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Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of hepatocellular carcinoma

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Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of hepatocellular carcinoma

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ABSTRACT

Patients with advanced hepatocellular carcinoma (HCC) have historically had few options and faced extremely poor prognoses if their disease progressed after standard-of-care tyrosine kinase inhibitors (TKIs). Recently, the standard of care for HCC has been transformed as a combination of the immune checkpoint inhibitor (ICI) atezolizumab plus the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab was shown to offer improved overall survival in the first-line setting. Immunotherapy has demonstrated safety and efficacy in later lines of therapy as well, and ongoing trials are investigating novel combinations of ICIs and TKIs, in addition to interventions earlier in the course of disease or in combination with liver-directed therapies. Because HCC usually develops against a background of cirrhosis, immunotherapy for liver tumors is complex and oncologists need to account for both immunological and hepatological considerations when developing a treatment plan for their patients. To provide guidance to the oncology community on important concerns for the immunotherapeutic care of HCC, the Society for Immunotherapy of Cancer (SITC) convened a multidisciplinary panel of experts to develop a clinical practice guideline (CPG). The expert panel drew on the published literature as well as their clinical experience to develop recommendations for healthcare professionals on these important aspects of immunotherapeutic treatment for HCC, including diagnosis and staging, treatment planning, immune-related adverse events (irAEs), and patient quality of life (QOL) considerations. The evidence- and consensus-based recommendations in this CPG are intended to give guidance to cancer care providers treating patients with HCC.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and is among the top causes of cancer-related death worldwide.[1] Mortality due to HCC exerts a high human toll in most countries around the world, and in the United States (US), the incidence has increased markedly in recent years.[2] Risk factors for HCC are unevenly distributed around the globe. In the USA, Europe, and Japan, the predominant risk factors for HCC are overweight-related and obesity-related conditions, for example, non-alcoholic fatty liver disease (NAFLD), as well as hepatitis C virus (HCV), and alcohol abuse,[3] whereas in eastern Asia and sub-Saharan Africa hepatitis B virus (HBV) is more prevalent as an etiological agent. Additional risk factors include diabetes mellitus, obesity, exposure to aflatoxin B, hemachromatosis, and other hereditary disorders.[4 5]

Although curative interventions such as liver transplant, surgery, and ablation may offer favorable outcomes for patients with early-stage HCC, for many years options were limited and prognosis was very poor for advanced disease.[6–8] The 2007 approval of the multi-tyrosine kinase inhibitor (TKI), sorafenib, for the first-line treatment of advanced HCC represented a breakthrough as it was the first systemic therapy in several decades to demonstrate improved survival in liver cancer.[9] However, despite several additional approvals for TKIs including regorafenib[10] and lenvantinib[11] in the subsequent years,[12] the new modalities only offered incremental increases in overall survival (OS) for patients with advanced HCC, until the advent of immunotherapy and immune-based combination therapies.

In 2017, the US Food and Drug Administration (FDA) granted the first approval for an immune checkpoint inhibitor (ICI) for HCC. Nivolumab (targeting programmed cell death protein 1 [PD-1]) monotherapy received accelerated approval based on a significant response rate and prolonged duration of response (DOR) with manageable side effects in patients who had previously been treated with sorafenib.[13] This was followed by encouraging data for other ICIs—pembrolizumab (another anti-PD-1 ICI) monotherapy[14] and nivolumab in combination with the cytotoxic T lymphocyte antigen-4 (CTLA-4) antagonist ipilimumab[15]—resulting in further accelerated approvals by the FDA. The confirmatory phase III studies for single-agent nivolumab and permbrolizumab, however, did not meet their end points. In 2020, the anti-programmed death-ligand 1 (PD-L1) antibody atezolizumab in combination with the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab[16] gained full FDA approval for first-line treatment of HCC on the basis of the phase III study IMbrave150. This was the first regimen to demonstrate superiority to sorafenib in HCC since sorafenib's approval in 2007, in addition to being the first immunotherapy plus anti-VEGF combination to gain approval for liver cancer. Additional trials are ongoing and the therapeutic landscape continues to evolve and expand.

HCC often develops on a background of chronic inflammation, metabolic stress, cirrhosis, or fibrosis, and thus, the use of immunotherapy in the setting of a compromised liver is a complex but common challenge. Although HCC is frequently an immunogenic cancer, characterized by tumor-infiltrating lymphocytes (TILs) in the tumor microenvironment, the intratumoral milieu has been shown to be generally immunosuppressive—in part due to the acquired immune dysfunction that occurs with cirrhosis, viral infection, or environmental insults that contribute to disease development, but also partially related to the liver's intrinsic tolerogenicity.[17 18] Despite these hurdles, the incorporation of immunotherapy into HCC care has offered more options to clinicians and has extended survival considerably for a subset of patients.

The approval of immunotherapy agents for the treatment of HCC is relatively recent as compared with other malignancies and experience with these new therapies is still limited. Additionally, immunotherapy carries unique considerations in many clinical aspects including patient selection, management of immune-related adverse events (irAEs), and evaluation of response to therapy compared with other systemic treatments. To support the oncology community and provide evidence- and consensus-based recommendations on immunotherapy for HCC, the Society for Immunotherapy of Cancer (SITC) convened an international panel of experts to develop a new clinical practice guideline (CPG), covering topics including recommended therapies, emerging agents, diagnostics and biomarkers, monitoring response to treatment, special patient populations, toxicity management, and quality of life (QOL). Although the guideline focuses on therapies approved by the FDA, the authors, as an international team, acknowledge that recommendations may not fully align with approval or reimbursement policies in other countries outside the US, and they encourage harmonization. The recommendations within this guideline are meant to complement rather than supplant sound clinical judgment, and their aim is to provide clinicians with the most current thinking on integrating immunotherapy into the treatment of patients with HCC.

GUIDELINE DEVELOPMENT METHODS

The Institute of Medicine's (IOM) Standards for Developing Trustworthy Clinical Practice Guidelines were used as a model to develop the recommendations in this manuscript. IOM standards dictate that guideline development is led by a multidisciplinary expert panel using a transparent process where both funding sources and conflicts of interest are readily reported. This CPG is intended to provide guidance and is not a substitute for the professional judgment of individual treating physicians.

Conflict of interest management

As outlined by IOM standards, all financial relationships of expert panel members that might result in actual, potential, or perceived conflicts of interest were individually reported. Disclosures were made prior to the onset of manuscript development and updated on an annual basis. In addition, panel members were asked to articulate any actual or potential conflicts at all key decision points during guideline development, so that participants would understand all possible influences, biases, and/or the diversity of perspectives on the panel. Although some degree of relationships with outside interests are to be expected among experts, panel candidates with significant financial connections that may compromise their ability to fairly weigh evidence (either actual or perceived) were not eligible to participate in guideline development.

Recognizing that guideline panel members are among the leading experts on the subject matter under consideration and guideline recommendations should have the benefit of their expertize, any identified potential conflicts of interests were managed as outlined in SITC's disclosure and conflict of interest resolution policies. As noted in these policies, panel members disclosing a real or perceived potential conflict of interest may be permitted to participate in consideration and decision-making of a matter related to that conflict, but only if deemed appropriate after discussion and agreement by the expert panel.

The financial support for the development of this guideline was provided solely by SITC. No commercial funding was received.

Recommendation development

Panel recommendations are based on literature evidence, where possible, and clinical experience, where appropriate.[19] Consensus for the recommendations here was generated by open communication and scientific debate in small-group and whole-group settings, surveying and

Table 1 Summary of 'The Oxford Levels of Evidence 2' (Adapted from the OCEBM Levels of Evidence Working Group)				
Level 1	**Level 2**	**Level 3**	**Level 4**	**Level 5**
Systematic review or meta-analysis	Randomized trial or observational study with dramatic effect	Non-randomized, controlled cohort, or follow-up study	Case series, case-control, or historically controlled study	Mechanism-based reasoning

OCEBM, Oxford Centre for Evidence-Based Medicine.

responses to clinical questionnaires, as well as formal voting in consensus meetings.

For transparency, a draft of this CPG was made publicly available for comment during the development process and prior to publication. All comments were evaluated and considered for inclusion into the final manuscript according to the IOM standard.

Evidence rating

The evidence- and consensus-based recommendations of the panel were refined throughout the development process in order to obtain the highest possible agreement among the experts, however, the minimum threshold was defined as 75% approval among the voting members. Evidence supporting panel recommendations was graded according to the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence Working Group 'The Oxford Levels of Evidence 2' (2016 version). A summary of the OCEBM grading scale may be found in table 1. The level of evidence (LE) for a given recommendation is expressed in parentheses following the recommendation (eg, LE: 1). Recommendations without an associated LE were based on expert consensus.

DIAGNOSTICS AND STAGING FOR PATIENTS WITH HCC

Initial HCC diagnosis

The initial diagnostic workup of HCC typically comprises a histologic analysis of tumor samples obtained by biopsy or surgery, cross-sectional imaging, a detailed analysis of the liver's condition with laboratory studies, and an assessment of the potential etiology of the HCC including investigations of HBV and HCV viral status. Guidelines for surveillance screening, initial diagnosis, and staging of HCC have been developed by multiple organizations including, but not limited to, the American Association for the Study of Liver Diseases (AASLD),[7] the American College of Gastroenterology (AGC),[20] the European Society for Medical Oncology (ESMO),[21] the European Association for the Study of the Liver (EASL)[22] and the Japan Society of Hepatology (JSH).[23] These organizations and others have also put forth guidelines for non-immunotherapeutic approaches for the treatment of HCC.

HCC may be identified using computerized tomography (CT) and magnetic resonance imaging (MRI) with Liver Imaging Reporting And Data Systems (LI-RADS).[24] The LI-RADS system provides a standardized approach for radiologists to communicate with the treating physicians and provides a certain level of confidence that a lesion in a cirrhotic liver or a liver at risk for cirrhosis presents as HCC on imaging.[25] LI-RADS staging ranges from LR-1, for lesions that are definitely benign, to LR-5, which represents 100% probability of being HCC. The LI-RADS system acknowledges that limitations exist, and has included an LR-NC (for non-categorizable) category where diagnostic possibilities cannot be meaningfully narrowed. LI-RADS is endorsed by the AASLD,[7] as well as by the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS). Contrast agents have also greatly enhanced the diagnostic accuracy of MRIs. Multiple meta-analyses have determined that gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI has superior sensitivity, specificity, and diagnostic odds ratio (OR) as compared with multidetector CT.[26–28] However, most published guidelines do not recommend one imaging modality over the other.

Patients with HCC often present with underlying cirrhosis—two conditions with independent mortality risks. It is essential for a care team comprised of multiple specialties, including perspectives from both hepatology and oncology, to be established early so that a treatment plan that addresses all of the complex needs of a patient with HCC may be developed.[29] A multidisciplinary tumor board review of liver lesions is recommended for HCC diagnosis and management plans, particularly for patients with tumors that may be eligible for transplant, surgery, or liver-directed treatments.

Historically, avoiding tumor biopsy has been acceptable practice in patients with cirrhosis and imaging characteristics consistent with HCC. One concern of performing biopsies in this disease has been the putative risk for tumor dissemination outside the liver via needle track seeding. The occurrence of needle track seeding appears to be uncommon in the published literature, however, with incidence rates estimated to be as low as 2.7% overall, or 0.9% per year.[30] While biopsy may be less encouraged in certain clinical scenarios such as in patients where liver transplants are being considered, histologic diagnosis is increasingly encouraged for the diagnosis of HCC, particularly for more advanced tumors requiring systemic therapy. Other primary liver tumors such as cholangiocarcinoma or mixed cholangiohepatoma can occasionally present very similarly to HCC, and the treatment for these tumors can be distinct. Other entities such as metastatic neuroendocrine cancers can similarly demonstrate

Table 2 Radiographic T-staging by LI-RADS and OPTN/UNOS[236]

Stage	Definition
0	No HCC
1	One HCC <20 mm
2	One HCC ≥20 mm and ≤50 mm, or two or three HCCs, all ≤30 mm
3	One HCC >50 mm, or two or three HCCs, at least one >30 mm
4	4A. Four or more HCCs, regardless of size 4B. HCC + TIV

HCC, hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting And Data System; OPTN/UNOS, Organ Procurement and Transplantation Network/United Network for Organ Sharing; TIV, tumor in vein.

Table 3 Barcelona-Clínic Liver Cancer (BCLC) classification with stage definitions and typical survival outcomes

	Stage definition (BCLC 2018 update)	Estimated survival
Stage 0—Very early-stage	Single nodule ≤2 cm; ECOG PS 0*; Preserved liver function	>5 years
Stage A—Early-stage	Single or up to three nodules ≤3 cm; ECOG PS 0*; Preserved liver function	>5 years
Stage B—Intermediate-stage	Multinodular; ECOG PS 0*; Preserved liver function	>2 to 5 years
Stage C—Advanced-stage	Portal invasion; Extrahepatic spread; ECOG PS 1–2; Preserved liver function	>1 year
Stage D—Terminal-stage	ECOG PS 3–4; End-stage liver function	3 months

*The American Association for the Study of Liver Disease (AASLD) recommends including ECOG PS 0 to 1 in stage 0, A and B, because of the significant overlap between PS 0 and PS 1
BCLC, Barcelona-Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

arterial enhancement on multiphase imaging.[31] Additionally, in rare instances, tissue biopsy may uncover certain genetic alterations that render a patient eligible for a tissue-agnostic therapy or a clinical trial.

HCC staging

An ideal staging system in HCC serves two purposes: treatment indication and prognostic prediction. A variety of staging systems have been developed, and their performance and validation varies. While some staging systems focus on pathology, others incorporate radiological characteristics, serum biomarkers, liver function, and performance status. In most solid tumors, staging is performed at the time of surgery using resected specimens. The Tumor-Node-Metastases (TNM) classification, developed by the American Joint Committee on Cancer (AJCC), classifies the primary tumor (T) based on size, number, and vascular invasion.[32] However, the TNM classification is not currently used to guide treatment for HCC. Also, importantly, the TNM classification should not be confused with the radiologic T-staging system used by LI-RADS and OPTN/UNOS, which is summarized in table 2.

Radiographic T-staging is of limited pretreatment prognostic and predictive value for patients being considered for systemic therapy, as the system does not take into account liver function, which is an important risk factor for patients with HCC. Several alternative staging or scoring systems have been developed, including the Barcelona-Clinic Liver Cancer (BCLC) system,[33] Cancer of the Liver Italian Program (CLIP),[34] Japan Integrated Staging (JIS),[35] Chinese University Prognostic Index (CUPI),[36] Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire (GETCH)[37] plus many others.

The BCLC system, summarized in table 3, has gained wide recognition and has been endorsed by multiple international hepatology associations including AASLD[6] and EASL. Several large-scale cohort studies have validated the BCLC system, including in Korean patients with treatment-naïve HCC,[38] US patients,[39] and Italian patients undergoing radical surgery.[40] In addition, scoring by the BCLC system has been reported and studied in subgroup analyses for most of the phase III studies done in advanced HCC.

HCC is a highly heterogeneous disease with varied underlying etiologies depending on geography and demographics. Studies comparing the performance of staging systems for predicting prognosis have returned conflicting results depending on the patient population investigated and the treatments administered. The JIS score showed the best ability to predict OS by disease stage in an analysis of Japanese patients,[41] whereas an analysis of 1,713 prospectively enrolled patients with HCC in Taiwan found that CLIP was the best prognostic model in patients undergoing both curative and non-curative treatments.[42] In the advanced and metastatic disease setting, another comparison of the prognostic value of different systems determined CLIP and CUPI to be the most reliable staging systems for patients with HCV and HBV etiologies, respectively.[43] In these analyses of patients with advanced disease in need for systemic therapy, BCLC and TNM lacked prognostic value.

Liver function assessment is a critical component of HCC treatment that is required for every patient. Some of the staging systems embed within them the Child-Pugh classification, recognizing the need for assessing the extent of liver functionality as part of the staging of the disease. The Child-Pugh score evolved over time from the original system built in 1973 to help assess for survival of patients with bleeding esophageal varices.[44] Of note, in the original Pugh effort, none of the patients had HCC. The system evolved into a five-parameter staging system which consists of three laboratory values (serum albumin, bilirubin, and prothrombin levels) and two clinically assessed variables (presence and degree of ascites and hepatic encephalopathy). A final score ranging from 5 to 15 is calculated based on the range of laboratory values and severity of clinical symptoms, and then classified into one of three classes: A (5–6), B (7–9), and C (10–15).[44 45] Median survival of untreated HCC has been shown to be approximately 2.5 times lower in patients with Child-Pugh B disease compared with those with Child-Pugh A.[46] Recently, however, the limitations and subjectivity involved in the grading of clinical variables have called into question Child-Pugh scores in assessing liver function in HCC.[47]

The albumin-bilirubin (ALBI) grade, a simpler model to assess liver function based only on serum albumin and bilirubin, has been validated in study cohorts from multiple geographic regions and multiple clinical scenarios, including patients undergoing resection and sorafenib treatment. The score is calculated as ($\log_{10}$ bilirubin [μmol/L]×0.66) + (albumin [g/L] × −0.0852), leading to three possible grades: ALBI Score ≤ −2.60 (ALBI grade 1), ALBI Score > −2.60 to ≤ −1.39 (ALBI grade 2), and ALBI Score > −1.39 (ALBI grade 3).[48] The ALBI grade demonstrated superior prognostic value to the Child-Pugh score in a study of patients with HCC treated with radioembolization, particularly within patients with Child-Pugh A disease.[49] ALBI grade also predicts OS after surgical resection (p<0.001), transarterial chemoembolization (TACE) (p<0.001) and sorafenib treatment (p<0.001), with independent prognostic value across BCLC stages, geographic regions (p<0.001),[50] and for cancers being treated with immunotherapy.[50]

Diagnostic biomarkers

Several biomarkers have been put forward to predict prognosis in HCC, yet none are currently routinely used to guide treatment decisions for patients being considered for immunotherapy. Serum alpha-fetoprotein (AFP) has been the most widely used marker to increase the suspicion for a diagnosis of HCC, and has been included in international guidelines.[21 51] However, the value of AFP as a surveillance marker remains controversial,[52] and establishing a threshold value to diagnose HCC remains a challenge.[52 53] Tumor-derived AFP has also been implicated in impaired dendritic cell function.[54] Glypican 3 (GPC3), an antigen that is highly expressed on tumor cells and minimally present on healthy tissues,[55] has been proposed as a serum biomarker for HCC and is being pursued as a target for chimeric antigen receptor (CAR) T cell therapies.[56] However, neither AFP nor GPC3 have demonstrated predictive power for patients being treated with ICIs, although this is an active area of research.

The GALAD score, which determines risk of HCC based on patient sex, age, and serum levels of AFP, AFP isoform L3, and des-gamma-carboxy prothrombin has been validated for detection of HCC in patients with non-alcoholic steatohepatitis (NASH) with and without cirrhosis.[57] A combination of GALAD and ultrasound (GALADUS) score has been shown to further improve performance, with an area under the curve of 0.98 (95% CI 0.96 to 0.99; cut-off −0.18; sensitivity 95%; specificity 91%) in a single-center cohort of 111 patients with HCC and 180 controls with cirrhosis or chronic HBV.[58] In March of 2020, the FDA granted breakthrough device designation to the Elecsys GALAD score to aid in early diagnosis of HCC (for further discussion of immunotherapy-specific biomarkers, including PD-L1 status, see the **Patient selection and management** section).

Panel recommendations

- A multidisciplinary tumor board review of liver lesions is recommended for HCC diagnosis and the development of a management plan.
- Notwithstanding that LI-RADS-5 is nearly 100% specific for HCC (LE: 1), histologic confirmation is recommended for patients with unresectable disease particularly prior to the initiation of systemic therapy. Histologic diagnosis is mandatory for non-cirrhotic patients.
- Despite the controversy regarding the scoring and staging systems that could be used, before initiation of systemic therapy, an evaluation of liver function, including aspartate transaminase (AST)/alanine aminotransferase (ALT), bilirubin, prothrombin time (PT)/international normalized ratio (INR), albumin, plus platelets, is critical (LE: 2).
- For patients being considered for immunotherapy, an HCC-specific staging system incorporating liver function assessment is suggested (LE: 2).
- To evaluate patients prior to receiving immunotherapy, Child-Pugh classification would be the most appropriate to date (LE: 1) to measure liver function.

RECOMMENDED IMMUNOTHERAPIES FOR HCC

Available agents and indications

For more than 10 years, sorafenib was the only systemic therapy approved by the FDA for the treatment of HCC. Since 2017, four ICI regimens have entered the clinic after having received full or accelerated approval by the FDA for the treatment of advanced HCC. Only one combination, atezolizumab with bevacizumab, had full FDA approval at the time of guideline preparation, the remaining regimens (nivolumab and pembrolizumab monotherapy and nivolumab with ipilimumab) received accelerated approvals, and FDA review of confirmatory trials is ongoing. Results of the landmark trials leading to these approvals are described in table 4. Further details for each indication are discussed in chronological order of their FDA approvals.

Table 4 Landmark trials leading to FDA approvals for immunotherapy for HCC

Trial (NCT#)	Phase	Agent(s) evaluated	Study population	Patients	Outcomes
CheckMate 040 (NCT01658878)	I/II	Nivolumab*†	Patients with histologically confirmed advanced HCC with or without HCV or HBV infection. Previous sorafenib treatment was allowed. CP A or B7 disease for dose escalation; CP A disease for dose expansion.	262	ORR 20% (95% CI 15% to 26%) in dose-expansion phase ORR 14.3% (95% CI 6% to 28%) in population with progressive disease on/intolerance to sorafenib
KEYNOTE-224 (NCT02702414)	I	Pembrolizumab*	Patients with disease progression on or after sorafenib or intolerant to sorafenib, and measurable CP A disease.	104	ORR 17% (95% CI 11% to 26%)
CheckMate 040 (NCT01658878)	I/II	Nivolumab+ipilimumab*	Patients with histologically confirmed advanced HCC with or without HCV or HBV infection. Previous sorafenib treatment was allowed.	148	ORR 33% (95% CI 20% to 48%)
IMbrave150‡	III	Atezolizumab+ bevacizumab vs sorafenib	Patients with unresectable HCC who had received no prior systemic therapy and had well-compensated liver disease.	501	OS HR 0.58 (95% CI 0.42 to 0.79; p<0.001) ORR 27.3% vs 11.9% (p<0.001)

*Accelerated approval contingent on confirmatory trials
†Indication voluntarily withdrawn July 2021
‡Updated data with 12 additional months of follow-up found ORR of 29.8% (95% CI 24.8% to 35.0%) for atezolizumab+bevacizumab versus 11.3% (95% CI 6.9% to 17.3%) for sorafenib[66]
CI, confidence interval; CP, Child-Pugh; FDA, US Food and Drug Administration; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ORR, overall response rate; OS, overall survival.

Prior sorafenib therapy

In 2017, nivolumab received accelerated approval as monotherapy for the treatment of patients with HCC with progression following or intolerance to sorafenib. Approval was based on data from a cohort of patients from the CheckMate 040 Trial, a phase I/II, open-label, multicenter study. Among the 154 patients treated with nivolumab, 22 (14.3%; 95% CI 9.2% to 20.8%) had an objective radiologic response based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Three patients (1.9%) had complete responses (CRs) and 19 (12.3%) had partial responses (PRs). DORs ranged from 3.2 months to 38.2+ months with 91% lasting 6 months or longer and 55% lasting 12 months or longer. The overall response rate (ORR), based on modified RECIST (mRECIST), was 18.2% (28 patients; 95% CI 12.4% to 25.2%) and the CR rate was 3.2% (5 patients) with a PR rate of 14.9% (23 patients). No differences in response rates were observed across PD-L1 expression levels.[13] Postregistration studies support the safety of single-agent nivolumab in patients with Child-Pugh B disease[59] where treatment is associated with shorter OS compared with Child-Pugh A disease (7.3 months vs 16.3 months; p<0.001).[60] Data from cohort 5 of CheckMate 040, which included 25 sorafenib-naïve and 24 sorafenib-treated patients with Child-Pugh B7-B8 advanced HCC, also showed safety and efficacy for single-agent nivolumab in a setting of mild to moderate liver impairment[61] (for further details on immunotherapy in special patient populations, see the **Patient selection and management** section). Continued accelerated approval for nivolumab monotherapy was contingent on the confirmatory trial CheckMate 459 (described below).

On March 10, 2020, nivolumab in combination with ipilimumab received accelerated approval by the FDA to treat patients with HCC who were previously treated with sorafenib. Approval was based on the results of an additional cohort (cohort 4[15]) from CheckMate 040. In the CheckMate 040 cohort 4, 148 patients were randomized 1:1:1 to three different treatment arms to evaluate different dosing regimens of the combination: high-dose ipilimumab, low-dose ipilimumab and continuous nivolumab/ipilimumab for arms A, B, and C, respectively. For approval, efficacy was evaluated in the 49 patients who received nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg every 3 weeks for 4 doses, followed by single-agent nivolumab every 2 weeks until disease progression or unacceptable toxicity. Data from all arms support anti-HCC activity of the regimen, however. The ORR reported for accelerated approval was 33% (n=16; 95% CI

20% to 48%), with 4 CRs and 12 PRs. DORs ranged from 4.6 months to 30.5+ months, with 31% of responses lasting 24 months or longer.[62] An updated analysis at a minimum follow-up of 44 months found ORRs by blinded independent central review of 32%, 31%, and 31% for arms A, B, and C, respectively. Median DORs were 17.5 months, 22.2 months, and 16.6 months for arms A, B, and C, and median OS for each arm was 22.2 months, 12.5 months, and 12.7 months, respectively.[63]

In CheckMate 459, a phase III trial evaluating the efficacy of nivolumab as a first-line monotherapy, the ORR was 15% in the nivolumab group and 7% in the group receiving sorafenib. Median OS was 16.4 months for nivolumab-treated patients and 14.7 months for sorafenib-treated patients (HR 0.85; 95% CI 0.72 to 1.02; p=0.0752). The difference in OS between the two groups did not meet prespecified thresholds for statistical significance (HR 0.84; p=0.0419).[64] Nevertheless, nivolumab demonstrated a favorable safety profile, better response rate, improved tolerability, and better QOL outcomes when compared with sorafenib. A trend towards better survival and response rate was noted in patients with PD-L1 tumor proportion score (TPS) ≥1% (about 19% of the randomized subjects) measured by the Dako PD-L1 immunohistochemistry (IHC) assay, supporting the importance of predictive biomarker development. In a 4:5 vote, the FDA Oncologic Drugs Advisory Committee (ODAC) recommended rescinding the indication for nivolumab for the treatment of patients with HCC and prior sorafenib therapy. There was unanimous agreement from committee members that voting was difficult due to the many factors, including the earlier vote to maintain the indication for pembrolizumab monotherapy. Those in favor of continued accelerated approval for nivolumab in this patient population highlighted the unmet need for second-line options. Rationale against continuing the indication centered on the lack of OS benefit in CheckMate 459 and the inadequacy of the proposed alternative studies to generate satisfactory evidence for efficacy in the second-line setting. Discussion also narrowed in on whether data exist to recommend nivolumab monotherapy over an ipilimumab plus nivolumab combination regimen, including debate over whether the group of patients deemed unfit for the dual checkpoint inhibitor combination represent a new indication that was not formally defined nor evaluated in trials to date. In July 2021, the nivolumab monotherapy indication for HCC was voluntarily withdrawn.

Accelerated approval was granted to pembrolizumab in 2018 for patients with HCC who have previously received sorafenib based on results from the phase II KEYNOTE-224 Trial. The study enrolled 104 patients to receive single-agent pembrolizumab with advanced HCC and radiographic progression or intolerance to sorafenib. The ORR was 17% (95% CI 11% to 26%) and among the 18 patients who responded, there was 1 CR and 17 PRs. At data cut-off, 12 of the 18 responses were ongoing and the median DOR was not reached (range 3.1–14.6+ months). Of the responders, 89% had a DOR ≥6 months, and 56% had a DOR ≥12 months.[14]

The phase III KEYNOTE-240 confirmatory trial evaluating pembrolizumab versus placebo was negative based on the co-primary end point of median OS and PFS. Median OS was 13.9 months (95% CI 11.6 to 16.0) for pembrolizumab versus 10.6 months (95% CI 8.3 to 13.5) for placebo (HR 0.781; 95% CI 0.611 to 0.998; p=0.0238), and median PFS for pembrolizumab was 3.0 months (95% CI 2.8 to 4.1) versus 2.8 months (95% CI 1.6 to 3.0; HR 0.718; 95% CI 0.570 to 0.904; p=0.0022), but this did not meet statistical significance by the prespecified statistical plan.[65] The study did confirm the single-agent response rate of pembrolizumab in this setting with an ORR of 18.3 (95% CI 14.0 to 23.4) and a DOR of 13.8 months (range 1.5–23.6+ months). Despite the confirmatory trial not meeting prespecified end points, when the FDA ODAC reviewed the accelerated approval in April 2021 the vote to maintain the indication for pembrolizumab was unanimous, citing unmet medical need for patients who cannot receive first-line atezolizumab with bevacizumab (described below) and who have disease progression with or become intolerant to TKIs.

First-line therapy

The first ICI regimen to receive full approval and the first to receive first-line approval for the treatment of HCC is atezolizumab in combination with bevacizumab for patients who have not received prior systemic therapy, which was approved in 2020. Approval was based on the global, open-label, phase III IMbrave150 trial, in which 501 patients with unresectable HCC were randomly assigned in a 2:1 ratio to receive either first-line atezolizumab plus bevacizumab or sorafenib monotherapy until unacceptable toxic effects or loss of clinical benefit occurred. At the primary analysis, the HR for death with atezolizumab plus bevacizumab compared with sorafenib was 0.58 (95% CI 0.42 to 0.79; p<0.001). The 12-month OS rate was 67.2% (95% CI 61.3% to 73.1%) with atezolizumab plus bevacizumab and 54.6% (95% CI 45.2% to 64.0%) with sorafenib. Median PFS was 6.8 months (95% CI 5.7 to 8.3) versus 4.3 months (95% CI 4.0 to 5.6) with atezolizumab plus bevacizumab versus sorafenib, respectively (HR for disease progression or death 0.59; 95% CI 0.47 to 0.76; p<0.001).[16] In an updated post hoc survival analyses, median OS was 19.2 months with atezolizumab plus bevacizumab compared with 13.4 months with sorafenib (HR 0.66; 95% CI 0.52 to 0.85; p=0.0009). The OS rates at 18 months were 52% vs 40% with atezolizumab plus bevacizumab versus sorafenib, respectively.[66]

The combination therapy also delayed deterioration in QOL compared with sorafenib monotherapy. In terms of the tolerability profile, grade 3–4 adverse events (AEs) occurred in 57% of patients treated with atezolizumab with bevacizumab.[16] Additionally, the development of anti-drug antibodies (ADAs) is a possibility in patients treated with atezolizumab.[67] In IMbrave150, among 318 ADA-evaluable patients with HCC, 30% (n=94) tested positive for treatment-emergent ADAs at one or more post-dose time points. In exploratory adjusted analyses, patients who were ADA-positive at landmark week 6 had a similar OS with atezolizumab plus bevacizumab versus sorafenib, whereas those with ADA-negative status had an improved OS compared with sorafenib. However, similar PFS and ORR benefit was seen with the combination over sorafenib regardless of ADA status.[68]

Panel recommendations

- For first-line treatment of patients with advanced Child-Pugh A HCC, atezolizumab plus bevacizumab is recommended, unless either medication is contraindicated (LE: 2).
- General contraindications to bevacizumab include high risk of cardiac disease, stroke, hemorrhage, hemoptysis, gastrointestinal perforation, or non-healing wounds (LE: 1). (For contraindications to immunotherapy, see the **Patient selection and management** section). Consideration should be given to timing of prior events. Additional contraindications specifically relevant to HCC include untreated or incompletely treated gastroesophageal varices at risk for bleeding (LE: 2).
- For patients with contraindications to atezolizumab plus bevacizumab treatment, lenvatinib or sorafenib should be considered as standard first-line therapy (LE: 2).
- Nivolumab monotherapy has demonstrated activity in Child-Pugh B7-B8 HCC for both first-line treatment of sorafenib-naïve patients and for second-line treatment of patients who were intolerant to or progressed on sorafenib (LE: 3).
- For patients with good performance status who have progressed on first-line therapy and have not received prior immunotherapy, other non FDA-approved or conditionally approved anti-PD-1 checkpoint inhibitors may be considered as immunotherapeutic options (LE: 3).

IMMUNOTHERAPIES IN DEVELOPMENT FOR HCC

The potential benefit of ICIs as monotherapies or in combination regimens including other ICIs or anti-VEGF agents for advanced HCC is being evaluated in several ongoing trials. Additionally, mechanistic rationale supports the integration of ICIs with locoregional therapies for disease in early stages, and some studies have reported tolerable safety with evidence for efficacy with the combination of checkpoint blockade and liver-directed therapy. Finally, the development of novel strategies such as vaccines or adoptive cell therapies is an active area of investigation, although still in early stages at the time of publication.

Checkpoint inhibitors and novel combinations

Tremelimumab, an anti-CTLA-4 ICI, has been evaluated in a pilot trial of patients with HCC with chronic HCV infection. Among the 17 patients who were assessable for tumor response, the PR rate was 17.6% and disease control rate (DCR) was 76.4% with a median time to progression of 6.48 months (95% CI 3.95 to 9.14). Significant drops in viral load were observed in the 20 patients who were evaluable for toxicity and viral responses, and no patients needed steroids because of severe irAEs.[69] Single-agent tislelizumab (anti-PD-1),[70] camrelizumab (anti-PD-1),[71] and durvalumab (anti-PD-L1)[72] are all also being studied in phase III trials.

Combination ICI regimens are also under investigation. The FDA has approved nivolumab at 1 mg/kg with ipilimumab at 3 mg/kg regimen as a second-line treatment option for patients with prior sorafenib exposure.[73] Recently, another combination regimen, durvalumab in combination with tremelimumab, reported an ORR of up to 22.7% and a median OS of up to 18.7 months in the advanced HCC population using one single dose of tremelimumab at 300 mg, with further enhancement of response among patients with $CD8^+$ $Ki67^+$ proliferative T cells.[74] The phase III HIMALAYA trial investigating one single dose of tremelimumab with durvalumab as first-line treatment in patients with unresectable HCC is ongoing[75] and this combination regimen has been granted orphan drug designation by the FDA.

In the CheckMate 040 trial cohort 6,[76] the efficacy and safety profile of the triplet combination of cabozantinib, nivolumab, and ipilimumab were analyzed and compared with the cabozantinib plus nivolumab doublet. A total of 71 sorafenib-naïve or sorafenib-experienced patients with advanced HCC were randomized to either receive nivolumab 240 mg every 2 weeks with cabozantinib 40 mg daily (n=36) or nivolumab 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks and cabozantinib 40 mg daily (n=35). Although the study was not powered to directly compare efficacy of the triplet versus doublet regimens, numerically higher response rates (29% vs 19%), better PFS (median 6.8 vs 5.4 months) and improved median OS (not reached vs 21.5 months; 15-month OS rates: 70% vs 64%) were observed with the three-drug combination. Nevertheless, a higher rate of treatment-emergent AEs was also observed in the triplet arm, without the emergence of new safety signals in either treatment arms.

HCC is one of the most vascularized solid tumors and anti-angiogenic agents may complement immunotherapies. Multiple anti-angiogenic multikinase inhibitors are being evaluated in combination with checkpoint inhibitors for HCC. The combination with the most available data at the time of manuscript preparation is pembrolizumab plus lenvatinib. In Study 116, an ongoing phase Ib multicenter open-label study of lenvatinib plus pembrolizumab in 104 patients with unresectable HCC, the confirmed ORRs at data cut-off were 46.0% (95% CI 36.0% to 56.3%) by mRECIST and 36.0% (95% CI 26.6% to 46.2%) by RECIST v1.1 with median DORs of 8.6 months (95% CI 6.9 to not estimable [NE]) and 12.6 months (95% CI 6.9 to NE), respectively. Median OS was 22 months and treatment-related AEs of grade

≥3 occurred in 67% of patients.[77] The ongoing phase III LEAP-002 trial is also studying the combination and enrolling patients for treatment with pembrolizumab plus lenvatinib for first-line treatment of advanced HCC.[78] Other ICI/TKI combination studies include avelumab with axitinib, which led to tumor shrinkage in 15 (68.2%) and 16 (72.7%) patients and an ORR of 13.6% (95% CI 2.9% to 34.9%) and 31.8% (95% CI 13.9% to 54.9%) by RECIST and mRECIST, respectively in one study.[79] Cabozantinib is being combined with atezolizumab for patients who have not received prior systemic therapy for HCC in the phase III study COSMIC-312.[80]

Integration with local and regional therapies

Locoregional therapies such as TACE and drug-eluting bead TACE (DEB-TACE) may induce immunogenic cell death, thus promoting $CD8^+$ T cell infiltration into the tumor microenvironment, potentially synergizing with anti-PD-(L)1 therapy.[81] Doxorubicin, which has been shown to cause immunogenic cell death,[82] is the most commonly administered drug during TACE and DEB-TACE, and patients undergoing chemoembolization have been shown to develop AFP-specific $CD4^+$ T cell responses[83] as well as GPC3-specific cytotoxic T cell responses.[84]

A few studies have reported tolerable safety and initial efficacy outcomes with the combination of ICIs and locoregional therapies such as TACE and radiofrequency ablation (RFA). One trial enrolled 32 patients with HCC for tremelimumab therapy at two dose levels (3.5 mg/kg and 10 mg/kg intravenous [IV]) every 4 weeks for 6 doses, followed by infusions every 3 months until off-treatment criteria were met. On day 36, patients underwent subtotal RFA or chemoablation. Of the 19 evaluable patients, 5 (26.3%; 95% CI 9.1% to 51.2%) achieved PR. The median time to tumor progression was 7.4 months (95% CI 4.7 to 19.4) and median OS was 12.3 months (95% CI 9.3 to 15.4).[85]

Integration with transplant

Checkpoint inhibitors are considered contraindicated in patients undergoing transplantation due to fears of graft rejection.[86] Reports have emerged of immunotherapy being used as salvage therapy in liver transplant recipients with malignancies other than HCC, but rejection was frequent. A review of 14 cases of liver transplant recipients who were treated with ICIs identified four cases of liver graft rejection and three cases with lethal outcomes.[87] Another retrospective study including 39 patients with solid organ transplants reported permanent discontinuation of ICIs in 31% because of allograft rejection. Graft loss occurred in 81%, leading to death in 46%.[88]

Vaccines

Some vaccines have demonstrated manageable safety and preliminary efficacy in early phase trials in HCC. Although no antitumor effects or immune responses were detected among 40 patients with advanced HCC who were treated with low-dose cyclophosphamide in combination with a telomerase peptide vaccine (GV1001),[89] other strategies have posted more promising results.

Several groups have attempted to develop peptide vaccines based on GPC3. One GPC3 peptide vaccine was well tolerated in a phase I trial that included 33 patients with advanced HCC. Vaccination induced a GPC3-specific cytotoxic T lymphocyte response in 90% of patients—there was 1 PR and 19 cases of stable disease at 2 months.[90] That same vaccine was shown to lead to numerically lower rates of recurrence compared with surgery alone at 1 year (28.6% vs 54.3%) and 2 years (39.4% vs 54.5%) in the adjuvant setting in a phase II trial of 35 patients with HCC who had undergone resection.[91]

AFP-based vaccines have been shown to elicit T cell responses in early trials. Four immunodominant, human leukocyte antigen (HLA)-A*0201-restricted epitopes of AFP that are recognized by the human T cell repertoire have been identified.[92] In a pilot phase I clinical trial that enrolled six HLA-A*0201 patients with AFP-positive HCC for intradermal vaccinations with the four peptides emulsified in incomplete Freund's adjuvant, T cell responses were observed against most or all of the epitopes.[93] Subsequently, a phase I/II trial that included 10 HLA-A*0201 patients with AFP-positive HCC who were immunized with intradermal vaccinations of the four AFP peptides pulsed onto autologous dendritic cells found statistically significant levels of AFP-specific T cells to at least one peptide by major histocompatibility complex (MHC) tetramer in 60% of participants.[94]

Tumor lysate-based vaccines have also been evaluated in HCC. One study found that autologous tumor vaccination significantly delayed time to recurrence in 60 patients with HCC who had undergone curative resection. The 1-year, 2-year and 3-year recurrence rates in the 30 patients in the vaccine group were 16.7%, 29.2%, and 33.3%, respectively, compared with 30.8%, 53.8%, and 61.5%, respectively, in the control group.[95] Another phase II trial of autologous dendritic cells pulsed with tumor lysate observed a radiologically determined DCR of 28% in 35 patients with advanced HCC.[96] Hepcortespenlisimut-L, a tableted oral formulation derived from a heat-inactivated pooled blood of patients with HCC and viral hepatitis, has entered phase III trials in patients with HCC and demonstrated clear improvements in ALT, AST, alkaline phosphatase, and bilirubin levels compared with placebo.[97]

The dramatically high efficacy rates seen with RNA-based vaccines during the COVID-19 pandemic has re-invigorated the study of RNA-vaccinology—a concept with roots in the immunotherapy discipline.[98,99] RNA has been used as both a vaccine platform and an adjuvant to boost immunogenicity for HCC-specific epitopes, such as HLA-A*02-restricted tumor-associated peptides.[100,101]

Adoptive cell therapies

To date, the most advanced clinical studies for cellular therapies in HCC are with cytokine-induced killer cells

(CIKs), which are characterized by coexpression of CD3 and CD56 and can be generated by expanding human peripheral blood mononuclear cells in the presence of interferon-gamma (IFNγ).[102 103] One randomized phase III trial of CIKs as adjuvant therapy for patients with HCC undergoing resection demonstrated a median recurrence-free survival (RFS) of 44 months in the cell therapy group and 30 months in the control group (HR 0.63; 95% CI 0.43 to 0.94; p=0.010 by one-sided log-rank test).[104] A meta-analysis of 13 phase II and phase III trials involving CIKs for HCC that included a total of 1,212 patients found that cellular therapy was associated with a significantly improved 1-year survival (OR 0.25; 95% CI 0.12 to 0.52; p<0.001) and 2-year survival (OR 0.17; 95% CI 0.07 to 0.43; p<0.001), as well as a favorable DCR (OR 0.09; 95% CI 0.04 to 0.25; p<0.001) and ORR (OR 0.21; 95% CI 0.13 to 0.35; p<0.001).[105]

Allogenic natural killer (NK) cell-based adoptive therapies have also been evaluated in HCC. One study that included 40 patients with stage IV HCC found that NK cell therapy synergized with irreversible electroporation (IRE), leading to decreased AFP expression and higher median OS compared with IRE alone (10.1 months vs 8.9 months; p=0.0078).[106] Allogenic NK cell therapy also showed synergy with cryoablation in a study that included 61 patients with advanced HCC. After a median follow-up of 8.7 months (range 3.9–15.1 months), median PFS and DCR were higher among the 35 patients who received cryoablation plus NK cells compared with the 26 patients treated with cryoablation alone (PFS 9.1 months vs 7.6 months; p=0.0107; DCR 85.7% vs 69.2%; p<0.01).[107]

Panel recommendations

- Clinicians should encourage patients' participation in clinical trials.
- Future biomarker development might help to select a subgroup of patients benefitting from single-agent nivolumab treatment. Designing a biomarker strategy based on pretreatment and on-treatment tissue and blood samples to assess immune cell changes and other correlatives is critical to elucidate mechanisms of response or resistance to immunotherapy in combination with local therapy in early-stage HCC.
- Studies evaluating combinations of other immunotherapies with ICIs should be based on solid scientific rationale.
- Future randomized studies to compare local therapy alone to local therapy combined with immunotherapy are essential to assess the expected synergy and favorable treatment outcome of the combination strategy.

PATIENT SELECTION AND MANAGEMENT

Patient selection

In selecting the appropriate patient for consideration of treatment with a standard immunotherapy-based approach (as opposed to within the context of a clinical trial), there are both general oncologic considerations as well as HCC-specific or liver-specific considerations. It is critical to account for the singular nature of HCC, as it generally arises in a damaged and potentially dysfunctional liver. As many as 43% of patients with HCC will die as a direct result of cirrhosis as opposed to cancer progression.[108] Therefore, clinical trials needed for patients with more advanced liver function decompensation than Child-Pugh B7 are encouraged, especially when the main factor behind liver function deterioration is HCC progression rather than the underlying liver disease. Additional considerations include the patient's performance status and history of comorbidities, in particular the presence of any known autoimmune disorders. A patient's eligibility for treatment with anti-VEGF therapy—either with TKIs (eg, sorafenib) or monoclonal antibodies (eg, bevacizumab)—will also inform a treatment plan. Liver-specific factors that need to be considered include the stage of the HCC and the indication for treatment, the underlying synthetic liver function, and disease etiology and its bearing—if any—on outcome. There are also certain specific situations such as recurrence in the setting of liver transplant that need further study, as well as the role of biomarkers in predicting efficacy or toxicity. For many of these considerations, the data are varied in terms of the weight of evidence, which should be taken into account in regard to the degree to which they should influence the physician's decision.

General considerations

Clinical trials demonstrating efficacy for immunotherapy have largely been performed in patient populations who were required to have a good performance status (ie, Eastern Cooperative Oncology Group (ECOG) 0 to 1) in order to take part. This, of course, is a general and widely accepted principle of oncology trials which also applies to immunotherapy treatment, although two meta-analyses have demonstrated no significant differences in OS between patients stratified by performance status between the groups with ECOG 0 and with ECOG 1–2.[109 110] The efficacy and tolerability of immunotherapy in patients with a performance status of >2 is largely unknown. Another population that is frequently excluded from trials and sometimes undertreated due to concerns about frailty is the elderly. Subgroup analyses from IMbrave150, however, found that the safety of atezolizumab in combination with bevacizumab was largely identical between elderly (aged ≥65 years) and non-elderly (aged <65 years) patients. Furthermore, clinical benefit with atezolizumab in combination with bevacizumab compared with sorafenib was confirmed, with elderly patients having similarly improved OS, PFS, and ORR as non-elderly patients.[111]

Cardiovascular toxicity risk is a major consideration if anti-VEGF therapy is being considered as part of the treatment plan for a patient with HCC. Anti-VEGF therapies are associated with increased bleeding risk, which is an important consideration in this patient population, many of whom will have portal hypertension. Awareness of contraindications to anti-VEGF therapy is important, particularly as these agents become further incorporated into evolving immune-based standards of care. A recent analysis found that as many as 35% of patients with cancer receiving bevacizumab were treated despite the presence of contraindicating comorbidities.[112]

HCC is often diagnosed at an advanced stage in patients living with HIV, and the hepatotoxicity of highly active antiretroviral drugs may further exacerbate underlying liver damage.[113 114] Historically, patients with HIV have been excluded from trials, leading to an unmet need for effective therapies in this population—a group that also has poorer outcomes in HCC, specifically, compared with HIV-negative individuals.[115] Although not yet studied specifically in HCC, tolerable safety and efficacy with ICI therapy for a variety of solid tumors has been demonstrated for patients living with HIV.[116 117]

Patients with a history of autoimmune disorders have also historically been excluded from immunotherapy clinical trials given the mechanisms of action of immunotherapy agents and the risk of exacerbating existing autoimmunity. At present, the evidence for safety of ICIs in patients with pre-existing autoimmunity is limited to retrospective studies and case reports,[118] which likely are not generalizable. Although one meta-analysis found that flares and irAEs in patients with autoimmune diseases treated with ICIs could often be managed, some events were severe and fatal. The overall incidence, however, could not be determined due to a lack of prospective studies.[119] In addition, several studies have shown worse outcomes after ICI therapy among patients who were already taking steroids or immunosuppressive medication at baseline.[120 121]

Finally, racial and ethnic minorities have been reported to have higher rates of mortality from HCC in the USA.[122] Minority groups also have a history of underrepresentation in clinical trials,[123] meaning that often these patients not only often lack access to the best care for their disease but also that clinicians must extrapolate from data on the majority population for decision-making due to lack of direct evidence for efficacy.[124] Awareness of historical disparities and efforts to include diverse populations in future studies is important to improve outcomes for all patients.

HCC-specific considerations

At present, the data in support of immunotherapy for HCC apply to patient populations who are not amenable to curative approaches for early-stage disease such as resection, ablation, transplantation, or locoregional approaches for intermediate-stage disease (see **Immunotherapies in development for HCC** section for a discussion of integration of immunotherapy with these approaches). While immunotherapy for HCC in the neoadjuvant setting cannot be recommended at this time, studies are ongoing that will evaluate the safety and feasibility of immunotherapy in the neoadjuvant or postoperative/ablation setting. Encouraging results were reported in the final analysis of a phase II study evaluating nivolumab alone or nivolumab with ipilimumab as neoadjuvant therapy with an overall pathologic CR rate of 24% among 21 evaluable patients (2 patients in the nivolumab monotherapy group and 3 in the nivolumab plus ipilimumab group). Grade 3 toxicity was experienced by five patients receiving nivolumab plus ipilimumab and one receiving nivolumab monotherapy, and no grade ≥4 toxicity was reported.[125] The phase Ib PRIME-HCC trial will also assess safety and bioactivity of preresection nivolumab with ipilimumab in patients with HCC.[126] Additionally, the combination of neoadjuvant nivolumab and cabozatinib has been evaluated in an open-label, single-arm, phase I study in patients with borderline resectable or locally advanced HCC. Among the 12 patients who underwent successful surgical resection, 41.7% (n=5) had a major or complete pathologic response with 80% of the pathologic responders (n=4) remaining recurrence-free at a median follow-up of 1 year. Resection specimens from patients with responsive disease showed evidence for enrichment of IFNγ^+ effector memory CD4$^+$ T cells as well as granzyme B$^+$ effector CD8$^+$ T cells.[127]

HBV infection is the etiological agent for as much as 50% of the incidence of HCC worldwide,[128] and HCV is estimated to account for up to one-third of cases.[129] HCV-associated advanced HCC was the first setting in which ICIs were evaluated, although modest response rates and a median time to progression of 6.4 months were observed in the initial study's 21-patient cohort treated with tremelimumab.[69] Adequate viral control was reported in hepatitis-infected, ICI-treated patients in CheckMate 040 and KEYNOTE-224, and no worsening of hepatitis was observed.[13 14] Published trials, however, required patients with HBV infections to be on antiviral therapy. Another retrospective study of outcomes among immunotherapy-treated patients with concomitant HBV or HCV infections (among which HCC was the most common tumor type) found no evidence for viral reactivation and similar incidences of grade ≥3 irAEs, as well as ORRs compared with those observed in registration trials of approved anti-PD-1 therapy.[130] However, the immune landscape of HBV-associated HCC is generally thought to be profoundly suppressed and exhausted, which could potentially alter the efficacy of ICI therapy. A pooled analysis of anti-PD-(L)1 therapy trials for HCC found that although HBV-positive patients achieved ORRs comparable to those of HBV-negative patients (OR 0.68; 95% CI 0.37 to 1.25; p=0.21), the DCRs were significantly lower for HBV-positive patients compared with HBV-negative patients (OR 0.49; 95% CI 0.27 to 0.89; p=0.02).[131]

A recent meta-analysis by Pfister *et al*[132] found differential survival outcomes depending on HCC etiology in 1,656 patients in randomized trials of ICIs as monotherapy or in combination with bevacizumab. In the analysis, checkpoint blockade was not associated with improved survival in patients with non-viral HCC, in marked contrast to the overall cohort and patients with viral etiology. In addition, survival was also diminished in two smaller cohorts of patients with HCC and documented NAFLD. Although provocative and interesting, future prospective confirmatory studies are needed to understand if and how etiology affects the liver immune microenvironment. Of note, a separate study that did not include patients treated in IMbrave150 found no differences in ORRs nor features of the tumor microenvironment (TME) that are known to modulate responses to ICIs between patients with viral and non-viral HCC.[133]

Relatively few trials have included patients with Child-Pugh B cirrhosis, a population for which few treatment options are available. In a retrospective case series of 18 patients with Child-Pugh B cirrhosis and advanced HCC who were treated with nivolumab, 94% (17 of 18) experienced a grade ≥3 AE, with treatment-related grade ≥3 AEs reported in 28% (5 of 18). IrAEs were reported in 50% of patients (9 of 18), and 28% (5 of 18) required steroids. Treatment-related AEs led to discontinuation of therapy in four patients (22%).[59] In the Child-Pugh B cohort of CheckMate 040, 49 patients with Child-Pugh B7 to B8 advanced HCC who were sorafenib-naïve (n=25) or sorafenib-experienced (n=24) received nivolumab monotherapy. Investigator-assessed ORR was 12% (95% CI 5% to 25%) and the DCR was 55% (95% CI 40% to 69%). Safety was similar to that seen with nivolumab in patients with Child-Pugh A disease. At a median follow-up of 16.3 months, median OS was 7.6 months for the entire cohort—median OS in sorafenib-naïve and sorafenib-treated patients were 9.8 and 7.4 months, respectively.[61] Importantly, there is no evidence to date indicating that immunotherapy causes further damage to impaired livers.

Patients with tumor invasion of the main trunk of the portal vein, invasion of the portal vein branch contralateral to the primarily involved lobe (Vp4), bile duct invasion, and/or tumor occupying ≥50% of the liver are considered high risk. Data from IMbrave150 indicates that atezolizumab with bevacizumab is safe and effective in patients with high-risk features. Although more grade 5 upper gastrointestinal hemorrhage events were reported in high-risk patients receiving atezolizumab with bevacizumab, none of these grade 5 events were considered by investigators to be related to treatment.[134] However, variceal bleeding is a potential toxicity of anti-VEGF agents. Therefore, for patients treated with atezolizumab in combination with bevacizumab, esophagogastroduodenoscopy to evaluate for varices within 6 months of initiating therapy is recommended.[135]

Finally, patients who have received liver transplants are typically excluded from clinical trials due to concerns about graft rejection, and high rates of rejection and mortality have been reported in the limited cases published thus far.[87]

Biomarkers for ICI efficacy and safety in HCC

ICIs provide benefit for only a subset of patients. The ability to identify intrinsic resistance to ICIs would allow patients to attempt other therapies, which could, most importantly, lead to better outcomes, while also saving healthcare resources. Unfortunately, validated blood or tissue biomarkers for ICI resistance are currently lacking in the clinical setting. Early studies have also returned conflicting results. High serum AFP levels are associated with increased sensitivity to the anti-VEGF receptor (VEGFR) monoclonal antibody ramucirumab.[136] Post hoc subgroup analysis of randomized trials have shown that the HR for OS was slightly lower among patients with high AFP in KEYNOTE-240 (pembrolizumab vs placebo)[65] and CheckMate 459 (nivolumab vs sorafenib),[137] while the contrary was observed in IMbrave150 (atezolizumab with bevacizumab vs placebo).[16 69] Furthermore, objective remissions occur irrespective of AFP levels after nivolumab or pembrolizumab monotherapies, or the combination of ipilimumab and nivolumab.

A number of features of the tumor microenvironment have been associated with HCC prognosis, including overall lymphocyte infiltration, density of Tregs, and tumor-associated macrophages (TAMs), especially if M2-polarized. In melanoma, the presence of conventional type 1 dendritic cells seems critical to promote a T and NK cell infiltrate and for the action of ICIs.[138] In HCC animal models, β-catenin-mutations in HCC (which are present in around 25% of human HCCs) result in a paucity of intratumoral conventional type 1 dendritic cells,[139] and it has been proposed that β-catenin defects may be used to identify patients with disease that will fail to respond to PD-1 blockade.[140] This feature awaits investigation in clinical trials. Soluble factors also modulate the immune response against HCC. For example, transforming growth factor beta (TGF-β) downregulates antitumor responses through a variety of different mechanisms, and high levels of the cytokine shape the response to pembrolizumab.[141]

Pretreatment tumor infiltration by T cells and their activity status are key to determine response to ICIs in various cancers. In advanced HCC, $CD4^+$ and $CD8^+$ T cell infiltration showed weak correlations with survival after second-line treatment with PD-1 inhibitors in CheckMate 040.[142] In the trial, deep antitumor responses were observed regardless of PD-L1 expression after nivolumab treatment, although the response rate was higher among patients with at least 1% of tumor cells expressing PD-L1.[142]

On the other hand, PD-L1 expression in tumor or stromal immune cells was higher among responders to pembrolizumab, but remissions also occurred in the absence of expression in both cell types.[65] In CheckMate 459, median OS after nivolumab and sorafenib was 16.1 months versus 8.6 months among patients that had tumor PD-L1 expression ≥1% (HR 0.80), and 16.7 months versus 15.2 months among those that had tumor PD-L1 expression <1% (HR 0.84).[137] Interestingly, macrophage infiltration, including M2-polarized TAMs, was not associated with clinical outcomes after nivolumab treatment. A meta-analysis including 894 patients across nine trials of ICIs in advanced HCC found a positive association between PD-L1 expression and response to therapy—especially for single-agent anti-PD-1. Strikingly, in the analysis, PD-L1 expression status had minimal association with response to therapy for patients being treated with anti-CTLA-4-containing combinations.[143] Analytical heterogeneity in PD-L1 expression is substantial, however, and may contribute to the performance of this test as a predictive biomarker.[144]

Several inflammatory gene signatures are correlated with higher response rate and improved OS after nivolumab treatment.[142] Interestingly, the most complex transcriptomic classifications of inflammatory HCC including a large number of genes[145] were not identified as predictive of response in this analysis, suggesting that short gene signatures may be more relevant for clinical development. Regarding ICI combinations, objective remissions occurred with ipilimumab plus nivolumab irrespective of PD-L1 expression in tumor cells.[146] An early burst of $Ki67^{+}CD8^{+}$ cells in the peripheral blood was also seen in one of the randomized expansion cohorts for Study 22, which evaluated combinations of durvalumab and tremilimumab at different dosing regimens,[74] hinting that cytotoxic T cell proliferation after therapy may predict response. Altogether, though, it seems unlikely that a single biomarker could be used to inform clinical decisions in a timely fashion. However, it is probable that composed and integrative multifactorial indexes might help identify patient subsets who are likely to benefit, further underscoring the importance of obtaining pretreatment tumor biopsies for future translational studies.

Pembrolizumab is FDA-approved for two tissue-agnostic indications based on tumor-intrinsic characteristics. Approval for pembrolizumab for the treatment of microsatellite-high (MSI-H) or mismatch repair deficient (dMMR) tumors was based on a pooled ORR of 39.6% (95% CI 31.7% to 47.9%), with a 7% CR rate among 149 patients with 15 different tumor types in five single-arm multi-cohort multicenter trials: KEYNOTE-016,[147] KEYNOTE-164,[148] KEYNOTE-012[149] KEYNOTE-028,[150] and KEYNOTE-158.[151] Approval for pembrolizumab for non-MSI-H/dMMR tumors with high mutation burden (TMB-H)—defined as ≥10 mutations per megabase (mut/Mb) as assayed by the FoundationOne CDx companion diagnostic—was based on KEYNOTE-158.[152] No patients with HCC were included in the cohorts upon which the tissue-agnostic indications for pembrolizumab were approved, however.

TMB correlates with the number of neoantigens and response to ICIs in tumors with >20 somatic mut/Mb, such as melanoma.[153 154] However, HCC is infrequently MSI-H/dMMR or TMB-H. One study that performed comprehensive genomic profiling of 755 patients with advanced HCC found a median TMB of 4 mut/Mb and that only six tumors (0.8%) were TMB-H. Furthermore, out of 542 cases assessed, only one (0.2%) was MSI-H.[155] Another analysis found a rate for MSI-H as low as 6%.[156]

Markers of systemic inflammation like neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have shown a strong prognostic impact in HCC across tumor stages. Lower NLR has been associated with better outcomes after sorafenib,[157 158] and similar trends are emerging from trials of ICIs. In CheckMate 040, patients progressing on nivolumab had a higher NLR and PLR than patients who had disease control as the best overall response.[142] Consistent with this observation, a retrospective analysis of 103 patients who received nivolumab found that patients with Child-Pugh A disease who achieved PR or CR had significantly lower post-treatment NLR and PLR ($p<0.001$ for both) compared with patients who had stable or progressive disease.[159]

The composition of the gut microbiota, which has been linked to the promotion of HCC development and progression through secreted metabolites,[160 161] may also predict response to treatment, although current analyses in the liver cancer setting are small and preliminary. Gut microbial diversity has been linked to ICI efficacy in epithelial tumors,[162] and retrospective analysis has shown that antibiotic use is associated with worse outcomes with immunotherapy in lung and renal cancer,[163] a finding that has also been replicated in a prospective trial including several additional tumor types.[164] One pilot study of eight patients with HCC treated with anti-PD-1 therapy after progression on sorafenib found that patients with responsive disease displayed higher taxa richness and more gene counts in their microbiota compared with non-responders, with enrichment for 20 distinct species of bacteria, including *Akkermansia muciniphila* and the *Ruminococcaceae* family.[165] The potential for the gut microbiota to shape responses to immunotherapy is an ongoing area of research, but, at present, the state of the data is not sufficient to alter management in this regard and clinical judgment outweighs other considerations.

An additional ongoing area of research is the identification of biomarkers for the prediction of which patients will experience irAEs with ICI therapy. Several studies have reported a link between various clinical and blood-based or serological factors and the onset of immune-related toxicity, although none have been prospectively validated for HCC. Patients with sarcopenia[166 167] and of female sex[168 169] have both been shown to have higher incidences of irAEs. Additionally, the composition of the gut microbiota may play a role in predicting which patients will develop ICI-associated colitis.[170] Additional factors under active investigation for prediction of toxicity include elevated cytokine levels at baseline, such as interleukin (IL)-6[169] and IL-17,[171] as well as the presence of autoantibodies.[172 173] Currently there are no clinically validated biomarkers to predict the risk of irAEs.

Recognition and management of irAEs

The same mechanisms by which immunotherapy drugs exert their therapeutic effects also underlie their unique toxicities—suppression of the inhibitory mechanisms that protect tissues from uncontrolled immune responses. Unlike AEs with chemotherapy or other treatment modalities, irAEs may be delayed in onset and have prolonged duration, sometimes months or years after initial exposure to therapy. The overall incidence and severity of irAEs reported in phase III trials of anti-PD-(L)1 agents varies depending on disease state and comorbidities. Most irAEs are of mild-to-moderate severity, but life-threatening events have been reported. A meta-analysis of fatal ICI-associated toxicities encompassing more than 16,000,000 adverse drug reactions from the medical records from the VigiBase-VigiLyze database found a total of 613 deaths related to ICIs. The fatalities related to anti-CTLA-4 therapy were most often from colitis (n=135, 70%), while fatalities associated with anti-PD-(L)1 were most often from pneumonitis (n=333, 35%), hepatitis (n=115, 22%), and neurotoxic effects (n=50, 15%).[174] A systematic review including 48 clinical trials involving 7,936 patients treated with nivolumab monotherapy or combination nivolumab and ipilimumab found that the double regimen was associated with more all-grade and grade ≥3 irAEs categorized by system, organ, or class (p<0.05). Additionally, the ORR of nivolumab combined with ipilimumab was positively correlated with the incidence rate of skin (r=0.54; p=0.04) and gastrointestinal irAEs (r=0.60; p=0.02), but not endocrine, hepatic, pulmonary, or renal irAEs.[175] Similarly a recent observational study including 331 patients with HCC receiving anti-PD-(L)1 monotherapy or combinations found that the emergence of treatment-related AEs of grade ≥2 while on ICI therapy predicted for improved OS (median 19.7 vs 11.0 months; HR 0.32; 95% CI 0.16 to 0.65; p=0.001) and increased ORR (30% vs 16%; χ^2 5.9; p=0.01).[176]

Typically, the management of irAEs includes interruption of ICIs, corticosteroids, and occasionally the administration of immunomodulatory agents including tumor necrosis factor (TNF) inhibitors. Detailed recommendations on the recognition and management of ICI-associated AEs have been published elsewhere[177] and the general principles contained therein may guide treatment decisions for irAEs, which are not specific to patients with HCC.

IrAEs specific to the treatment of HCC

Outside of immune-mediated hepatotoxicity, the commonly reported AEs in published trials leading to ICI approvals for HCC have been generally comparable to those seen in other disease settings. Pembrolizumab monotherapy showed a tolerable safety profile in KEYNOTE-224, with the most common irAEs of any grade being hypothyroidism (n=8, 8%) and adrenal insufficiency (n=3, 3%).[14] In the cohort of patients receiving nivolumab monotherapy in CheckMate 040, the most common AEs were pruritus (n=9, 11%) and rash (n=11, 23%).[13] The addition of ipilimumab to nivolumab, as evaluated in cohort 4 of CheckMate 040, was associated with a wider variety of toxicities with the most common AEs of any grade being rash (n=14, 29%), pruritus (n=22, 45%), diarrhea (n=12, 24%), decreased appetite (n=6, 12%), fatigue (n=9, 18%), adrenal insufficiency (n=7, 14%), and hypothyroidism (n=10, 20%).[178] For the combination of atezolizumab with bevacizumab in IMbrave150, the most common adverse reactions were hypertension (n=98, 29.8%), fatigue (n=67, 20.4%), and proteinuria (n=66, 20.1%), and no serious AEs with a difference in incidence of >2% were noted between the atezolizumab with bevacizumab and sorafenib treatment groups.[16]

Drug-induced hepatotoxicity

HCC usually develops in a background of chronic liver disease, which itself may give rise to systemic manifestations. Cirrhosis is characterized by diffuse fibrosis of the liver, altered hepatic blood flow and portal hypertension, and progressive failure of liver functions. In parallel, other organs frequently develop secondary dysfunction. Many extrahepatic disorders associated with cirrhosis cause symptoms that may mimic irAEs and therefore lead to overdiagnosis or underdiagnosis of toxicities with immunotherapy. Late recognition of irAEs may delay treatment and worsen the prognosis. Overdiagnosis may result in inappropriate interruption of ICIs, complications caused by immunosuppressive therapy, unnecessary diagnostic procedures, and increased cost. Such disorders can also synergize in causing deteriorating organ function when irAEs occur. The most important cirrhosis-related disorders that may compromise the management of irAEs are summarized in table 5.

Patients with HCC and underlying liver disease are at high risk for decompensation with additional insult to the organ. Some studies have found that underlying liver disease as opposed to cancer progression is the ultimate cause of death in almost half of patients with HCC.[108] Elevated liver enzymes without clinical impairment in hepatic function were commonly reported in all of the trials that led to approvals of ICIs for HCC.[13–15] Grade 3 or 4 elevations in liver enzymes were reported in 16% of patients in the dose-escalation arm of CheckMate 040 and in 12% of the patients in KEYNOTE-224.[14] In KEYNOTE-240, immune-mediated hepatitis events were seen in 10 patients (3.6%) in the pembrolizumab group, approximately 90% of which resolved.[65]

No prospective trials have defined the best treatment approach for drug-induced hepatotoxicity in patients with HCC receiving immunotherapy. The package inserts for pembrolizumab, nivolumab, and atezolizumab all recommend monitoring for changes in liver function and administering corticosteroids for hepatitis followed by a taper. ICIs should also be withheld or discontinued if liver enzymes or bilirubin become elevated, with the thresholds varying depending on baseline values and the drug regimen being given.[179] Exclusion of other causes of acute liver damage—including toxicities from concomitant medications, use of herbal supplements, viral hepatitis, and particularly tumor progression—is key to adequate management.

Response evaluation

Measurement of response rate in HCC has been controversial. The WHO (WHO) criteria[180] and the RECIST

Table 5 Cirrhosis-related disorders that should be considered in the diagnostic workup of irAEs in patients with HCC (Adapted from Sangro *et al*, *J Hepatol* 2020)[179]

Organ	irAE	Chronic liver disease
Skin	► Pruritus ► Rash ► Erythema multiforme, psoriasis, urticaria and rosácea ► Severe cutaneous adverse reactions	► Pruritus ► Skin disorders, including lichen planus, polyarteritis nodosa, cryoglobulinemic vasculitis, and porphyria cutanea tarda (HCV- and HBV-related)
GI tract	► Diarrhea ► Colitis	► Small intestine bacterial overgrowth ► Chronic pancreatitis
Liver	► Hepatitis	► Flares or viral infection
Lung	► Pneumonitis	► Hepatopulmonary syndrome ► Porto-pulmonary hypertension
Thyroid	► Hypothyroidism ► Hyperthyroidism ► Graves' disease	► Reduced peripheral conversion of T4 to T3 ► Thyroid dysfunction
Adrenal glands and pituitary glands	► Adrenal insufficiency ► Hypophysitis	► Hypogonadism ► Hypothalamic-pituitary dysfunction ► Relative adrenal insufficiency
Kidney	► Nephritis	► Hepatorenal syndrome ► Mixed cryoglobulinemia (HCV-related) ► HBV-related nephropathy ► IgA nephropathy
Nervous system	► Encephalitis ► Aseptic meningitis ► Peripheral neuropathy ► Myasthenia gravis ► Guillain-Barre syndrome ► Autonomic neuropathy ► Transverse myelitis	► Porto-systemic encephalopathy (typical and atypical) ► Viral-related peripheral neuropathy ► Wernicke's encephalopathy ► Autonomic neuropathy (HCV-related)
Blood and bone marrow	► Cytopenias ► Hemolytic anemia ► Red cell aplasia ► Bone marrow failure ► Hemophilia A ► Hemophagocytic lymphohistiocytosis ► Macrophage activation syndrome	► Hypersplenism and bone marrow depression ► Anemia due to folate or iron deficiency ► Hemolytic anemia ► Viral-related thrombotic thrombocytopenic purpura and aplastic anemia ► Immune thrombocytopenia (HCV-related) ► Lymphopenia related to HCC therapies

GI, gastrointestinal; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; irAE, immune-related adverse event.

guidelines[181] define standard measurement methods for converting radiology image observations into quantitative and statistically tractable frameworks for measuring changes in tumor size associated with therapy. However, assessments based solely on tumor size are misleading when applied to molecular targeted therapies and immunotherapies. For HCC in particular, poor correlation has been shown between the clinical benefits provided by sorafenib or locoregional interventional therapies and RECIST-based responses.[182] Subsequently, the concept of 'viable tumor' was endorsed by the guidelines for the design of HCC clinical trials developed by AASLD[183] and eventually incorporated into a formal proposal to amend standard RECIST criteria to address the unique complexity of HCC response assessment. The amended criteria were named mRECIST for HCC.[184] In published trials of immunotherapy for HCC, RECIST v1.1 was used. In the immunotherapy setting, no significant differences exist between RECIST and mRECIST.

Several clinical investigations have shown that objective response measured by mRECIST predicts survival in patients treated by locoregional therapies. A meta-analysis including seven trials and 1,357 patients reported an OS HR (responders vs non-responders) of 0.39 (95% CI 0.26 to 0.61; p<0.0001).[185] Another study found that EASL and mRECIST both outperformed the WHO criteria and

RECIST for patients undergoing DEB-TACE.[186] Recently, data from randomized trials confirmed that objective response by mRECIST predicts survival in patients with advanced-stage HCC receiving systemic therapies with TKIs, and suggested that objective response by mRECIST can be considered as a candidate surrogate end point of OS, although further research is needed to support this finding.[187 188]

Although late response after apparent disease progression on imaging has been reported in the context of immunotherapy for HCC,[189] the overall incidence of pseudoprogression with ICI treatment is rare. Estimated rates of psuedoprogression across published studies range from 2%–10%.[190 191] Also rare, though possible, is a rapid acceleration in tumor growth after anti-PD-(L)1 therapy, a phenomenon called hyperprogression.[191 192] Although published evidence is limited, hyperprogression has been reported in small case series of patients with HCC treated with ICIs,[193] and retrospective analyses.[194] Importantly, the evidence to date has only reported hyperprogression in the setting of anti-PD-(L)1 monotherapy—it is unclear whether the addition of VEGF-directed antibodies to ICI therapy affects the likelihood of hyperprogressive disease after treatment.

Panel recommendations

- For patients with advanced-stage HCC and for patients with earlier-stage disease where liver-directed therapies are not considered appropriate or who have progressed after liver-directed therapy, the data at present supports first-line and subsequent-line ICI therapy use (LE: 2). Further studies are needed to confirm the efficacy of immunotherapy in the curative setting (neoadjuvant/adjuvant/perioperative) or in conjunction with intra-arterial therapies.
- In patients with HCC with cirrhosis, the data supports the use of immunotherapy in patients with underlying synthetic liver function consistent with well-compensated cirrhosis, specifically Child-Pugh A (LE: 2). The panel recognizes, however, that some carefully selected patients with Child-Pugh B may derive benefit (LE: 3).
- Patients who have contraindications for the use of TKIs or anti-VEGF therapies (eg, cardiovascular comorbidities) may be suitable for anti-PD-1 monotherapy (LE: 1).
- The panel recommends against the use of immunotherapy in the post-transplant setting (LE: 4) due to the high risk of graft failure, given known mechanisms of ICIs.
- Additional studies are needed to assess the potential risks and benefits of immunotherapy in the pretransplant setting.
- The panel agrees that patients can be considered for immunotherapy treatment irrespective of hepatitis viral etiology (LE: 3), though it is strongly recommended that patients with HBV be on concomitant antiviral medication and adherent.
- While patients living with HIV have not been included in clinical trials to date, the panel believes that this is not an absolute contraindication to treatment with immunotherapy as long as the appropriate HIV therapy is instituted as per expert guidance (LE: 2), while further dedicated studies to assess such therapies in patients living with HIV remain critical.
- Historical disparities in access to clinical trial participation for underrepresented groups should be considered, with efforts made to support diversity, equity, and inclusion.
- The panel recommends against the use of routine testing of biomarkers for predicting immunotherapy efficacy, which, at this point, remains exploratory.
- The panel recommends against the use of routine testing of biomarkers for predicting irAEs, which, at this point, remains exploratory.
- Response assessment can be performed according to mRECIST criteria in patients receiving locoregional interventional therapies (LE: 3).
- Limited data are available concerning the value of mRECIST and immune-related RECIST (irRECIST) criteria in the setting of HCC response assessment, especially in the context of ICI therapy. Further studies are needed to compare outcomes between patients with response to treatment by mRECIST versus irRECIST.
- Pseudoprogression, while a real phenomenon, occurs rarely (LE: 4). A comprehensive assessment is encouraged. In published trials, treatment beyond progression has been allowed.
- Hyperprogression may occur (LE: 4). It is uncommon, cannot be anticipated, and remains poorly understood.
- Caution should be exercised in translating response assessment models developed for clinical trials into clinical practice.
- For management of irAEs in patients with HCC, refer to general principles in published guidelines.

PATIENT SUPPORT AND QOL

Immunotherapies and targeted therapies have extended survival for patients with HCC, but these new agents are not curative in most cases, and their unique toxicities can affect QOL. The importance of QOL as an independent prognostic factor for response to treatment or predicting disease progression is becoming more appreciated—several studies have demonstrated associations between baseline patient-reported QOL and survival in HCC.[195–197] Therefore, immunotherapy treatment plans should take patient QOL at baseline and on therapy into account. Additionally, it is important for clinicians to provide patients with necessary and sufficient information to help them navigate treatment without undue emotional or financial distress. Referral to support groups is also highly encouraged, including the American Liver Foundation, Blue Faery: The Adrienne Wilson Liver Cancer Association, Cancer Support Community, the Fatty Liver Foundation, and the Global Liver Institute. In addition, information provided by the National Cancer Institute and SITC may be helpful for patients.

Patient and caregiver education

Prior to diagnosis, the majority of patients and their caregivers will likely be unfamiliar with HCC, and they may harbor misconceptions about the etiology of the disease, potentially leading to stigma and shame over and above the emotional distress associated with a cancer diagnosis.[198] Among different types of cancer, HCC has been found to rank third highest in terms of levels of emotional distress experienced by patients.[199] Rehabilitation, palliative care, and psycho-oncology have been insufficiently studied in liver cancer.

Perceived stigma surrounding liver disease may cause patients to delay care or avoid seeking social support, which negatively impacts QOL.[200] The majority of HCC cases worldwide are secondary to HBV or HCV infection,[4] with NASH increasingly becoming the primary cause in the US and Europe.[5] However, a survey of HCC caregivers in the US found that 72% were under the mistaken impression that heavy alcohol use was the most common risk factor for liver cancer.[201] Stigma surrounding HBV may be more pronounced in certain populations, such as people of Asian descent,[202 203] so it is important for healthcare providers to be sensitive and culturally informed in their communications with patients.

HCC is a disease within a disease, and patients as well as their caregivers need to understand that their treatment journey will involve both the cancer itself as well as underlying liver damage. Patients with HCC often receive care from a multidisciplinary team that may include oncologists, hepatologists, surgeons, gastroenterologists, endocrinologists, and other specialists. In addition to the care team responsible for administering therapy targeting the tumor and the liver, patients will need 'whole-person' support for psychosocial and spiritual concerns, especially during end-of-life care.[204 205] Depending on the stage of their disease (for more details on staging systems for HCC, see the **Diagnostics and staging for patients with HCC** section), a patient may be receiving information from a large number of different providers, especially in cases of intermediate-stage HCC.[205] Additionally, practitioners from other specialties may have limited knowledge about the unique mechanisms of action of immunotherapies, and the accompanying potential for toxicities, making ongoing communication between a patient and their treating oncologist paramount.

Currently, immunotherapy is only approved for patients with advanced disease. Patients may be unfamiliar with the stages of liver cancer and the difference between treatments with curative intent and palliative therapy. Further complicating matters, patients may have preconceived notions shaped by media portrayals of high-profile immunotherapy success stories, while being less knowledgeable about the realistic efficacy and potential toxicities with treatment.[206] Early referral to palliative care has been shown to improve QOL in patients with non-small cell lung cancer,[207] yet palliative care is underutilized in patients with end-stage liver disease.[208 209] Patients with cirrhosis who are ineligible for transplant are also underserved with appropriate palliative care.[210] It is important for patients to understand that immunotherapy for HCC, even if it may extend OS, is a palliative treatment used in advanced stages of the disease and not curative in intent, so that they may be referred to advanced care planning early on in their treatment.

Considerations for administration, dosing and monitoring

The tolerability of immunotherapy is, for the most part, better than conventional cancer treatments, although future combination strategies (eg, ICIs with TKIs) may be associated with less favorable toxicity profiles.[211] The administration, dosing, and monitoring considerations for immunotherapy may be distinct from what a patient or caregiver is expecting based on experience with prior therapies or conversations with other healthcare providers who do not specialize in immunotherapy. Therefore, it is important to discuss the potential for irAEs and the signs and symptoms of expected toxicities with patients and caregivers. Additionally, patients must understand how liver comorbidities may affect the efficacy of immunotherapy for HCC (see the **Patient selection and management** section for considerations for healthcare providers). It is important for patients and caregivers to have clear and detailed instructions for when to contact their healthcare providers due to symptoms of irAEs, and examples of call parameters are provided in box 1.

Box 1 Patient and caregiver education for call parameters for irAEs

You should contact your healthcare providers for any of the following symptoms (or call 911 or seek emergency services as indicated)*:

- Abdominal pain
- Change in stool (blood or mucus in stool, change in color, light or clay colored)
- Increase in bowel movements, >3 movements above a patient's baseline
- Diarrhea, >3 watery stools
- Nausea or vomiting
- Jaundice (yellowish skin color)
- Difficulty breathing, shortness of breath, or chest tightness
- New non-productive dry cough
- Mental status changes
- New visual disturbances
- Headache
- New or worsening fatigue
- Fever with temperature >100.4°F (38°C)
- New weakness, muscle or joint pains
- Unintentional weight loss >3 lbs (1.5 kg)
- Significant weight gain with obvious abdominal swelling
- Rash which may or may not be accompanied by tenderness or itching

*Note to providers: Call parameters for patients highlight the following conditions: colitis, pneumonitis, endocrinopathies, dermatologic toxicities. It should be noted that many conditions have overlapping symptoms.

The ICIs that are currently approved for HCC are typically given as IV infusions, whereas TKIs such as sorafenib are oral medications. Because immunotherapy is usually administered at an infusion center, access to care may be a challenge for some patients, especially those in rural areas.[212 213] However, a potential benefit of the requirement for inperson infusions is the opportunity for contact with a treating physician if AEs do occur. Additionally, although patients receiving palliative chemotherapy have been found to prefer oral administration over IV, the majority are not willing to accept a decreased response rate or shorter DOR,[214] which is likely also true when deciding between IV immunotherapy versus other oral medications.

Multiple liver-specific assessment instruments have been developed to monitor QOL in patients with HCC, including the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-18 (EORTC QLQ-HCC18),[215] the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep),[216] the FACT Hepatobiliary Symptom Index (FHSI),[217] and the QOL-liver cancer (QOL-LC).[218] However, multiple systematic reviews have found that the most used assessment tool is the EORTC Quality of Life Questionnaire Core-30 (EORTC QLQ-C30).[219 220]

Special considerations for patients with HCC

Patients with HCC have been found to have lower health-related QOL (HRQOL) than the general population, especially for measures of physical, psychological, and functional well-being, as well as hepatobiliary symptoms.[219] Both physical and psychological factors may influence a patient's QOL, and a person's self-perception and coping mechanisms may modulate their status. In patient interviews, HCC has been found to be perceived as a long-term and chronic disease that cannot be cured but might be controlled, and coping strategies can include focusing as much as possible on managing HCC and its symptoms, emotional responses, and leading a normal life.[221] Those mental constructs can affect feelings about physical symptoms, and it has been demonstrated that patients with negative illness perceptions who use more emotion-oriented coping had worse HRQOL.[222] However, rigorous studies on interventions targeting disease perception or coping mechanisms are currently lacking.

Pain, particularly upper quadrant abdominal pain, is common in patients with HCC.[223] Pain management may be difficult because approximately 80% of patients with HCC have cirrhosis,[224] and liver damage can alter drug pharmacokinetics. Perhaps due to confusion about efficacy and safety for opioid and non-opioid analgesics, patients with HCC are undertreated for pain.[225] However, some generally safe options for pain management for patients with impaired liver function exist, including opioids, non-steroidal anti-inflammatory drugs (NSAIDs) in some cases, topical lidocaine patches (which have low levels of systemic absorption) for localized analgesia, tricyclic antidepressants, and anticonvulsants such as gabapentin (which is not metabolized by the liver).[226]

Financial toxicity is a major concern for patients with cancer,[227] and immunotherapies are among the most expensive agents on the pharmaceutical market.[228 229] Patients with cancer shoulder the burden of an increasing number of out-of-pocket costs for their treatment, even if they have insurance coverage.[230] Treatment may cause both material and psychological financial hardship, and the risk factors for each vary. Patients of younger age, female sex, non-white race, and who change employment because of cancer are more likely to experience material financial hardship, whereas psychological hardship is more likely among those who are uninsured or have lower family income.[231] The degree to which cancer causes financial burden has been shown to be the single most important predictor for poor QOL,[232] and healthcare costs for HCC are substantial. In both North America and Asia, costs are highest for patients with HCC in the terminal phase of care.[233] Although a comprehensive analysis of the healthcare costs associated with immunotherapy in the HCC setting has not yet been performed, oncologists should communicate with patients about how treatment may affect their financial well-being, as health insurance may not cover the costs of immunotherapy drugs.

Importantly, however, immunotherapy has generally been associated with favorable QOL outcomes compared with previous standards of care. In the landmark trials leading to FDA approval of checkpoint inhibitors for HCC, no adverse effects on QOL were observed when outcomes were reported for the patients receiving immunotherapy. Nivolumab was associated with stable patient-reported outcomes, including indicators of health status and QOL regardless of prior sorafenib in CheckMate 040.[13] It is noteworthy to mention that even in a subcohort of patients from the CheckMate 040 trial with impaired liver function (Child-Pugh B), the AE profile was comparable to what was seen in patients with Child-Pugh A disease.[59] Additionally, IMbrave150 provided a large and rich data set on patient-reported QOL outcomes, which complemented the efficacy data, with a reporting rate of greater than 90%. The study found that fewer patients treated with the combination of atezolizumab with bevacizumab experienced QOL deterioration compared with those receiving sorafenib. Furthermore, for the patients who did experience QOL deterioration on immunotherapy, the onset was later.[234] Pembrolizumab also was shown to preserve HRQOL in a prespecified exploratory analysis of patients enrolled in KEYNOTE-240. Among the 271 and 127 patients randomly assigned to pembrolizumab and placebo, respectively, who completed the EORTC QLQ-C30 and the HCC supplement EORTC QLQ-HCC18, changes in both scores were similar across arms and global health status/QOL scores were stable.[235] It will be important to prospectively study QOL outcomes in future immunotherapy trials, especially as new combination regimens advance through clinical development.

Panel recommendations

- Patient and caregiver education for HCC should include an overview of the liver's function in the body, an explanation of underlying liver diseases such as HBV, HCV, and NASH, and a discussion of how immunotherapy works to treat their cancer.
- Patients must know which provider is coordinating their treatment, and they need to have clear instructions to promptly report any signs or symptoms of potential immune-related toxicities.
- Patients need counseling on the goals of treatment in advanced HCC, which is not curative in most patients, despite significant advances. Management of HCC should include focus on supportive care for uncontrolled symptoms and inclusion of palliative care specialists.
- Patients should receive education on the expected toxicities associated with immunotherapies, including hepatitis, colitis, pneumonitis, and immune-related endocrinopathies. Detailed call parameters should be provided to promptly report signs and symptoms of irAEs.
- Assessment of patients' physical function and symptoms should be performed before, during, and after therapy.
- Patients should be referred to a treatment team including a social worker and a financial manager to assist in navigating healthcare costs and identifying support systems.
- Conversations should be initiated with patients about how the costs of immunotherapy treatment will be covered, including contributions from private insurance, Medicare and Medicaid, clinical trials, patient assistance programs, or compassionate use as needed.
- Patients should be provided information about local advocacy and support groups specific to primary liver cancer.

CONCLUSION

Immunotherapy represents a major breakthrough for the treatment of advanced HCC, offering some of the first demonstrated improvements for patient outcomes over standard-of-care systemic therapies since the late 2000s. Despite these advances, immunotherapy for HCC is currently only applicable to patients with advanced-stage disease and largely not curative in intent. Furthermore, the question of how to manage disease that progresses after ICI therapy remains unanswered. Additionally, the use of immunotherapy for early-stage disease remains largely investigational. As additional trials continue to report results, more options may become available for later lines of therapy. Future trials are needed to address the impact of immunotherapy in combination strategies with locoregional approaches, to assist oncologists and their patients in balancing the potential for harm and benefit in early-stage cancer. In the future, the indications for existing therapies are likely to continue to expand and novel combinations may be approved. These guidelines will be updated as the field continues to develop.

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