Phase 3 studies in uHCC: second-line therapy

Study	RESORCE [26]	KEYNOTE-394 [27]	CELESTIAL [28]	REACH-2 [30]	AHELP [29]
Drug	Regorafenib vs placebo	Pembrolizumab vs placebo	Cabozantinib vs placebo	Ramucirumab vs placebo	Apatinib vs placebo
Geographical area	Global (152 centers in 21 countries)	Asia	Global (95 centers in 19 countries)	Global (92 centres in 20 countries)	China (31 centers in China)
N	379 vs 194	300 vs 153	470 vs 237	197 vs 95	267 vs 133
mOS(m)	10.6 vs 7.8	14.6 vs 13.0	10.2 vs 8.0	8.5 vs 7.3	8.7 vs 6.8
PFS(m)	3.1 vs 1.5	2.6 vs 2.3	5.2 vs 1.9	2.8 vs 1.6	4.5 vs 1.9
Absolute survival gain					
OS	2.8	1.6	2.2	1.2	1.9
PFS	1.6	0.3	3.3	1.2	2.6
HR (95% CI)					
OS	0.63 (0.50–0.79) $p<0.001$	0.79 (0.63–0.99) $p=0.0180$	HR: 0.76 (0.63–0.92) $p=0.005$	0.71 (0.53–0.95) $p=0.0199$	0.79 (0.62–1.00) $p=0.048$
PFS	0.46 (0.37–0.56) $p<0.001$	0.74 (0.60–0.92) $p=0.0032$	0.44 (0.36–0.52) $p<0.001$	0.45 (0.34–0.60) $p<0.001$	0.47 (0.37–0.60) $p<0.0001$

a.First-line systemic therapy for advanced HCC



b. Second line systemic therapy for advanced HCC

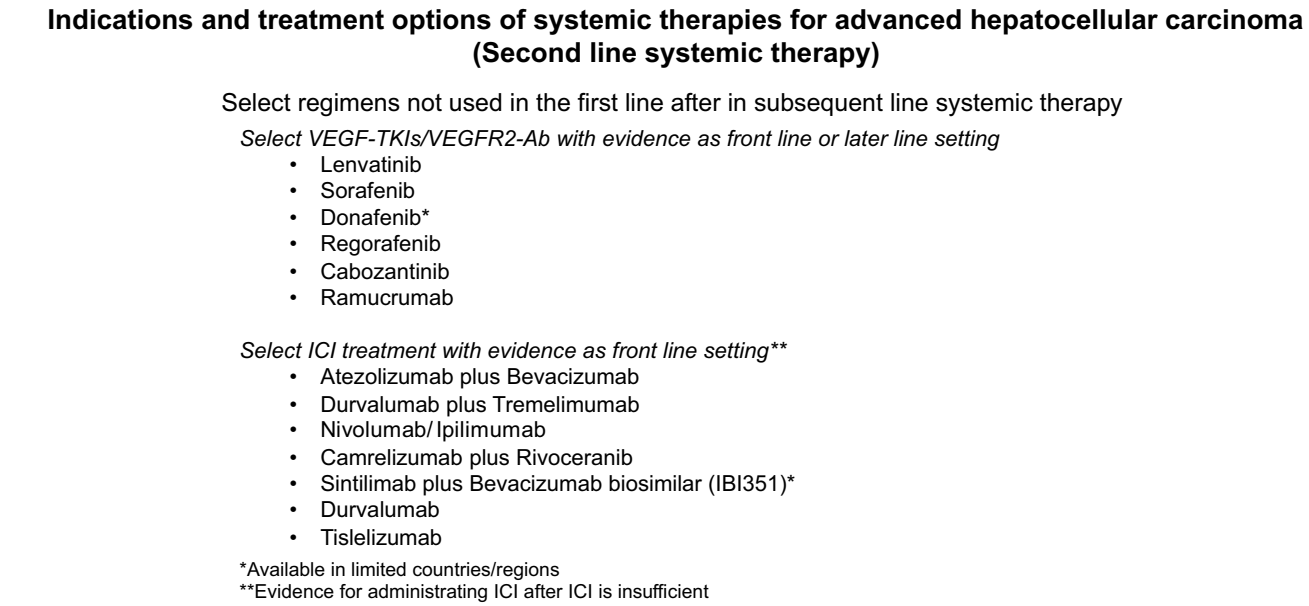


Fig. 3 Indications and treatment options of systemic therapies for advanced HCC. a. First-line systemic therapy for advanced HCC. b. Second-line systemic therapy for advanced HCC

Most of the second-line therapy was based on the use of sorafenib as first-line therapy. However, with the rapid development of new first-line therapy (see above) with ICIs-based therapy, there are limited data on the choice of second-line after such ICIs-based therapy [66, 67].

In the RESORCE study, adults with uHCC who progressed on sorafenib, and regorafenib at the dose of 160 mg once daily

during weeks 1–3 of each 4-week cycle, as compared to placebo, had improved OS with a hazard ratio of 0·63 (95% CI 0·50–0·79; one-sided $P < 0·0001$). The median survival was 10·6 months (95% CI 9·1–12·1) for regorafenib versus 7·8 months (6·3–8·8) for placebo. However, AEs were reported in all regorafenib recipients (374 [100%] of 374) and 179 (93%) of 193 placebo recipients. The most common clinically relevant grade 3 or 4 treatment-emergent AEs were hypertension, hand–foot skin reaction, fatigue and diarrhea [26].

In KEYNOTE-394, 453 Asian with uHCC with disease progression or intolerance with sorafenib or oxaliplatin-based chemotherapy were randomly assigned in a 2:1 ratio to receive pembrolizumab (200 mg) or placebo once every 3 weeks for ≤ 35 cycles plus best supportive care. The median OS was longer in the pembrolizumab group than in the placebo group (14.6 versus 13.0 months; hazard ratio for death, 0.79; 95% CI, 0.63 to 0.99; $p = 0.0180$). Median PFS was also longer in the pembrolizumab group than in the placebo group (2.6 versus 2.3 months; hazard ratio for progression or death, 0.74 95% CI, 0.60 to 0.92; $p = 0.0032$). Treatment-related AEs occurred in 66.9% of patients (grade 3, 12.0%; grade 4, 1.3%; grade 5, 1.0%) in the pembrolizumab group and 49.7% of patients (grade 3, 5.9%; grade 4, 0%; grade 5, 0%) in the placebo group [27].

In the CELESTIAL study, the efficacy and safety of cabozantinib (inhibitor of tyrosine kinases, including vascular endothelial growth factor receptors 1, 2, and 3, MET, and AXL) was evaluated in uHCC. Seven hundred and seven patients were randomly assigned in a 2:1 ratio to receive cabozantinib (60 mg once daily) or matching placebo. Median OS was 10.2 months with cabozantinib and 8.0 months with placebo (hazard ratio for death, 0.76; 95% confidence interval [CI], 0.63 to 0.92; $p = 0.005$). Median PFS was 5.2 months with cabozantinib and 1.9 months with placebo (HR for disease progression or death, 0.44; 95% CI 0.36 to 0.52; $p < 0.001$), and the objective response rates were 4% and less than 1%, respectively ($p = 0.009$). Grade 3 or 4 AEs occurred in 68% of patients in the cabozantinib group and in 36% in the placebo group. The most common high-grade events were palmar–plantar erythrodysesthesia (17% with cabozantinib vs. 0% with placebo), hypertension (16% vs. 2%), increased aspartate aminotransferase level (12% vs. 7%), fatigue (10% vs. 4%), and diarrhea (10% vs. 2%) [28].

In REACH-2, sorafenib-experienced uHCC with α-fetoprotein concentrations of 400 ng/mL or greater were randomly assigned to the ramucirumab ($n = 197$) or placebo (n = 95) group. As compared to the placebo group, the ramucirumab group had a significantly improved median OS (8·5 months [95% CI 7·0–10·6] vs 7·3 months [5·4–9·1]; HR 0·710 [95% CI 0·531–0·949]; $P = 0·0199$) and PFS (2·8 months [2·8–4·1] vs 1·6 months [1·5–2·7]; 0·452 [0·339–0·603]; $p < 0·0001$). Grade 3 or worse treatment-emergent AEs that occurred in at least 5% of patients in either group were hypertension (25 [13%] in the ramucirumab group vs 5 [5%] in the placebo group), hyponatremia (11 [6%] vs 0) and increased aspartate aminotransferase (6 [3%] vs 5 [5%]) [30].

In the AHELP study conducted in China, patients with uHCC, who failed at least one line of systemic chemotherapy or targeted therapy, were randomly assigned (2:1) to receive apatinib 750 mg or placebo orally once daily in 28-day treatment cycles. The OS was significantly improved in the apatinib group compared to the placebo group (median 8·7 months [95% CI 7·5—9·8] vs 6·8 months [5·7—9·1]; HR 0·785 [95% CI 0·617—0·998], $p = 0·048$). The most common treatment-related AEs of grade 3 or 4 were hypertension (71 [28%] patients in the apatinib group vs 3 [2%] in the placebo group), hand–foot syndrome (46 [18%] vs none) and decreased platelet count (34 [13%] vs 1 [1%]) [29].

Recommendation 3b (Fig. 3b)

Second-line therapy should be considered when there is disease progression after 8–12 weeks of first-line therapy.

[Grading: Evidence_II__ Recommendation__2__].

Second-line therapy for consideration includes dual ICIs with anti-CTLA-4 and anti-PD1/anti-PDL1 or lenvatinib for those who failed anti-VEGF + anti-PD-1/anti-PD-L1*. For those who failed dual ICIs with anti-CTLA-4 and anti-PD1/anti-PDL1, one should consider anti-VEGF + anti-PD-1/anti-PD-L1* or lenvatinib.

[Grading: Evidence_III__ Recommendation__2__].

Third-line therapy for those who failed second-line therapy includes regorafenib/cabozantinib/ramucirumab**

**AFP greater than or equal to 400 ng/mL.

[Grading: Evidence_2__ Recommendation__2__].

*Immune-related adverse events (irAEs) and their management (*Table 5*)*

The use of ICIs, either as monotherapy or in combination with anti-VEGF or with another ICIs, has greatly improved the OS of the patients with uHCC [19, 20, 23–25]. However, its use is associated with a spectrum of side effects, termed immune-related adverse events (irAEs) which are quite different from other systemic therapies such as cytotoxic chemotherapy. IrAEs may involve any organ or system of the body, but is mainly related to gastrointestinal, dermatologic, hepatic, endocrine, and pulmonary system. The exact mechanism is still largely unknown and might be related to increasing T-cell activity against antigens that are present in the tumors and healthy tissue, increasing levels of preexisting autoantibodies or inflammatory cytokines, and enhanced complement-mediated inflammation due to direct binding of an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) with CTLA-4 expressed on normal tissue, such as the pituitary gland [69–71].

Table 5 Summary of treatment-related adverse events

Study	IMbrave150 [19, 20]	ORIENT-32 [21]	CARES-310 [22]	RATIONALE-301 [23]	HIMALAYA [24]	CheckMate-9DW [25]
Event	Atezolizumab + bevacizumab ($n=329$)	Sintilimab + IBI305 ($n=380$)	Camrelizumab + rivoceranib ($n=272$)	Tislelizumab ($n=338$)	Tremelimumab + durvalumab ($n=388$)	Nivolumab + ipilimumab ($n=332$)
Immune-mediated event requiring high-dose steroids	n.a	n.a	n.a	47 (13.9%)	78 (20.1%)	96 (29%)
Any grade 3 or 4 immune-mediated event	n.a	n.a	45 (17%)	28 (8.3%)	49 (12.6%)	93 (28%)
Immune-mediated event leading to death	n.a	n.a	1 (0.4%)	0	6 (1.5%)	0
	Treatment-related adverse events					
Any	284 (86%)	337 (89%)	265 (97%)	259 (76.6%)	294 (75.8%)	278 (84%)
Any serious	76 (23%)	65 (17%)	66 (24.3%)	40 (11.8%)	68 (17.5%)	94 (28%)
Grade 3 or 4	143 (43%)	128 (34%)	220 (81%)	75 (22.2%)	100 (25.8%)	137 (41%)
Leading to discontinuation	34 (10%)	52 (14%)	41 (15.1%)	21 (6.2%)	32 (8.2%)	59 (18%)
Leading to dose delay	195 (59%)	188 (49%)	n.a	68 (20.1%)	83 (21.4%)	0
Leading to death	6 (2%)	6 (2%)	1 (0.4%)	3 (0.9%)	9 (2.3%)	12 (4%)

Most of the toxic effects are reversible, aside from the effects on the endocrine system, which may be permanent. The early identification and timely management of irAEs is key to preventing irAE progression and mitigating severity [72–74]. However, due to the incomplete understanding of the pathophysiology of irAE, there is a lack of precise treatment for this important clinical problem. Several professional organizations have provided expert consensus on managing specific irAE, based largely on retrospective studies and case series rather than prospective studies. These treatment guidelines have been formulated to enable earlier recognition, appropriate management, and better patient outcomes related to irAEs [75, 76].

Furthermore, the understanding of the overall incidence of irAEs is hampered by the different or unclear definition used in various studies. In HIMALAYA, irAEs were defined as AEs of special interest associated with exposure ICIs therapy and consistent with an immune-mediated mechanism of action for which there is no alternate etiology. Participants with ≥ 1 irAEs were counted once. With such definition, among participants in HIMALAYA who received STRIDE or durvalumab monotherapy, irAEs were manageable and generally low grade. In keeping with other reports, the majority of the irAEs occurred within the first 3 months of treatment and were more frequent with combination therapy with anti-CTLA-4 and anti-PDL1 (STRIDE) than with monotherapy with anti-PDL1 [69–76] Very importantly, the occurrence of irAEs did not preclude participants from experiencing an OS benefit with STRIDE, and long-term survival was observed with STRIDE, irrespective of irAEs occurrence [74].

Recommendation 4 (Fig. 4)

Patients should be monitored 1–2 weekly for irAEs toxicity if dual ICIs therapy is given and 2–4 weekly if only anti-PD-1/PD-L1 is given.

Diagnosis of irAEs should be made only after careful ruling out other differential diagnoses. Management will be based on grading of the irAEs per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 6, and classified according to the Medical Dictionary for Regulatory Activities, version 26.1.

For grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities, one should consider continuing ICIs with close monitoring for further toxicities,

For grade 2 toxicities, one should consider withholding ICIs and initiating prednisone with an initial dose of 0.5 to 1 mg/kg/day. Apart from prednisone, other corticosteroids at equivalent doses may be considered. ICI can be resumed when symptoms and/or laboratory values revert to grade 1 or less.

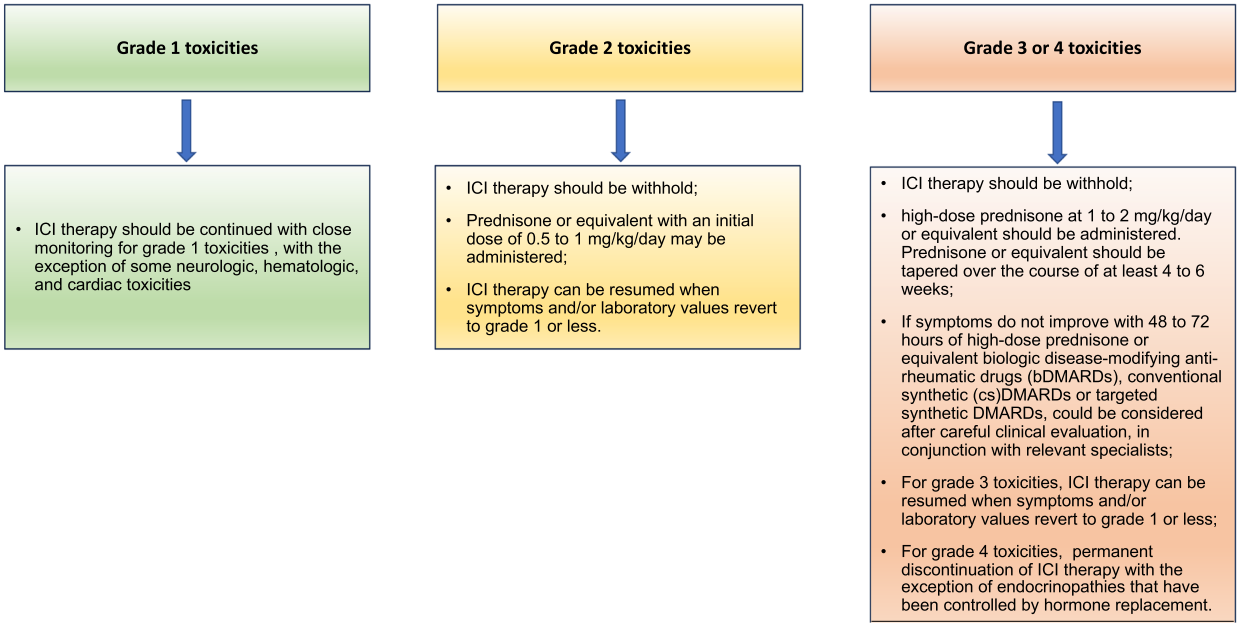


Fig. 4 Management of immune-related adverse events

For grade 3 or 4 toxicities, one should consider withholding ICIs and initiating high-dose prednisone at 1 to 2 mg/kg/day or other corticosteroids at equivalent doses. Relevant specialist should be consulted. Prednisone or other corticosteroids at equivalent doses should be tapered over the course of at least 4–6 weeks. If symptoms do not improve with 48 to 72 h of high-dose prednisone or equivalent biologic disease-modifying anti-rheumatic drugs (bDMARDs), conventional synthetic (cs)DMARDs or targeted synthetic DMARDs could be considered after careful clinical evaluation, in conjunction with relevant specialists. For grade 3 toxicities, ICIs can be resumed when symptoms and/or laboratory values revert to grade 1 or less. For grade 4 toxicities, permanent discontinuation of ICIs with the exception of endocrinopathies that have been controlled by hormone replacement.

[Grading: evidence_III__ recommendation__2__].

Management for uHCC treated with local regional therapy

Patients with uHCC treated with locoregional therapy such as drug-eluting bead (DEB)-transcatheter arterial chemoembolization (TACE) or conventional TACE (cTACE) usually will have disease progression within 1 year with a median PFS of 7–8 months [31]. In EMERALD-1, 616 patients with uHCC who received (DEB)-TACE/cTACE were randomized 1:1:1 to durvalumab during TACE and then following the last TACE procedure, durvalumab + placebo (D + TACE) or durvalumab + bevacizumab (D + B + TACE), or DEB-TACE/ cTACE (TACE). Durvalumab was given after at least 7 days following the initial TACE procedure. Durvalumab ± bevacizumab began after at least 14 days following the last TACE procedure. Patients with a history of nephrotic or nephritic syndrome, clinically significant cardiovascular disease, extrahepatic disease or main portal vein thrombosis (Vp3/Vp4) is excluded. As compared to TACE alone, PFS was significantly improved with D + B + TACE (median PFS 8.2 vs 15.0 months; hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.61–0.98; $p = 0.032$ [threshold 0.0434]). ORR was 43.6%, 41.0% and 29.6%, and mTTP was 22.0, 11.5 and 10.0 months for D + B + TACE, D + TACE, and TACE, respectively. However, PFS was not significantly improved with D + TACE versus TACE alone. The incidence of maximum grade 3 or 4 AEs was low across all arms D + B + TACE (32.5%), D + TACE (15.1%), and TACE alone (13.5%), with no unexpected safety signals [31].

Recommendation 5

For those embolization-eligible uHCC, DEB-TACE or cTACE + durvalumab, followed by durvalumab + bevacizumab should be considered.

[Grading: Evidence_II__ Recommendation__2__].

Prevention of HCC recurrence after "curative" surgery or ablation

After curative-intent resection or ablation defined by the Milan Criteria**,** HCC recurs in 70–80% of cases [77, 78]. From both in vivo and in vitro studies, the immunosuppressive liver microenvironment, modulated by VEGF and/or immune checkpoints such as PD-L1, has been implicated to play a key role in recurrence [79]. Based on this observation, IMbrave 050, a phase III randomized multicenter open-label study was designed to evaluate atezolizumab plus bevacizumab versus active surveillance in patients at high risk of disease recurrence following curative resection or ablation (tumor size > 5 cm, tumor number ≥ 3, vascular invasion such as microvascular invasion or macrovascular invasion—Vp1/Vp2—of the portal vein and grade 3 or 4 tumor differentiation). Altogether, 668 patients were randomly assigned in a 1:1 ratio to receive intravenous 1200 mg atezolizumab plus 15 mg/kg bevacizumab every 3 weeks for 17 cycles (12 months) or to active surveillance. For the first interim analysis with the median duration of follow-up of 17·4 months (IQR 13·9–22·1), adjuvant atezolizumab plus bevacizumab was associated with significantly improved recurrence-free survival (median, not evaluable [NE]; [95% CI 22·1-NE]) compared with active surveillance (median, NE [21·4-NE]; HR 0·72 [adjusted 95% CI 0·53–0·98]; $P = 0·012$). As the recurrence-free survival curve of the two arms start to merge on follow-up, one needs longer follow-up data to understand whether the benefit of recurrence-free survival could be sustained over time and whether there is any significant difference in overall survival. Grade 3 or 4 adverse events occurred in 136 (41%) of 332 patients who received atezolizumab plus bevacizumab and 44 (13%) of 330 patients in the active surveillance group. Grade 5 adverse events occurred in six patients (2%, two of which were treatment related) in the atezolizumab plus bevacizumab group, and one patient (< 1%) in the active surveillance group. Both atezolizumab and bevacizumab were discontinued because of adverse events in 29 patients (9%) who received atezolizumab plus bevacizumab [32].

Recommendations 6

For those patients who received curative-intent surgery or local ablation for HCC at high risk of disease recurrence, combination therapy with atezolizumab plus bevacizumab post-operatively is premature to be recommended.

[Grading: Evidence_II__ Recommendation__2__].

Use of systemic therapy for HCC in the setting of liver transplantation

One of the major indications for liver transplantation (LT) is for the treatment of uHCC within LT-eligible criteria [[80–83] and systemic therapy for HCC might be considered as a "bridging" or "downstaging" strategy before transplantation [84–100]. Despite strict adherence to LT-eligibility criteria, post-transplant HCC recurrence occurs in up to 20% of cases and constitute a significant clinical problem [101–117]. With the registration of ICIs as effective systemic therapy for uHCC, the major concern of its use in pre- and post-LT setting is whether the risk of rejection will be enhanced. To date, there is a lack of comprehensive evaluation of the safety and efficacy of ICIs in uHCC patients before and after LT. The use of ICIs in the LT setting needs a careful balance between cancer immunology and transplant tolerance. Through the activation of effector T cells, the ICIs will not only reduce tumor burden but also increase the risk of graft rejection.

Recently, several studies have shown positive outcomes post-LT after pre-transplant use of ICIs therapy for uHCC and this has enabled the use of ICIs not to be precluded from consideration of liver transplantation (Table 6) [88–100]. Although pre-LT ICIs may increase the incidence

Table 6 Summary of case reports on the use of ICI-based therapy in pre-LT patients with HCC [86–99]

No. of patients	Sex (M/F)	Age (yrs)	Cycles	Time between last ICI and LT (weeks)	Rejection	Outcome (successful LT at last FU)
ICI—monotherapy (anti-PD-1/PD-L1)						
32	26/ 6	58 (30–71)*	8 (1–44)*	4.3 (0.1–94)*	31.3% (10/32)	Alive 96.8% (31/32)
ICI—combination therapy (anti-PD-1/PD-L1 + anti-VEGF/TKIs)						
26	24/ 2	51 (37–68)*	6 (1–27)*	6.1 (1–32.7)*	38.5% (10/26)	Alive 96.2% (25/26)
ICI—dual immunotherapy (anti-PD-1/PD-L1 + anti-CTLA-4)						
2	2/0	60.5 (58–63)*	7.5 (7–8)*	4.65 (0.3–9)*	0% (0/2)	Alive 100% (2/2)
Total						
61	53/8	56 (30–71)*	7 (1–44)*	5 (0.1–94)*	34.4% (21/61)	Alive 96.7% (59/61)

HCC: hepatocellular carcinoma

*Median (range)

of post-LT rejection, it is not associated with increased immune-related graft loss and patient death. Short intervals (within 3 months) between ICIs and LT may increase the incidence of liver injury, including graft rejection. Therefore, the intervals between the last ICIs treatment and LT should be chosen appropriately. A multicenter prospective clinical trial mandates a 6-week washout period [87]. So far there is no definitive study to examine the "window" for the use of ICIs before and after LT. Therefore, the feasibility and optimal timing of LT after receiving ICIs need to be further investigated in the setting of clinical trial.

Despite the use of restrictive criteria, post-transplant HCC recurrence is still high, affecting between 8 and 20% of cases, usually within 2–3 years [118, 119]. Before the availability of ICIs, both sorafenib and lenvatinib had been shown to significantly prolong the survival of post-LT patients with HCC recurrence evaluated [120, 121]. Recently, several case series have suggested that ICIs may be used successfully in this population, although graft rejection has been reported (Table 7) [101–117]. For those patients with high immunological risk factors (transplantation performed less than 12 months ago, young women with autoimmune disease, preformed or de novo donor-specific antibodies (DSA) and previous episodes of rejection) [122], the use of ICIs is strongly discouraged. On the other hand, graft-negative PD-L1 expression in HCC recurrent patient, in whom other anti-tumor therapy is ineffective, might be considered for ICIs salvage therapy [114].

Recommendation 7

ICI-based systemic therapy can be used in the pre-transplant setting and transplant can be performed after a 6-week washout period for patients who meet local transplant criteria.

[Grading: evidence_II__ recommendation__2__].

Recommendation 8

Post-transplant, both sorafenib and lenvatinib can be used to treat HCC recurrence.

[Grading: evidence_II__ recommendation__2__].

ICIs may be used with extreme caution as salvage therapy for HCC recurrence in liver transplant recipients after weighing the individual immunological risk and oncological benefit.

[Grading: evidence_III__ recommendation__3__].

Future development

Due to the complexity in the management of HCC, with its different treatment modalities and diversity in tumor response, artificial intelligence (AI) with machine and deep learning has been proposed to play a future role [123]. Specifically, there are cumulating evidences suggesting that the application of deep learning with the date recorded by an electronic health system, imaging modalities, histopathology and biomarkers can improve the selection of therapy to enhance patient survival and quality of life [124–127]. However, to fully utilize AI in the clinical management of HCC patients to be treated with systemic therapy, one needs to develop robust approaches for structured data collection, sharing and storage, and to demonstrate the reliability and robustness of models. To this end, the APASL oncology working party has initiated A-hoc (**APASL** Hepatology/Oncology Consortium) study for HCC in Asia–Pacific region [128]. These type of registries will allow one to capturing real-world data regarding treatment response and irAE in patient populations that are underrepresented in clinical trials should be undertaken. In the near future, AI will play a pivotal role in assisting MDT in the management of patients with HCC to be treated with systemic therapy.

Discussion

In 2024 and beyond, one is expected to see an increasing use of systemic therapy, especially those related to the ICIs in the management of HCC for disease progression in patients with unresectable HCC, TACE-treated patients and HCC recurrence after local ablative surgery or radiofrequency ablation and liver transplantation. With the proper selection and use of systemic therapy, preferably with MDT approach, new opportunities are available to prolong the progression-free and overall survival with good quality life. In the future, we should aim not just to control disease progression, but bring "cure" to our patients with HCC. More clinical research is also called upon to understand the basis of diverse response to systemic therapy, so that we can tailor therapy to our HCC patients. Very importantly, one also needs to elucidate the mechanisms of irAE (i.e., events mediated by antibodies, T cells, and cytokines) to develop more precise treatments for irAE.

With more clinical, radiological, histological and omics data, aided with the proper use of AI, especially machine and deep learning, the best up-to-date management could be brought to our patients. With the rapid development in the understanding of host immunity in the control of HCC, one is expected to see a new wave of immunotherapies available for the management of unresectable HCC. Since the burden of HCC in the Asian region is the highest, APASL will stay alert and provide updated clinical practice guidelines to aid our fellow colleagues and the global community who are managing HCC.

Table 7 Case reports on the use of ICI-based therapy in HCC recurrence patients post-LT

Case no.	Sex	Age	Time between LT and ICI-based therapy (years)	Treatment before ICIs	ICIs	Cycles	Immunosuppression drugs	Rejection	Outcome	Author (year of publication)
1	M	41	1	TACE/MWA	Nivolumab	15	Tacrolimus	No	PD	De Toni (2017) [101]
2	M	20	4	Sorafenib/ Capecitabine	Nivolumab	2	Sirolimus	Yes* (17 days after first ICIs)	Death (38 days after first ICIs)	Friend (2017) [102]
3	M	14	3	Gemcitabine/ Oxaliplatin	Nivolumab	1	Tacrolimus	Yes* (7 days after first ICIs)	Death (35 days after first ICIs)	Friend (2017) [102]
4	M	70	8	Sorafenib/ capecitabine/ external bean radiation	Pembrolizumab	4	Tacrolimus	No	PD	Varkaris (2017) [103]
5	M	57	2.7	Sorafenib	Nivolumab	2	Tacrolimus	No	PD	DeLeon (2018) [104]
6	M	56	7.8	Sorafenib	Nivolumab	2	Mycophenolate mofetil, sirolimus	No	PD	DeLeon (2018) [104]
7	M	35	3.7	Sorafenib	Nivolumab	2	Tacrolimus	No	PD	DeLeon (2018) [104]
8	M	64	1.2	Sorafenib	Nivolumab	1	Tacrolimus	No	N.A	DeLeon (2018) [104]
9	M	68	1.1	Sorafenib	Nivolumab	2	Sirolimus	Yes*	N.A	DeLeon (2018) [104]
10	F	53	3	Sorafenib	Nivolumab	1	Everolimus, mycophenolate mofetil, methylprednisolone, prednisone, tacrolimus	Yes (7 days after first ICIs)	Death (25 days after first ICIs)	Gassmann (2018) [105]
11	M	61	2	Sorafenib	Nivolumab	2	Corticosteroids, prednisone	Yes	N.A	Gomez (2018) [106]
12	M	57	4	Sorafenib	Pembrolizumab	15	Tacrolimus, mycophenolate mofetil	No	CR	Rammohan (2018) [107]
13	M	64	2	Sorafenib, carboplatin/ gemcitabine, combination folinic acid, fluorouracil and oxaliplatin	Nivolumab	3	Steroids, tacrolimus	Yes (2 months after first ICIs)	Death (2 months after first ICIs)	Kumar (2018) [108]

Table 7 (continued)

Case no.	Sex	Age	Time between LT and ICI-based therapy (years)	Treatment before ICIs	ICIs	Cycles	Immunosuppression drugs	Rejection	Outcome	Author (year of publication)
14	M	70	3	Sorafenib, gemcitabine, oxaliplatin	Nivolumab	4	Tacrolimus	No	PD	Al Jarroudi (2020) [109]
15	F	62	2	Sorafenib, regorafenib, 5-FU, oxaliplatin	Nivolumab	5	Tacrolimus	No	SD	Al Jarroudi (2020) [109]
16	M	66	2	Sorafenib, regorafenib, gemcitabine, oxaliplatin	Nivolumab	6	Tacrolimus	No	PD	Al Jarroudi (2020) [109]
17	F	62	2	TACE	Nivolumab	26	Tacrolimus, mycophenolate mofetil, prednisone	No	CR	Amjad (2020) [100]
18	F	54	7	Sorafenib, nanoknife, ethanol ablation	Ipilimumab	7	Tacrolimus, everolimus	No	CR	Pandey (2020) [101]
19	M	54	4	Sorafenib, RFA, lenvatinib	Camrelizumab	5	Sirolimus	No	CR	Qiu (2020) [112]
20	M	54	2	Sorafenib, mFOLFOX, gemcitabine, TACE	Nivolumab	12	Tacrolimus	No	PD	Zhuang (2020) [113]
21	M	46	1	Sorafenib, lenvatinib	Toripalimab	7	Sirolimus	No	PD	Shi (2021) [114]
22	M	46	1	TACE, PEI, resection, sorafenib, lenvatinib	Toripalimab	3	Sirolimus	No	SD	Shi (2021) [114]
23	M	62	1	Sorafenib, lenvatinib, TACE, PEI	Toripalimab	2	Sirolimus	No	Response not applicable	Shi (2021) [114]
24	M	66	1	Sorafenib, lenvatinib, regorafenib	Toripalimab	1	Sirolimus	No	Response not applicable	Shi (2021) [114]

Table 7 (continued)

Case no.	Sex	Age	Time between LT and ICI-based therapy (years)	Treatment before ICIs	ICIs	Cycles	Immunosuppression drugs	Rejection	Outcome	Author (year of publication)
25	M	35	4	Surgical, gemcitabine, oxaliplatin, fluorouracil, IFN alfa-2b	Atezolizumab + bevacizumab	15	N.A	No	PD	Ben Khaled (2021) [115]
26	M	53	N.A	Sorafenib, resection, external radiotherapy	Nivolumab, atezolizumab + bevacizumab	18 (11 + 7)	N.A	No	PD	Yang (2022) [116]
27	M	55	1	RFA, TACE, external radiotherapy	Atezolizumab + bevacizumab	2	N.A	No	PD	Yang (2022) [116]
28	F	53	2	Sorafenib, resection	Nivolumab	1	Sirolimus	No	PD	Di Marco (2023) [117]
29	M = 3 /F = 1	58.5 ± 8.5	1.8 ± 2.1	Sorafenib, resection	Nivolumab + bevacizumab	16 ± 4.5	Sirolimus, methylprednisolone, prednisolone	1	SD	Di Marco (2023) [117]
Total *n* = 32	**M (*n* = 26)/ F (*n* = 6)**	**56 (14–70)#**	**2 (1–8)#**			**3 (1–26)#**		**Rejection rate 18.8% (6/32)**		

HCC hepatocellular carcinoma

*Immunofluorescence analysis for PD-1 and PD-L1 expression of transplanted liver was positive

#Median (range)

Acknowledgements We acknowledge the contributions of Professor Masatoshi KUDO (Department of Gastroenterology and Hepatology, Kindai University of Medicine, Osaka-Sayama, Osaka, Japan), Professor Masafumi IKEDA (Department of Hepatobiliary & Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan) and Dr. Filza ASLAM (APAC Disease Area Network, HCC) for formulations of this CPG.

Author contributions GL, SS and MO contributed to the design of the work, drafting of the manuscript and critical revision. CCY, MR, HCL, MO and SKS performed critical revision. All authors have reviewed and agreed on the manuscript.

Funding The authors declare that no funds, grants or other support was received during the preparation of this manuscript.

Data availability This article does not have separate data to provide.

Declarations

Conflict of interest George LAU reported lecture fees from AstraZeneca. Shuntaro OBI reported research grants from Eisai, Otsuka pharmaceutical, and Mochida pharmaceutical. Ryosuke TATEISHI reported lecture fees from Abbvie, AstraZeneca, Chugai, Eisai, Gilead Sciences, MSD and Takeda. Sadahisa OGASAWARA reported honoraria from Bayer, Eisai, Eli Lilly, consulting or advisory fees from Bayer, Eisai, Merck & Co. Inc., Chugai Pharma, Eli Lilly, and research grants from Bayer and Eisai. Naoya KATO reported honoraria payment from Bayer and Chugai; research funding from Bayer, Chugai, and Roche. Stephen L CHAN reported consulting or advisory board fees from AstraZeneca, Eisai, and MSD; reports being an invited speaker for AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, IPSEN, MSD, and Roche; and research funding from Bayer, Eisai, IPSEN, MSD, and Sirtex Medical. Yoshiyuki UENO reported honoraria payment from Chugai and Eisai. Ann-Lii CHENG reported consulting or advisory board fees from AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Eisai, Genentech/Roche, Ipsen, IQVIA, MSD, Ono Pharmaceutical, and Roche; and honoraria from AstraZeneca, Bayer, Eisai, and Genentech/Roche. Yock Young DAN reported consulting or advisory board fees from Boehringer Ingelheim, MSD, Norvo Nordisk, Roche, and research grants from MSD, Norvo Nordisk, Perspectum, Siemens. Jeong Min LEE reported lecture fees from Samsung Medison, GE Healthcare, Philips Healthcare, Starmed, and research grants from Samsung Medison, Siemens Healthineers, Philips Healthcare, GE Healthcare, Bayer, Guerbet, CMS, Canon Healthcare, Dongkuk Pharma. Diana A. Payawal reported lecture, consulting or advisory board fees from Gilead Sciences, Mylan Pharmaceuticals, Echosense, Getz and Abbott. Ekaphop SIRACHAINAN reported honoraria payment from MSD, Sanofi/Aventis, Merck, Amgen, Roche, Mundipharma, AstraZeneca, LF Asia, Diethelm Keller Group, Bristol Myers Squibb, Boehringer Ingelheim, Taiho Pharmaceutical, Dr Reddy's Laboratories, Zuellig Pharma, Meda Pharmaceuticals, Pfizer, Novo Nordisk, Novartis. Tawesak Tanwandee reported research grants from Bristol Myers Squibb and Merck. Masao Omata reported lecture, consulting or advisory board fees from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Otsuka, Astellas, Gilead Sciences, Chugai, Mitsubishi Tanabe, Kyorin, Merck Sharp and Dohme, Dainippon Sumitomo, Vertex Pharmaceuticals, Takeda, Merck Serono, and Zeria. Jian ZHOU, Shukui QIN, Haitao ZHAO, Motoyuki OTSUKA, Jacob GEORGE, Pierce KH CHOW, Jianqiang CAI, Shuichiro SHIINA, Osamu YOKOSUKA, Kyoko OURA, Thomas YAU, Ming KUANG, Minshan CHEN, Gregory CHENG, Wan-Long CHUANG, Oidov BAATARKHUU, Feng BI, Rino A GANI, Atsushi TANAKA, Wasim JAFRI, Ji-Dong JIA, Jia-Horng KAO, Kiyoshi HASEGAWA, Patrick LAU, Jun LIANG, Zhenwen LIU, Yinying LU, Hongming PAN, Salimur RAHMAN, Jinsil SEONG, Feng SHEN, Gamal SHIHA, Tianqiang SONG, Hui-Chuan SUN, Tsutomu MASAKI, Lai WEI, Jin Mo YANG, Jose D SALLANO, Yanqiao ZHANG,, A Kadir DOKMECI, Shu-sen ZHENG, Jia FAN, Sheung-Tat FAN and Shiv Kumar Sarin reported that they have no conflict of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

References

1. Omata M, Lesmana LA, Tateishi R, Chen PJ, Lin SM, Yoshida H, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int. 2010;4:439–474
2. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia–Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017;11(4):317–370
3. Su GL, Altayar O, O'Shea R, Shah R, Estfan B, Wenzell C, et al. AGA clinical practice guideline on systemic therapy for hepatocellular carcinoma. Gastroenterology. 2022;162(3):920–934
4. Yang C, Zhang H, Zhang L, Zhu AX, Bernards R, Qin W, et al. Evolving therapeutic landscape of advanced hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2023;20(4):203–222
5. Llovet JM, Pinyol R, Kelley RK, El-Khoueiry A, Reeves HL, Wang XW, et al. Molecular pathogenesis and systemic therapies for hepatocellular carcinoma. Nat Cancer. 2022;3(4):386–401
6. Gordan JD, Kennedy EB, Abou-Alfa GK, Beal E, Finn RS, Gade TP, et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline update. J Clin Oncol. 2024;19:JCO2302745. https://doi.org/10.1200/JCO.23.02745. (**Epub ahead of print. PMID: 38502889**)
7. Zhang CH, Cheng Y, Zhang S, Fan J, Gao Q. Changing epidemiology of hepatocellular carcinoma in Asia. Liver Int. 2022;42(9):2029–2041
8. Chen J, Lau G. HBV "Viral Elimination" in the Asia–Pacific region: current status and challenges. Clin Liver Dis (Hoboken). 2024;23(1):e0132
9. Singal AG, Kanwal F, Llovet JM. Global trends in hepatocellular carcinoma epidemiology: implications for screening, prevention and therapy. Nat Rev Clin Oncol. 2023;20(12):864–884
10. Kim DS, Yoon YI, Kim BK, et al. Asian Pacific association for the study of the liver clinical practice guidelines on liver transplantation. Hepatol Int. 2024;18:299–383
11. Tsilimigras DI, Bagante F, Moris D, et al. Recurrence patterns and outcomes after resection of hepatocellular carcinoma within and beyond the barcelona clinic liver cancer criteria. Ann Surg Oncol. 2020;27:2321–2331
12. Shim JH, Jun MJ, Han S, Lee YJ, Lee SG, Kim KM, et al. Prognostic nomograms for prediction of recurrence and survival after curative liver resection for hepatocellular carcinoma. Ann Surg. 2015;261(5):939–946
13. Sarin SK, Kumar M, Eslam M, George J, Al Mahtab M, Akbar SMF, et al. Liver diseases in the Asia–Pacific region: a lancet gastroenterology & hepatology commission. Lancet Gastroenterol Hepatol. 2020;5(2):167–228
14. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185

countries. CA Cancer J Clin. 2024. https://doi.org/10.3322/caac.21834. (**Epub ahead of print. PMID:38572751**)
15. Xie DY, Zhu K, Ren ZG, Zhou J, Fan J, Gao Q. A review of 2022 Chinese clinical guidelines on the management of hepatocellular carcinoma: updates and insights. Hepatobiliary Surg Nutr. 2023;12(2):216–228
16. Crane H, Eslick GD, Gofton C, Shaikh A, Cholankeril G, Cheah M, et al. Global prevalence of MAFLD-related hepatocellular carcinoma: A systematic review and meta-analysis. Clin Mol Hepatol. 2024. https://doi.org/10.3350/cmh.2024.0109
17. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163–1173
18. Qin S, Bi F, Gu S, Bai Y, Chen Z, Wang Z, et al. Donafenib Versus Sorafenib in first-line treatment of unresectable or metastatic hepatocellular carcinoma: a randomized, open-label, parallel-controlled phase II-III Trial. J Clin Oncol. 2021;39(27):3002–3011
19. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020;382(20):1894–1905
20. Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2022;76(4):862–873
21. Ren Z, Xu J, Bai Y, Xu A, Cang S, Du C, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2–3 study. Lancet Oncol. 2021;22(7):977–990
22. Qin S, Chan SL, Gu S, Bai Y, Ren Z, Lin X, et al. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study. Lancet. 2023;402(10408):1133–1146
23. Qin S, Kudo M, Meyer T, Bai Y, Guo Y, Meng Z, et al. Tislelizumab vs Sorafenib as first-line treatment for unresectable hepatocellular carcinoma: a phase 3 randomized clinical Trial. JAMA Oncol. 2023;9(12):1651–1659
24. Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM Evid. 2022;1(8):EVIDoa2100070. https://doi.org/10.1056/EVIDoa2100070
25. Galle PR, Decaens T, Kudo M, Qin S, Fonseca LD, Sangro B, Karachiwala H, Park JW, Gane E, Pinter M, Tai D, Santoro A, Pizarro G, Chiu CF, Schenker M, He A, Wang Q, Stromko C, Hreiki J, Yau T. Nivolumab (NIVO) plus ipilimumab (IPI) vs lenvatinib (LEN) or sorafenib (SOR) as first-line treatment for unresectable hepatocellular carcinoma (uHCC): First results from CheckMate 9DW. 2024 ASCO Annual Meeting, LBA4008.
26. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, 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(10064):56–66
27. Qin S, Chen Z, Fang W, Ren Z, Xu R, Ryoo BY, et al. Pembrolizumab versus placebo as second-line therapy in patients from asia with advanced hepatocellular carcinoma: a randomized, double-blind. Phase III Trial J Clin Oncol. 2023;41(7):1434–1443
28. Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med. 2018;379(1):54–63
29. Qin S, Li Q, Gu S, Chen X, Lin L, Wang Z, et al. Apatinib as second-line or later therapy in patients with advanced hepatocellular carcinoma (AHELP): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol. 2021;6(7):559–568
30. Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(2):282–296
31. Lencioni R, Kudo M, Erinjeri J, Qin S, Ren Z, Chan S, et al. EMERALD-1: A phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization. J Clin Oncol. 2024. https://doi.org/10.1200/JCO.2024.42.3_suppl.LBA432
32. Qin S, Chen M, Cheng AL, Kaseb AO, Kudo M, Lee HC, et al. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2023;402(10415):1835–1847
33. Haber PK, Puigvehí M, Castet F, Lourdusamy V, Montal R, Tabrizian P, et al. Evidence-based management of hepatocellular carcinoma: systematic review and meta-analysis of randomized controlled trials (2002–2020). Gastroenterology. 2021;161(3):879–898
34. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6
35. Cohen GS, Black M. Multidisciplinary management of hepatocellular carcinoma: a model for therapy. J Multidiscip Healthc. 2013;9(6):189–195
36. Brown ZJ, Tsilimigras DI, Ruff SM, Mohseni A, Kamel IR, Cloyd JM, et al. Management of hepatocellular carcinoma: a review. JAMA Surg. 2023;158(4):410–420
37. [Chinese multidisciplinary expert consensus on combined immunotherapy for hepatocellular carcinoma(2023 version)]. Zhonghua Gan Zang Bing Za Zhi. 2023;31(1):16–34. Chinese.
38. [Expert consensus on multidisciplinary diagnosis and treatment of precancerous lesions of hepatocellular carcinoma (2020 edition)]. Zhonghua Gan Zang Bing Za Zhi. 2020;28(1):14–20. Chinese.
39. Oh JH, Sinn DH. Multidisciplinary approach for hepatocellular carcinoma patients: current evidence and future perspectives. J Liver Cancer. 2024;24(1):47–56
40. Sinn DH, Choi G-S, Park HC, Kim JM, Kim H, Song KD, et al. Multidisciplinary approach is associated with improved survival of hepatocellular carcinoma patients. PLoS ONE. 2019;14(1):e0210730
41. Yopp AC, Mansour JC, Beg MS, Arenas J, Trimmer C, Reddick M, et al. Establishment of a multidisciplinary hepatocellular carcinoma clinic is associated with improved clinical outcome. Ann Surg Oncol. 2014;21(4):1287–1295
42. Yang L, Yan C, Wang J. Effect of multi-disciplinary team care program on quality of life, anxiety, and depression in hepatocellular carcinoma patients after surgery: a randomized, controlled study. Front Surg. 2023;6(9):1045003
43. Agarwal PD, Phillips P, Hillman L, Lucey MR, Lee F, Mezrich JD, et al. Multidisciplinary management of hepatocellular carcinoma improves access to therapy and patient survival. J Clin Gastroenterol. 2017;51(9):845–849
44. Seif El Dahan K, Reczek A, Daher D, Rich NE, Yang JD, Hsiehchen D, et al. Multidisciplinary care for patients with HCC: a systematic review and meta-analysis. Hepatol Commun. 2023. https://doi.org/10.1097/HC9.0000000000000143
45. Lim KC, Chow PK, Allen JC, Siddiqui FJ, Chan ES, Tan SB. Systemic review of outcomes of liver resection for early

hepatocellular carcinoma within the Milan criteria. Br J Surg. 2012;99:1622–1629
46. Angeli-Pahim I, Chambers A, Duarte S, Zarrinpar A. Current trends in surgical management of hepatocellular carcinoma. Cancers (Basel). 2023;15(22):5378. https://doi.org/10.3390/cancers15225378
47. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022;76(3):681–693
48. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236
49. Hasegawa K, Takemura N, Yamashita T, Watadani T, Kaibori M, Kubo S, et al. Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2021 version (5th JSH-HCC Guidelines). Hepatol Res. 2023;53(5):383–390
50. Korean Liver Cancer Association (KLCA), National Cancer Center (NCC) Korea. KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. Clin Mol Hepatol. 2022;28(4):583–705
51. Kumar A, Acharya SK, Singh SP, Duseja A, Madan K, Shukla A, et al. 2023 Update of Indian national association for study of the liver consensus on management of intermediate and advanced hepatocellular carcinoma the puri III recommendations. J Clin Exp Hepatol. 2024;14(1):101269
52. Kudo M, Kawamura Y, Hasegawa K, Tateishi R, Kariyama K, Shiina S, et al. Management of hepatocellular carcinoma in Japan: JSH Consensus Statements and Recommendations 2021 Update. Liver Cancer. 2021;10:181–223
53. Association KLC, (KLCA) and National Cancer Center (NCC) Korea,. KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. Clin Mol Hepatol. 2022;2022(28):583–705
54. Xie D, Shi J, Zhou J, Fan J, Gao Q. Clinical practice guideline and real-life practice in hepatocellular carcinoma: Chinese perspective. Clin Mol Hepatol. 2022. https://doi.org/10.3350/cmh.2022.0402
55. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–90
56. Cheng AL, Guan Z, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: subset analyses of the phase III Sorafenib Asia–Pacific trial. Eur J Cancer. 2012;48(10):1452–1465
57. Lau G, Abou-Alfa GK, Cheng AL, Sukeepaisarnjaroen W, Dao TV, Kang YK, et al. Outcomes in the Asian subgroup of the phase III randomised HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. J Hepatol. 2024;S0168–8278(24):02424–02433
58. Sangro B, Chan SL, Kelley RK, Lau G, Kudo M, Sukeepaisarnjaroen W, et al. Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. Ann Oncol. 2024;35(5):448–457
59. Lau G, Rimassa L, Chan SL, Sangro B, Kudo M, Breder V, Varela M, Crysler O, Bouattour M, Dao TV, Faccio A, Furuse J, Jeng LB, Kang YK, Kelley RK, Paskow MJ, Makowsky M, Ran D, Negro A, Abou-Alfa GK. Five-year overall survival and overall survival by tumour response from the global population and Asian subgroup of the Phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. CSCO 2024 (in press)
60. Costa F, Wiedenmann B, Roderburg C, Mohr R, Abou-Alfa GK. Systemic treatment in patients with Child-Pugh B liver dysfunction and advanced hepatocellular carcinoma. Cancer Med. 2023;12(13):13978–13990
61. McNamara MG, Slagter AE, Nuttall C, et al. Sorafenib as first-line therapy in patients with advanced Child-Pugh B hepatocellular carcinoma-a meta-analysis. Eur J Cancer. 2018;105:1–9
62. Xie E, Yeo YH, Scheiner B, Zhang Y, Hiraoka A, Tantai X, et al. Immune checkpoint inhibitors for child-pugh class B advanced hepatocellular carcinoma: a systematic review and meta-analysis. JAMA Oncol. 2023;9(10):1423–1431
63. 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(18):3234–3241
64. 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(10):1323–1333
65. Fessas P, Kaseb A, Wang Y, Saeed A, Szafron D, Jun T, et al. Post-registration experience of nivolumab in advanced hepatocellular carcinoma: an international study. J Immunother Cancer. 2020;8(2):e001033. https://doi.org/10.1136/jitc-2020-001033
66. Yoo C, Kim JH, Ryu MH, Park SR, Lee D, Kim KM, et al. Clinical outcomes with multikinase inhibitors after progression on first-line atezolizumab plus bevacizumab in patients with advanced hepatocellular carcinoma: a multinational multicenter retrospective study. Liver Cancer. 2021;10(2):107–114
67. de Castro T, Jochheim LS, Bathon M, Welland S, Scheiner B, Shmanko K, et al. Atezolizumab and bevacizumab in patients with advanced hepatocellular carcinoma with impaired liver function and prior systemic therapy: a real-world experience. Ther Adv Med Oncol. 2022;26(14):17588359221080298. https://doi.org/10.1177/17588359221080298
68. Tanaka T, Hiraoka A, Tada T, Real-life Practice Experts for HCC (RELPEC) Study Group, HCC 48 Group, et al. Therapeutic efficacy of atezolizumab plus bevacizumab treatment for unresectable hepatocellular carcinoma in patients with Child-Pugh class A or B liver function in real-world clinical practice. Hepatol Res. 2022;52(9):773–783
69. Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, et al. Immune-related adverse events of checkpoint inhibitors. Nat Rev Dis Primers. 2020;6(1):38
70. Wang SJ, Dougan SK, Dougan M. Immune mechanisms of toxicity from checkpoint inhibitors. Trends Cancer. 2023;9(7):543–553
71. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378(2):158–168
72. Yin Q, Wu L, Han L, Zheng X, Tong R, Li L, et al. Immune-related adverse events of immune checkpoint inhibitors: a review. Front Immunol. 2023;25(14):1167975
73. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714–1768
74. Lau G, Cheng AL, Sangro B, Kudo M, Kelly RK, Tak WY, Gasbarrini A, Lim HY, Makowsky M, Negro A. Outcomes by occurrence of immune-mediated adverse events in HIMALAYA study in unresectable HCC. APASL Annual Meeting 2024, O-0618
75. Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, et al. Management of immune-related adverse events

in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol. 2021;39(36):4073–4126
76. Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(12):1217–1238
77. Lim KC, Chow PKH, Allen JC, Siddiqui FJ, Chan ESY, Tan SB. Systematic review of outcomes of liver resection for early hepatocellular carcinoma within the Milan criteria. Br J Surg. 2012;99(12):1622–1629
78. Li L, Zhang J, Liu X, Li X, Jiao B, Kang T. Clinical outcomes of radiofrequency ablation and surgical resection for small hepatocellular carcinoma: a meta-analysis. J Gastroenterol Hepatol. 2012;27(1):51–58
79. Donne R, Lujambio A. The liver cancer immune microenvironment: Therapeutic implications for hepatocellular carcinoma. Hepatology. 2023;77(5):1773–1796
80. Lei JY, Wang WT, Yan LN. Up-to-seven criteria for hepatocellular carcinoma liver transplantation: a single center analysis. World J Gastroenterol. 2013;19(36):6077–6083
81. Shimamura T, Goto R, Watanabe M, Kawamura N, Takada Y. Liver transplantation for hepatocellular carcinoma: how should we improve the thresholds? Cancers (Basel). 2022;14(2):419
82. Toniutto P, Fumolo E, Fornasiere E, Bitetto D. Liver transplantation in patients with hepatocellular carcinoma beyond the milan criteria: a comprehensive review. J Clin Med. 2021;10(17):3932
83. Chen J, Shen T, Li J, Ling S, Yang Z, Wang G, et al. Clinical practice guideline on liver transplantation for hepatocellular carcinoma in China. Chin Med J (Engl). 2022;135(24):2911–2913
84. Tabrizian P, Holzner ML, Mehta N, Halazun K, Agopian VG, Yao F, et al. Ten-year outcomes of liver transplant and downstaging for hepatocellular carcinoma. JAMA Surg. 2022;157(9):779–788
85. Katariya NN, Lizaola-Mayo BC, Chascsa DM, Giorgakis E, Aqel BA, Moss AA, et al. Immune checkpoint inhibitors as therapy to down-stage hepatocellular carcinoma prior to liver transplantation. Cancers (Basel). 2022;14(9):2056
86. Wang T, Chen Z, Liu Y, Jia Y, Ju W, Chen M, et al. Neoadjuvant programmed cell death 1 inhibitor before liver transplantation for HCC is not associated with increased graft loss. Liver Transpl. 2023;29(6):598–606
87. Tabrizian P, Abdelrahim M, Schwartz M. Immunotherapy and transplantation for hepatocellular carcinoma. J Hepatol. 2024;80(5):822–825
88. Nordness MF, Hamel S, Godfrey CM, Shi C, Johnson DB, Goff LW, 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(3):879–883
89. Cui CX, Yang LX, Wang Y, Huang JF, Huang XW, Fan J, et al. The effect of PD-1 inhibitor treatment before liver transplantation on posttransplant rejection in liver cancer patients. Chin J Clin Med. 2020;27(3):444–447
90. Schwacha-Eipper B, Minciuna I, Banz V, Dufour JF. Immunotherapy as a downstaging therapy for liver transplantation. Hepatology. 2020;72(4):1488–1490
91. Sogbe M, López-Guerra D, Blanco-Fernández G, Sangro B, Narváez-Rodriguez I. Durvalumab as a successful downstaging therapy for liver transplantation in hepatocellular carcinoma: the importance of a washout period. Transplantation. 2021;105(12):e398–e400
92. Tabrizian P, Florman SS, Schwartz ME. PD-1 inhibitor as bridge therapy to liver transplantation? Am J Transplant. 2021;21(5):1979–1980
93. Aby ES, Lake JR. Immune checkpoint inhibitor therapy before liver transplantation-case and literature review. Transplant Direct. 2022;8(4):e1304
94. Schnickel GT, Fabbri K, Hosseini M, Misel M, Berumen J, Parekh J, et al. Liver transplantation for hepatocellular carcinoma following checkpoint inhibitor therapy with nivolumab. Am J Transplant. 2022;22(6):1699–1704
95. Rudolph M, Shah SA, Quillin R, Lemon K, Olowokure O, Latif T, et al. Immune checkpoint inhibitors in liver transplant: a case series. J Gastrointest Oncol. 2023;14(2):1141–1148
96. Chen GH, Wang GB, Huang F, Qin R, Yu XJ, Wu RL, et al. Pretransplant use of toripalimab for hepatocellular carcinoma resulting in fatal acute hepatic necrosis in the immediate postoperative period. Transpl Immunol. 2021;66:101386
97. Qiao ZY, Zhang ZJ, Lv ZC, Tong H, Xi ZF, Wu HX, et al. Neoadjuvant programmed cell death 1 (PD-1) inhibitor treatment in patients with hepatocellular carcinoma before liver transplant: a cohort study and literature review. Front Immunol. 2021;19(12):653437
98. Abdelrahim M, Esmail A, Umoru G, Westhart K, Abudayyeh A, Saharia A, et al. Immunotherapy as a neoadjuvant therapy for a patient with hepatocellular carcinoma in the pretransplant setting: a case report. Curr Oncol. 2022;29(6):4267–4273
99. Ohm H, Khwaja R, Karachiwala H. Immunotherapy before liver transplant in unresectable hepatocellular carcinoma: a case report. J Gastrointest Oncol. 2023;14(6):2644–2649
100. Lizaola-Mayo BC, Mathur AK, Borad MJ, Jadlowiec CC, Lam-Himlin DM, Corey RL, et al. Immunotherapy as a downstaging tool for liver transplantation in hepatocellular carcinoma. Am J Gastroenterol. 2021;116(12):2478–2480
101. De Toni EN, Gerbes AL. Tapering of immunosuppression and sustained treatment with nivolumab in a liver transplant recipient. Gastroenterology. 2017;152(6):1631–1633
102. Friend BD, Venick RS, McDiarmid SV, Zhou X, Naini B, Wang H, 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. https://doi.org/10.1002/pbc.26682
103. Varkaris A, Lewis DW, Nugent FW. Preserved liver transplant after PD-1 pathway inhibitor for hepatocellular carcinoma. Am J Gastroenterol. 2017;112(12):1895–1896
104. DeLeon TT, Salomao MA, Aqel BA, Sonbol MB, Yokoda RT, Ali AH, 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(6):1054–1062
105. Gassmann D, Weiler S, Mertens JC, Reiner CS, Vrugt B, Nägeli M, et al. Liver allograft failure after nivolumab treatment-a case report with systematic literature research. Transpl Direct. 2018;4(8):e376
106. Gomez P, Naim A, Zucker K, Wong M. A case of hepatocellular carcinoma (HCC) immunotherapy inducing liver transplant rejection. Am J Gastroenterology. 2018;113:S1347
107. Rammohan A, Reddy MS, Farouk M, Vargese J, Rela M. Pembrolizumab for metastatic hepatocellular carcinoma following live donor liver transplantation: the silver bullet? Hepatology. 2018;67(3):1166–1168
108. Kumar S. Nivolumab-induced severe allograft rejection in recurrent post- transplant hepatocellular carcinoma. Am J Gastroenterol. 2019;114:S1251–S1252
109. Al Jarroudi O, Ulusakarya A, Almohamad W, Afqir S, Morere JF. Anti-Programmed cell death protein 1 (PD-1) immunotherapy for metastatic hepatocellular carcinoma after liver transplantation: a report of three cases. Cureus. 2020;12(10):e11150
110. Amjad W, Kotiah S, Gupta A, Morris M, Liu L, Thuluvath PJ. Successful treatment of disseminated hepatocellular carcinoma after liver transplantation with nivolumab. J Clin Exp Hepatol. 2020;10(2):185–187
111. Pandey A, Cohen DJ. Ipilumumab for hepatocellular cancer in a liver transplant recipient, with durable response,

tolerance and without allograft rejection. Immunotherapy. 2020;12(5):287–292
112. Qiu J, Tang W, Du C. Immune checkpoint inhibitors in patients with recurrent hepatocellular carcinoma after liver transplantation: A case report and literature review. Curr Cancer Drug Targets. 2020;20(9):720–727
113. Zhuang L, Mou HB, Yu LF, Zhu HK, Yang Z, Liao Q, et al. Immune checkpoint inhibitor for hepatocellular carcinoma recurrence after liver transplantation. Hepatobiliary Pancreat Dis Int. 2020;19(1):91–93
114. Shi GM, Wang J, Huang XW, Huang XY, He YF, Ji Y, et al. Graft programmed death ligand 1 expression as a marker for transplant rejection following anti-programmed death 1 immunotherapy for recurrent liver tumors. Liver Transpl. 2021;27(3):444–449
115. Ben Khaled N, Roessler D, Reiter FP, Seidensticker M, Guba M, De Toni EN. Extending the use of Atezolizumab and Bevacizumab to a liver transplant recipient: need for a posttransplant registry. Liver Transpl. 2021;27(6):928–929
116. Yang Z, Sun J, Zhuang L, Mou H, Zheng S. Preliminary evaluation of atezolizumab plus bevacizumab as salvage treatment for recurrent hepatocellular carcinoma after liver transplantation. Liver Transpl. 2022;28(5):895–896
117. Di Marco L, Pivetti A, Foschi FG, D'Amico R, Schepis F, Caporali C, et al. Feasibility, safety, and outcome of second-line nivolumab/bevacizumab in liver transplant patients with recurrent hepatocellular carcinoma. Liver Transpl. 2023;29(5):559–563
118. Sapisochin G, Bruix J. Liver transplantation for hepatocellular carcinoma: Outcomes and novel surgical approaches. Nat Rev Gastroenterol Hepatol. 2017;14(4):203–217
119. Straś WA, Wasiak D, Łągiewska B, Tronina O, Hreńczuk M, Gotlib J, et al. Recurrence of hepatocellular carcinoma after liver transplantation: risk factors and predictive models. Ann Transplant. 2022;26(27):e934924
120. Li Z, Gao J, Zheng S, Wang Y, Xiang X, Cheng Q, et al. Therapeutic efficacy of sorafenib in patients with hepatocellular carcinoma recurrence after liver transplantation: a systematic review and meta-analysis. Turk J Gastroenterol. 2021;32(1):30–41
121. Chen YY, Chen CL, Lin CC, Wang CC, Liu YW, Li WF, et al. Efficacy and safety of lenvatinib in hepatocellular carcinoma patients with liver transplantation: a case-control study. Cancers (Basel). 2021;13(18):4584
122. Montano-Loza AJ, Rodríguez-Perálvarez ML, Pageaux GP, Sanchez-Fueyo A, Feng S. Liver transplantation immunology: Immunosuppression, rejection, and immunomodulation. J Hepatol. 2023;78(6):1199–1215
123. Kann BH, Thompson R, Thomas CR Jr, Dicker A, Aneja S. Artificial intelligence in oncology: current applications and future directions. Oncology (Williston Park). 2019;33(2):46–53
124. Liu JQ, Ren JY, Xu XL, Xiong LY, Peng YX, Pan XF, et al. Ultrasound-based artificial intelligence in gastroenterology and heJ. Gastroenterol. 2022;28(38):5530–5546
125. Zeng Q, Klein C, Caruso S, Maille P, Allende DS, Mínguez B, et al. Artificial intelligence-based pathology as a biomarker of sensitivity to atezolizumab-bevacizumab in patients with hepatocellular carcinoma: a multicentre retrospective study. Lancet Oncol. 2023;24(12):1411–1422
126. Sheikh A, Anderson M, Albala S, Casadei B, Franklin BD, Richards M, et al. Health information technology and digital innovation for national learning health and care systems. Lancet Digit Health. 2021;3(6):e383–e396
127. Mansur A, Vrionis A, Charles JP, Hancel K, Panagides JC, Moloudi F, et al. The role of artificial intelligence in the detection and implementation of biomarkers for hepatocellular carcinoma: outlook and opportunities. Cancers (Basel). 2023;15(11):2928
128. https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000057707

Authors and Affiliations

George Lau[1] · Shuntaro Obi[2] · Jian Zhou[3] · Ryosuke Tateishi[4] · Shukui Qin[5] · Haitao Zhao[6] · Motoyuki Otsuka[7] · Sadahisa Ogasawara[8] · Jacob George[9] · Pierce K. H. Chow[10] · Jianqiang Cai[11] · Shuichiro Shiina[12] · Naoya Kato[13] · Osamu Yokosuka[14] · Kyoko Oura[15] · Thomas Yau[16] · Stephen L. Chan[17] · Ming Kuang[18] · Yoshiyuki Ueno[19] · Minshan Chen[20] · Ann-Lii Cheng[21] · Gregory Cheng[22,58] · Wan-Long Chuang[23] · Oidov Baatarkhuu[24] · Feng Bi[25] · Yock Young Dan[26] · Rino A. Gani[27] · Atsushi Tanaka[28] · Wasim Jafri[29] · Ji-Dong Jia[30] · Jia-Horng Kao[31] · Kiyoshi Hasegawa[32] · Patrick Lau[33] · Jeong Min Lee[34] · Jun Liang[35] · Zhenwen Liu[36] · Yinying Lu[37] · Hongming Pan[38] · Diana A. Payawal[39] · Salimur Rahman[40] · Jinsil Seong[41] · Feng Shen[42] · Gamal Shiha[43,59,60,61] · Tianqiang Song[44] · Hui-Chuan Sun[45] · Tsutomu Masaki[15] · Ekaphop Sirachainan[46] · Lai Wei[47] · Jin Mo Yang[48] · Jose D. Sallano[49] · Yanqiao Zhang[50] · Tawesak Tanwandee[51] · AKadir Dokmeci[52] · Shu-sen Zheng[53] · Jia fan[54] · Sheung-Tat Fan[55] · Shiv Kumar Sarin[56] · Masao Omata[57]

✉ George Lau
gkklau@hnhmgl.com; gkklau@netvigator.com

[1] Humanity and Health Clinical Trial Center, Humanity and Health Medical Group, Zhongshan Hospital, Fudan University, Hong Kong SAR, Shanghai, China

[2] Department of Internal Medicine, Teikyo University Chiba Medical Center, Chiba, Japan

[3] Department of Liver Surgery and Transplantation, Key Laboratory of Carcinogenesis and Cancer Invasion (Fudan University), Ministry of Education, Shanghai Key Laboratory of Organ Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Zhongshan Hospital, Fudan University, Shanghai, China

[4] Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[5] Cancer Centre of Jinling Hospital, Nanjing University of Chinese Medicine, Nanjing, China

[6] Department of Liver Surgery, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

[7] Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama 700-8558, Japan

[8] Department of Gastroenterology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-Ku, Chiba 260-8670, Japan

[9] Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, Westmead, NSW 2145, Australia

[10] Department of HPB Surgery and Transplantation, Duke-NUS Medical School, National Cancer Center Singapore and Singapore General Hospital, Surgery Academic Clinical Program, Singapore, Singapore

[11] Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[12] Department of Gastroenterology, Juntendo University, 2-1-1, Hongo, Bunkyo-Ku, Tokyo 113-8421, Japan

[13] Department of Gastroenterology and Nephrology, Graduate School of Medicine, Chiba University, Chiba, Japan

[14] Department of Gastroenterology, Graduate School of Medicine, Chiba University, Chiba, Japan

[15] Department of Gastroenterology and Neurology, Faculty of Medicine, Kagawa University, 1750-1 Ikenobe, Kita, Miki, Kagawa 761-0793, Japan

[16] Department of Medicine, The University of Hong Kong, Hong Kong, China

[17] Department of Clinical Oncology, State Key Laboratory of Translational Oncology, Sir YK Pao Centre for Cancer, The Chinese University of Hong Kong, Hong Kong SAR, China

[18] Center of Hepato-Pancreato-Biliary Surgery, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China

[19] Faculty of Medicine, Department of Gastroenterology, Faculty of Medicine, Yamagata University, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan

[20] Department of Liver Surgery, Collaborative Innovation Center for Cancer Medicine, State Key Laboratory of Oncology in South China, Sun Yat-Sen University Cancer Center, Guangzhou 510060, China

[21] Department of OncologyDepartment of Medical OncologyGraduate Institute of OncologyDepartment of Internal Medicine, National Taiwan University Cancer CenterNational Taiwan University HospitalNational Taiwan University College of Medicine, Taipei, Taiwan

[22] Humanity and Health Clinical Trial Center, Humanity & Health Medical Group, Hong Kong SAR, China

[23] Hepatobiliary Division, Department of Internal Medicine, and Hepatitis Center, Center for Infectious Disease and Cancer Research, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

[24] School of Medicine, Mongolian National University of Medical Sciences, Ulan Bator, Mongolia

[25] Department of Medical Oncology, Laboratory of Molecular Targeted Therapy in Oncology, West China Hospital, Sichuan University, Chengdu, China

[26] Division of Gastroenterology and Hepatology, Department of Medicine, National University Health System, Singapore, Singapore

[27] Hepatobiliary Division, Staff Medic Group of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital, Jakarta 10430, Indonesia

[28] Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan

[29] The Aga Khan University Hospital, Karachi, Pakistan

[30] Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China

[31] Department of Internal Medicine Division of Gastroenterology and Hepatology, Department of Internal MedicineHepatitis Research Center, Graduate Institute of Clinical Medicine, National Taiwan University Hospital Bei-Hu BranchNational Taiwan University HospitalNational Taiwan University College of Medicine, Taipei, Taiwan

[32] Department of Surgery, Graduate School of Medicine, Hepato-Biliary-Pancreatic Surgery Division, The University of Tokyo, Tokyo, Japan

[33] Humanity and Health Clinical Trial Center, Humanity & Health Medical Group, Hong Kong SAR, China

[34] Department of Radiology, Seoul National University College of Medicine, Seoul, Korea

[35] Department of Medical Oncology, Peking University International Hospital, Beijing, China

[36] Senior Department of Hepatology, The Fifth Medical Center of Chinese People's Liberation, Army General Hospital, Beijing, China

[37] Department of Comprehensive Liver Cancer Center, The Fifth Medical Center of Chinese, PLA General Hospital, Beijing, China

[38] Department of Medical Oncology, College of Medicine, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China

[39] Department of Medicine, Fatima University Medical Center, Manila, Philippines

[40] Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka 1000, Bangladesh

[41] Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

[42] Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), Shanghai, China

[43] European Liver Patients' Association (ELPA), Brussels, Belgium

[44] Department of Hepatobiliary, HCC Research Center for Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin, China

[45] Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China

[46] Division of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[47] Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital, Tsinghua University, Beijing, China

[48] Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea

[49] Section of Gastroenterology, University of Santo Tomas, Manila, Philippines

[50] Department of Gastrointestinal Medical Oncology, Institute of Prevention and Treatment of Cancer of Heilongjiang Province, Harbin Medical University Cancer Hospital, Harbin, Heilongjiang, China

[51] Division of Gastroenterology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[52] Department of Medicine, Ankara University School of Medicine, Ankara, Turkey

[53] Department of Hepatobiliary and Pancreatic Surgery, Department of Liver Transplantation, Shulan (Hangzhou) Hospital, Zhejiang Shuren University School of Medicine, Hangzhou, China

[54] Department of Liver Surgery and Transplantation, Key Laboratory of Carcinogenesis and Cancer Invasion (Ministry of Education), Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China

[55] Liver Surgery and Transplant Centre, Hong Kong Sanatorium and Hospital, Hong Kong, Japan

[56] Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India

[57] Department of Gastroenterology, Yamanashi Prefectural Center Hospital, Kofu-City, Yamanashi, Japan

[58] Faculty of Health Science, Macau University, Macau SAR, China

[59] World Hepatitis Alliance, London, UK

[60] African Liver Patient Association (ALPA), Cairo, Egypt

[61] The Association of Liver Patients Care (ALPC), Hepatology and Gastroenterology Unit, Internal Medicine Department, Faculty of Medicine, Mansoura University, Egyptian Liver Research Institute and Hospital (ELRIAH), Sherbin, El Mansoura, Egypt