Liver Cancer

Review Article

Liver Cancer 2022;11:511–526
DOI: 10.1159/000526038

Received: January 18, 2022
Accepted: June 26, 2022
Published online: July 20, 2022

Chinese Expert Consensus on Immunotherapy for Hepatocellular Carcinoma (2021 Edition)

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Keywords
Hepatocellular carcinoma · Immune checkpoint inhibitors · Consensus

Abstract
Background: Hepatocellular carcinoma (HCC) is one of the most common malignancies in China. Most HCC patients are first diagnosed at an advanced stage, and systemic treatments are the mainstay of treatment. ***Summary:*** In recent years, immune checkpoint inhibitors have made a breakthrough in the systemic treatment of middle-advanced HCC, breaking the single therapeutic pattern of molecular-targeted agents. To better guide the clinical treatment for effective and safe use of immunotherapeutic drugs, the Chinese Association of Liver Cancer and Chinese Medical Doctor Association has gathered multidisciplinary experts and scholars in relevant fields to formulate the "Chinese Clinical Expert Consensus on Immunotherapy for Hepatocellular Carcinoma (2021)" based on current clinical studies and clinical medication experience for reference in China. ***Key Messages:*** The consensus contained 17 recommendations, including the preferred regimen for first- and second-line immunotherapy, evaluation and monitoring before/during/after treatment, management of complications, precautions for special patients, and potential population for immunotherapy.

Background

Primary liver cancer is a common malignancy in China, with morbidity and mortality ranking fourth and second among malignancies, respectively [1]. Hepatocellular carcinoma (HCC), which accounts for 85–90% of all

Table 1. Level of evidence in evidence-based medicine

Level of evidence	Description
Ia	The evidence comes from a meta-analysis of multiple randomized controlled studies
Ib	The evidence comes from at least one well-designed randomized controlled study
IIa	The evidence comes from at least one well-designed prospective non-randomized controlled study
IIb	The evidence comes from at least one well-designed interventional clinical study of other types
III	The evidence comes from well-designed non-interventional studies, such as descriptive and correlation studies
IV	The evidence comes from reports of the expert committee or clinical experience reports of authoritative experts

Table 2. Levels of expert recommendations

Level of evidence	Description
A	Good scientific evidence suggests that the medical treatment confers clear benefits; it is recommended that physicians perform the medical treatment on patients
B	Existing evidence shows that the medical treatment can confer moderate benefits that outweigh its potential risks; physicians can recommend or perform the medical treatment on patients
C	Existing evidence shows that the medical treatment may have little benefit, or the benefit is close to the risk; physicians can selectively recommend and perform the medical treatment on patients according to their individual condition
D	Existing evidence shows that the medical treatment has no benefit, or its potential risks outweigh the benefits; it is not appropriate for physicians to perform the medical treatment on patients
I	There is a lack of scientific evidence, or existing evidence cannot be used to evaluate the benefits and risks of the medical treatment; physicians should help the patients understand the uncertainty of the medical treatment

primary liver cancers, seriously threatens the lives and health of people. Most HCC patients in China are first diagnosed at an advanced stage [2], so surgical resection is not possible, and systemic treatment is the mainstay treatment. Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China (2019) recommended that patients with stage IIb, IIIa, or IIIb liver cancer can choose a systemic treatment [3]. In recent years, a breakthrough has been made in the systemic treatment of HCC. In particular, immunotherapy represented by immune checkpoint inhibitors (ICIs) has broken the single therapeutic pattern of molecular-targeted agents, and the treatment strategy combining immunotherapy with anti-angiogenesis targeted therapy shows superiority. Because immunotherapy for HCC has not been applied clinically for a long time, there is still a lack of experience in selecting the population to be treated, treatment regimen determination, efficacy evaluation, adverse event (AE) management, and application in a specific population. In order to better guide the clinical treatment for effective and safe use of immunotherapeutic drugs, the Chinese Association of Liver Cancer and Chinese Medical Doctor Association has gathered multidisciplinary experts and scholars in relevant fields to formulate the "Chinese Clinical Expert Consensus on Immunotherapy for Hepatocellular Carcinoma (2021)" based on the current clinical studies and clinical medication experience for reference in China. Recommendations in the consensus are divided into 5 levels, which are based on 6 levels of evidence (Tables 1, 2).

Recommendation of Treatment

Immunotherapy for Intermediate-Advanced HCC

This expert consensus recommends treatment regimens that have been approved by the National Medical Products Administration (NMPA) or the Food and Drug Administration (FDA) for HCC or have good data from early clinical trials and are being further explored in III clinical trials. Currently, the programmed death-1 ligand (PD-L1) antibody approved for HCC by NMPA is atezolizumab; the PD-1 antibodies approved for HCC include camrelizumab, tislelizumab, and sintilimab. The PD-L1 antibody approved for HCC by the FDA is atezolizumab; the PD-1 antibodies approved for HCC indications include nivolumab and pembrolizumab; the cytotoxic T lymphocyte (CTLA-4) antibody approved for HCC is ipilimumab (not marketed in China).

First-Line Treatment

Main sources of evidence: (1) immunotherapy combined with antiangiogenic targeted therapy: atezolizumab + bevacizumab (IMbrave150 trial), sintilimab + IBI305 (bevacizumab biosimilar) (ORIENT-32 trial), camrelizumab combined with apatinib (RESCUE trial),

Table 3. First-line immunotherapy regimens for HCC

Classification	Level-A recommendation	Level-B recommendation
Liver function of Child-Pugh Grade A or better part of Grade B (≤7 points), HBV DNA <2,000 IU/mL, ECOG PS 0–1	Atezolizumab combined with bevacizumab Atezolizumab 1,200 mg IV Q3W Bevacizumab 15 mg/kg IV Q3W	Camrelizumab combined with apatinib Camrelizumab 200 mg (body weight ≥50 kg) or 3 mg/kg (body weight <50 kg) IV Q2W Apatinib 250 mg PO QD
	Sintilimab combined with IBI305 Sintilimab 200 mg IV Q3W IBI305 15 mg/kg IV Q3W	Pembrolizumab combined with lenvatinib Pembrolizumab 200 mg IV Q3W Lenvatinib 8 mg PO QD (body weight <60 kg) or 12 mg PO QD (weight ≥60 kg)
	Tremelimumab(T) combined with durvalumab(D) T300+D (tremelimumab 300 mg plus durvalumab 1,500 mg [one dose each during the first cycle] followed by durvalumab 1,500 mg once every 4 weeks)	If there are contraindications for anti-angiogenesis targeted therapy: nivolumab 240 mg IV Q2W

pembrolizumab combined with lenvatinib (KEYNOTE-524 trial) and tremelimumab + durvalumab (HIMALAYA trial); (2) immunotherapy monotherapy: nivolumab (CheckMate 459 trial) (Table 3). The IMbrave150 trial was an international multicenter phase III clinical trial [4]. Compared with sorafenib, atezolizumab combined with bevacizumab could significantly improve the overall survival of patients (median overall survival [mOS]: 19.2 vs. 13.4 months, HR = 0.66, $p = 0.0009$), prolong progression-free survival (median progression-free survival [mPFS]) (6.9 months vs. 4.3 months, HR = 0.0001) (RECIST v1.1), and improve the objective response rate (ORR) (30% vs. 11%, $p < 0.0001$) [5]. The incidence rates of grade (G) 3/4 treatment-related AEs (TRAEs) in the combination therapy and sorafenib groups were 43% and 46%, respectively. In the Chinese subgroup, the combination therapy group had more significant benefits than the whole population (OS: 24.0 months vs. 11.4 months, HR = 0.53, 95% CI: 0.35–0.80) [5]. Based on this trial, the FDA- and NMPA-approved atezolizumab combined with bevacizumab for the treatment of unresectable HCC without previous systemic treatment in May and October 2020, respectively.

The ORIENT-32 trial was a multicenter phase III clinical trial conducted in China. Compared with sorafenib, sintilimab combined with IBI305 (bevacizumab biosimilar) significantly improved mOS (not reached vs. 10.4 months, HR = 0.57, $p < 0.0001$), prolonged mPFS (4.6 months vs. 2.8 months, HR = 0.56, $p < 0.0001$), and had a higher ORR (21% vs. 4%, $p < 0.0001$) (RECIST v1.1) [6]. Based on this trial, NMPA approved sintilimab combined with IBI305(bevacizumab biosimilar) as the first-line treatment for unresectable or metastatic HCC in June 2021.

A number of phase I and II clinical trials of combination immunotherapy have also initially shown good efficacy and controllable safety. The phase II RESCUE trial showed that the ORR of camrelizumab combined with apatinib for first-line treatment ($N = 70$ cases) reached 34% (RECIST v1.1). The mPFS was 5.7 months, and mOS was 20.1 months [7, 8]. In the phase Ib KEYNOTE-524 trial, the ORR of pembrolizumab combined with lenvatinib for first-line treatment ($N = 100$ cases) was 36% (RECIST v1.1). The mPFS was 8.6 months, and mOS was 22.0 months [9]. Currently, a number of phase III clinical trials assessing combination immunotherapy are ongoing, some of which are shown in Table 4.

The results of the CheckMate 459 phase III clinical trial showed that compared with sorafenib, nivolumab does not reach statistical significance in the primary endpoint of OS (16.4 months vs. 14.7 months, HR 0.85, $p = 0.0752$); its ORR was 15%. However, it still showed certain clinical significance and good safety. G3/4 TRAEs accounted for 22%, while those of the sorafenib group accounted for 49% [10].

Data from the phase III HIMALAYA trial showed that a single priming dose of tremelimumab added to durvalumab provided a statistically significant survival ben-

efit versus sorafenib in first line (3-year survival rate 30.7% vs. 20.2%, $p < 0.05$). Hence, availability of all the study data will likely impact on clinical decision-making in this setting. On November 20, the report of the COSMIC 312 trial testing the combination of cabozantinib and atezolizumab showed a significant benefit in progression-free survival (6.8 vs. 4.2 months, $p = 0.0012$), but while waiting for the final survival analysis, the interim data do not show a significant survival benefit compared to sorafenib (15.4 vs. 15.5 months, $p = 0.438$).

Recommendation 1:

*The preferred regimen for first-line immunotherapy in HCC is atezolizumab + bevacizumab (Ib, A), sintilimab + IBI305 (bevacizumab biosimilar) (Ib, A), and tremelimumab + durvalumab (Ib, A). Camrelizumab combined with apatinib (IIb, B) and pembrolizumab combined with lenvatinib (IIb, B) can also be considered. If there are contraindications to anti-angiogenesis targeted therapy, nivolumab monotherapy is recommended (Ib, B) (*Table 3*).*

Second-Line Treatment

Main sources of evidence: (1) immune monotherapy: nivolumab (CheckMate 040 trial), pembrolizumab (KEYNOTE-224 trial), camrelizumab (phase II trial), and tislelizumab (RATIONALE 208 trial); (2) immunotherapy combined with anti-angiogenesis-targeted therapy: camrelizumab combined with apatinib (RESCUE trial); (3) immunotherapy combined with immunotherapy: nivolumab combined with ipilimumab (CheckMate 040 trial)

The phase I/II clinical trial Checkmate 040 is the first reported clinical trial on PD-1 for the treatment of HCC. In this trial, in patients previously treated with sorafenib, the mOS of nivolumab was 15.6 months, and the ORR was 14%; the median duration of response was 17 months [11]. Based on this trial, the FDA approved nivolumab for second-line treatment of advanced HCC in September 2017, starting a new era of immunotherapy for HCC.

The results of cohort 1 of the phase II KEYNOTE-224 trial showed an ORR for pembrolizumab in second-line treatment of 17%; mPFS and mOS were 4.9 months and 12.9 months, respectively [12]. Based on this trial, the FDA approved pembrolizumab for second-line treatment of advanced HCC in November 2018. In the subsequent confirmatory phase III clinical trial KEYNOTE 240, second-line treatment with pembrolizumab failed to reach prespecified endpoint compared with placebo. The mOS (13.9 months vs. 10.6 months) and mPFS (3.0 months vs. 2.8 months) showed no significant statistical difference, and the ORR of pembrolizumab was 18.3% [13]. For efficacy and safety data, pembrolizumab therapy maintained a good consistency between the KEYNOTE-240 and KEYNOTE-224 trials, which still shows certain clinical significance. And the result of phase 3 clinical study (KEYNOTE 394) of second-line treatment with pembrolizumab carried out in Asia revealed that the ORR and median OS of pembrolizumab group were 13.7% and 14.6 months, which was significantly better than the placebo group (1.3% and 13.0 months). It is the world's first and only phase III clinical trial of single-use PD-1 inhibitor used in advanced HCC which achieved positive results.

A domestic phase II clinical trial of camrelizumab for advanced HCC in cases previously administered sorafenib and/or oxaliplatin-based systemic chemotherapy enrolled 217 patients. Patients received camrelizumab 3 mg/kg IV Q2W and Q3W, respectively. The overall ORR was 14.7%, for a DCR of 44.2% and an mOS of 13.8 months. There was no significant difference in efficacy and safety between the dosage regimens of Q2W and Q3W [14]. The most common TRAE was reactive cutaneous capillary endothelial proliferation (RCCEP), with an incidence of 66.8% (all in G1/2), which was positively correlated with ORR. The incidence of G3/4 TRAEs was 22%. Based on this trial, NMPA approved camrelizumab for advanced HCC patients previously administered sorafenib- and/or oxaliplatin-based systemic chemotherapy in March 2020.

A second-line and later line phase II clinical trial assessing tislelizumab for advanced HCC (RATIONALE 208) was carried out in multiple centers worldwide and enrolled 249 patients (49% Chinese patients; 44.6% had received at least 2 types of systemic therapies). The ORR of tislelizumab was 13.3%, for a DCR of 53%, an mPFS of 2.7 months, an mOS of 13.2 months, and a 12-month DOR rate of 79.2% [15]. Based on this trial, NMPA approved tislelizumab for HCC patients administered at least one kind of systemic therapy in June 2021.

Currently, there are no results of phase III clinical trials assessing combination immunotherapy as second-line treatment. Based on the data of multiple phase II trials, combination immunotherapy may still have certain advantages over immunotherapy monotherapy. The phase II trial RESCUE showed that the ORR of camrelizumab combined with apatinib for second-line treatment ($N = 120$ cases) was 23% (RECIST v1.1). The mPFS was 5.5 months, and mOS was 21.8 months [7, 8]. Cohort 4 of the CheckMate 040 trial was used to explore the efficacy and safety of nivolumab combined with ipilimumab in ad-

Table 4. Phase III clinical studies assessing first-line combined immunotherapy for HCC (in progress)

Study	Experimental group	Control group	Population
NCT03764293	Camrelizumab combined with apatinib	Sorafenib	Global
NCT03713593	Pembrolizumab combined with lenvatinib	Placebo combined with lenvatinib	Global
NCT04523493	Toripalimab combined with lenvatinib	Placebo combined with lenvatinib	Global
NCT04723004	Toripalimab combined with bevacizumab	Sorafenib	China
NCT04194775	CS1003 (PD-1 monoclonal antibody) combined with lenvatinib	Placebo combined with lenvatinib	Global
NCT03605706	Camrelizumab combined with FOLFOX4 chemotherapy	Placebo combined with FOLFOX4 chemotherapy	China

Table 5. Second-line immunotherapy regimens for HCC

Classification	Level-A recommendation	Level-B recommendation
Liver function of Child-Pugh Grade A or better part of Grade B (≤7 points), HBV DNA <2,000 IU/mL, ECOG PS 0–1	Camrelizumab 3 mg/kg IV Q3W	Camrelizumab combined with apatinib Camrelizumab 200 mg (body weight ≥50 kg) or 3 mg/kg (body weight <50 kg) IV Q2W Apatinib 250 mg PO QD
	Tislelizumab 200 mg IV Q3W	
	Nivolumab 3 mg/kg IV Q2W	Nivolumab combined with ipilimumab Nivolumab 1 mg/kg IV Q3W Ipilimumab 3 mg/kg IV Q3W After 4 cycles of combination therapy, sequential nivolumab 240 mg IV Q2W
	Pembrolizumab 200 mg IV Q3W	

vanced HCC patients with intolerance or progression to sorafenib [16]. The overall ORR in 148 patients treated with combined regimens of three different doses reached 31% (RECIST v1.1). Among them, group A (nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg Q3W for 4 cycles and sequential nivolumab 240 mg Q2W) had the longest mOS (reaching 22.8 months), an ORR of 32%, the highest incidence of TRAEs (G3/4: 53%), and acceptable safety. Based on the above results, the FDA approved nivolumab combined with ipilimumab (at the dose in group A) for second-line treatment of advanced HCC in March 2020. However, ipilimumab has not yet been marketed in China.

Recommendation 2:

*The second-line immunotherapy regimens for HCC are camrelizumab (IIb, A), tislelizumab (IIb, A), nivolumab (IIb, A), pembrolizumab (IIb, A), camrelizumab combined with apatinib (IIb, B), and nivolumab combined with ipilimumab (IIb, B) (*Table 5*).*

Conversion Immunotherapy for HCC

The conversion therapy for HCC includes converting unresectable tumors into resectable tumors, and patients with poor prognosis after resection (stage IIb and IIIa according to China Liver Cancer Staging [CNLC]) into patients with better prognosis after resection. Previous trials have shown that 11–27% of advanced HCC can be converted into resectable tumors with survival benefit from radiotherapy, intervention, and targeted therapy [17–19]. Compared with immunotherapy alone, immunotherapy combined with anti-angiogenesis therapy has a higher ORR (24–46%, mRECIST) and significantly prolongs the mOS of advanced HCC patients to about 20 months [5, 6, 8, 9]. Therefore, it has better potential for conversion therapy. Besides, adding radiotherapy for portal-vein tumor thrombus (PVTT) or interventional therapy on the basis of immunotherapy, conversion therapy for advanced HCC has become an important treatment strategy.

Recommendation 3:

For CNLC IIb (Child-Pugh A/B, performance status 0–2, the number of intrahepatic tumors ≥4, no extrahepatic metastases, and/or vascular tumor thrombus) and IIIa (Child-Pugh A/B, performance status 0–2, vascular tumor thrombus, no extrahepatic metastases) HCCs not suitable for surgical resection and IIIb (Child-Pugh A/B,

performance status 0–2, extrahepatic metastases) HCCs with localized metastasis, conversion immunotherapy followed by radical surgery may confer survival benefits to the patients. Immunotherapy combined antiangiogenic targeted therapy with a higher objective response rate (such as atezolizumab + bevacizumab, sintilimab + IBI305, etc.) is preferred for conversion therapy. For the timing of surgery and postoperative adjuvant treatment, it is recommended that a multidisciplinary diagnosis and treatment team make joint decisions (Ib, A).

Postoperative Adjuvant Immunotherapy for HCC

The 5-year postoperative recurrence rate of HCC is as high as 50–70%, but there is no recognized adjuvant treatment strategy at present. Currently, ICIs are a hotspot of postoperative adjuvant treatment in patients with high-risk recurrence of HCC, and a number of phase III clinical trials are ongoing, including nivolumab (NCT03383458), pembrolizumab (NCT03867084), toripalimab (NCT03859128), atezolizumab combined with bevacizumab (NCT04102098), durvalumab monotherapy or combined with bevacizumab (NCT03847428), and camrelizumab combined with apatinib (NCT04639180).

Recommendation 4:

There is no mature data of ICIs as adjuvant treatment for HCC patients with a high risk of recurrence after surgery from phase III clinical trials. Because of the lack of effective postoperative adjuvant treatment options, it is recommended that patients participate in clinical trials on adjuvant treatment with ICIs (III, I).

Biomarkers for Immunotherapy

At present, no clear biomarkers have been found to predict the efficacy of immunotherapy in HCC. PD-L1, tumor mutation burden, and microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR), are seldom mentioned in trials of HCC or do not show favorable predictive values because of the low frequencies of their occurrence or other reasons. It was reported HCCs with tumor mutation burdens > 10 mutations/Mb account for 0.8–5% [20, 21], and MSI-H cases account for only 0.2–3% [22]. The positive rate of PD-L1 in HCC tumor cells is about 10–20% [23]. Regardless of PD-L1 expression status, objective remission is observed after treatment with PD-1 inhibitors [11, 12]. In the KEYNOTE-224 trial, although patients with positive PD-L1 tumors and immune cells (CPS score ≥1) showed higher ORR ($p = 0.021$) and longer PFS ($p = 0.026$), the number of tested cases was only 52 [12]. Exploration and application of PD-L1 as a biomarker are also affected by different detection methods, spatial heterogeneity, evaluation criteria, and positive cutoff values of staining.

Recommendation 5:

At present, no clear biomarkers for predicting the efficacy of immunotherapy in HCC have been found. Histological or serological tests can be performed in patients based on actual clinical conditions to explore effective molecular markers for immunotherapy (III, C).

Evaluation of the Efficacy of Immunotherapy

Imaging-Assisted Evaluation of Efficacy

At present, most reported clinical trials of HCC immunotherapy adopt RECIST v1.1 as the evaluation criteria for primary endpoints, and the modified response evaluation criteria in solid tumors (mRECIST) and/or the modified RECIST v1.1 for immune-based therapeutics (iRECIST) to assess exploratory endpoints. RECIST v1.1 is mainly based on changes in tumor size in imaging and cannot reflect tumor density or necrosis after treatment or capture atypical tumor response patterns after ICI treatment, including pseudoprogression, which may cause undervaluation of the benefits in HCC treatment. iRECIST has introduced the concepts of immune unconfirmed progressive disease (iUPD) and immune confirmed progressive disease and temporarily regards PD evaluated by the previous RECIST v1.1 as iUPD. In iUPD patients, it is necessary to determine whether to continue immunotherapy based on clinical manifestations and laboratory tests and reevaluate them for confirmation 4–8 weeks later. iRECIST can be used as a reference for decision-making in the clinical application of immunotherapy but may increase the burden of image interpretation and data management. mRECIST takes the lesions showing the uptake of the contrast agent in the arterial phase during dynamic CT or MRI as the target lesions for evaluation, which can eliminate the interference of necrosis after HCC treatment. It remains concerning whether the response pattern of immunotherapy alone for HCC is similar to that of anti-angiogenesis targeted therapy, such as changes in tumor density and necrosis.

Recommendation 6:

Dynamic enhanced MRI or CT is used as the imaging examination for the evaluation of efficacy. The efficacy of

immunotherapy can be evaluated by RECISITv1.1 or mRECIST. mRECIST is preferred for combined anti-angiogenesis therapy (Ib, A). Imaging reexamination is performed every 6 weeks in the first 6 months of ICI treatment and every 9–12 weeks thereafter, which can be appropriately adjusted in combination with tumor markers and disease changes.

Hyperprogressive Disease after Immunotherapy

Hyperprogressive disease (HPD) after immunotherapy refers to abnormal acceleration of tumor growth after immunotherapy. The incidence of HPD differs greatly in different tumor types and different reports, varying from 4% to 29% [24], about 8–13% in HCC [25, 26]. The definitions of HPD in these studies are so different. At present, there is no recognized standard for HPD. The most commonly used standards are (1) the tumor has progressed for less than 2 months; (2) the tumor burden has increased by more than 50% compared with baseline; (3) the tumor growth rate has increased by >2 times after immunotherapy. The mechanism of HPD remains unclear, but the prognosis of patients with HPD tends to be worse. It was found that gene mutations and immune-cell subsets provide important directions for the exploration of markers of HPD risk. MDM2/MDM4 amplification, EGFR mutation, gene amplification on chromosome 11q13 (CCND1, FGF3, FGF4, and FGF19), significant reduction of effector/memory T-cell subsets (CCR7− CD45RA− CD8+ T cells), and significant increase of exhaustive T-cell subsets (TIGIT+ PD-1+ CD8+ T cells) may be related to HPD [24, 27, 28]. Retrospective studies of HCC have shown that patients with elevated neutrophil-lymphocyte ratio (>4.125), PVTT, decreased hemoglobin levels, and high Child-Pugh score may be more likely to develop HPD [25, 29], so physicians need to be alert in clinical practice.

AEs in Immunotherapy

The unique immune-related AEs (irAEs) of immunotherapy with ICIs are caused by the activation of the immune system. Their mechanism and management methods are completely different from those of chemotherapy and targeted therapy and cannot be predicted. irAEs often affect the skin, colon, endocrine organs, liver, and lungs. They are mostly G1/2 but in rare cases are more serious and even life-threatening (<1%), such as immune enteritis, immune pneumonia, immune hepatitis, and immune myocarditis.

Occurrence of AEs

Compared with PD-1/PD-L1 inhibitors, CTLA-4 inhibitors cause higher incidence rates of any grade and ≥G3 AEs [30, 31]. The AEs caused by PD-1/PD-L1 inhibitors are not dose-dependent. A meta-analysis showed that the incidence rates of any grade and ≥G3 AEs are 66% and 14%, respectively, while the risk of ≥G3 AEs caused by PD-1 inhibitors is higher than that of PD-L1 inhibitors (OR = 1.58) [30, 31]. The AEs of CTLA-4 inhibitors are dose-dependent. A meta-analysis showed that the incidence rates of any grade and ≥G3 AEs are 72% and 24%, respectively [31]. Common AEs induced by immunotherapy mainly include the following: (1) skin: rash, and mucositis; (2) heart: immune myocarditis; (3) digestive tract: nausea, vomiting, diarrhea, and enteritis; (4) endocrine abnormalities: thyroiditis, thyroid dysfunction, and adrenal-gland dysfunction; (5) lung: immune pneumonia; (6) kidney: renal dysfunction, or insufficiency; (7) liver: elevated transaminase or bilirubin, and abnormal liver function. The overall incidence of irAEs in HCC patients after ICI treatment is not significantly different from that of patients with other tumors, but the occurrence of immune hepatitis has increased. After treatment with PD-1 inhibitors, 14–26% of HCC patients have elevated AST (≥G3: 5–10%), and 9–24% have elevated ALT (≥G3: 2–6%). After double-immunotherapy combination, 13–20% of patients have elevated AST (≥G3: 4–16%), and 8–16% have elevated ALT (≥G3: 6–8%) [11, 12, 14, 16]. RCCEP is a unique irAE of camrelizumab, and its incidence after HCC treatment is 66.8% (all in G1/2). The incidence of RCCEP is significantly reduced to 22.0–29.5% when camrelizumab is combined with apatinib or chemotherapy [7, 32].

Baseline Examination and Toxicity Monitoring of Immunotherapy

HCC usually occurs after liver cirrhosis, so the patients may have manifestations of multiple system discomforts or organ dysfunction, which may become more obvious as the disease progresses. These symptoms and abnormal examinations may overlap with the manifestations of irAEs, leading to difficulties in the diagnosis and treatment of irAEs, delays in treatment because of failure to recognize them in time, or improper interruption of ICI treatment due to over-diagnosis. Therefore, sufficient baseline evaluation should be performed before HCC immunotherapy. It helps to perform the differential diagnosis of irAEs and take the best treatment decision.

The baseline examinations mainly include (1) general examinations, e.g., physical examination, inquiring about

Table 6. Baseline examination before immunotherapy

General examinations	Physical examination; inquiring about disease history of ADs; endocrine diseases and infectious diseases including HBV, HCV, and HIV; personal history; and family history
Imaging examinations	CT or MRI examination of the chest, abdomen, and pelvic cavity
Hematology examination	Blood routine, biochemical indexes, coagulation function, alpha-fetoprotein, abnormal prothrombin, and infectious disease screening (HBV serum markers, HCV antibodies [HBV DNA and/or HCV RNA in case of hepatitis markers positive], HIV antibodies and antigens, etc.)
Thyroid function examination	Thyroid-stimulating hormone and free thyroxine.
Assessment of pituitary and adrenal glands	Plasma cortisol and adrenocorticotropic hormone levels, etc., at 8 a.m.
Heart examination	ECG; echocardiogram; cTn, BNP, MB, or CK, CK-MB, and D-dimer
Patients with suspected organ disease	Other additional examinations based on clinical conditions

CK-MB, creatine kinase isoenzyme-MB.

disease history of autoimmune diseases (ADs), endocrine diseases and infectious diseases including HBV, HCV, and human immunodeficiency virus (HIV), personal history, and family history; (2) imaging examinations, including CT or MRI examination of the chest, abdomen, and pelvic cavity; (3) hematology examination, including blood routine, biochemical indexes, coagulation function, alpha-fetoprotein, abnormal prothrombin, and infectious disease screening (five HBV serum markers, HCV antibodies [HBV DNA and/or HCV RNA in case of hepatitis marker positive], HIV antibodies and antigens, etc.); (4) thyroid function examination, including thyroid-stimulating hormone and free thyroxine; (5) assessment of pituitary and adrenal glands, including plasma cortisol and adrenocorticotropic hormone levels, etc., at 8 o'clock in the morning; (5) heart examination, including ECG, echocardiogram, cardiac troponin (cTn), brain natriuretic peptide (BNP), myoglobin (MB) or creatine kinase (CK), creatine kinase isoenzyme-MB, and D-dimer; (6) in patients with suspected organ disease, other additional examinations can be performed based on clinical conditions (Table 6).

Recommendation 7:

Before ICI treatment, examinations including inquiry about medical history, physical examination, and laboratory and imaging examinations should be completed, to evaluate the tumor condition and basic organ functions (Ib, A).

Toxicity monitoring includes monitoring during ICI treatment and follow-up monitoring thereafter. Some toxic reactions appear late, even after the completion of ICI treatment. It is currently believed that symptoms should be monitored for at least 1 year from the completion of ICI treatment. It is recommended for clinical symptoms and AEs to be evaluated at each follow-up, including physical examination, and regular reexaminations should be performed during the treatment, covering blood routine, biochemical indexes, electrocardiogram, myocardial enzyme spectrum, monitoring of thyroid, pituitary and adrenal functions, and imaging examination. Although the incidence of immune myocarditis is less than 1%, it is the leading cause of fatal irAEs; consequently, it is necessary to be alert to this ailment. Totally, 81% of immune myocarditis cases occur within 3 months after medication, among whom, about 90% of patients have elevated cTn and abnormal electrocardiogram [33]. Therefore, in addition to the ECG reexamination before each ICI treatment, cTn needs to be monitored within 4 months of the initial medication. Combined evaluation of BNP, MB, or CK can be considered. cTn, BNP, MB, and CK should be retested when indicated.

Recommendation 8:

During the ICI treatment, clinical symptoms, and signs must be evaluated. Laboratory variables and organ function evaluations should be reviewed regularly or irregularly. Imaging examinations should be reviewed, follow-up should be performed after treatment, and irAEs should be alerted to, including late toxicity after completion of treatment (Ib, A).

Management of HBV in Immunotherapy

It has been shown in trials that PD-1 is highly expressed on HBV-specific CD8+ T cells in patients with chronic HBV infection, and the antiviral function of

Table 7. General principles for the treatment of irAEs

Treatment	Grade			
	G1 (hospitalization not required)	G2 (hospitalization not required)	G3 (hospitalization required)	G4 (hospitalization required, considering the ICU)
Glucocorticoids	Not recommended	Local use of glucocorticoids or systemic use of glucocorticoids, with oral administration of prednisone at 0.5–1 mg/(kg·day)	Systemic therapy with glucocorticoids, oral administration of prednisone, or intravenous administration of methylprednisolone at 1–2 mg/(kg·day)	Systemic therapy with glucocorticoids, intravenous administration of methylprednisolone at 1–2 mg/(kg·day). For 3 consecutive days, if the symptoms are relieved, gradually reduce the dose to 1 mg/(kg·day) for maintenance, and then gradually reduce the dose until discontinuing the drug about 6 weeks later
Other immunosuppressive agents	Not recommended	Not recommended	For patients whose symptoms are not relieved after 3–5 days of glucocorticoid treatment, consider using it under the guidance of a specialist	For patients whose symptoms are not relieved after 3–5 days of glucocorticoid treatment, consider treatment under the guidance of a specialist
ICI treatment	Continue the treatment	Suspend the treatment	Discontinue and discuss whether to resume ICI treatment based on the patient's risk/benefit ratio	Permanent withdrawal

ICU, intensive care unit.

HBV-specific CD8+ T cells can be restored or improved by blocking the PD-1/PD-L1 pathway [34]. However, in clinical practice, there is a risk of HBV activation after ICI treatment [35–37]. All previous clinical trials of HCC immunotherapy for marketing required patients with HBV infection to receive antiviral therapy, with a limited baseline viral load of <100 IU/mL or <500 IU/mL, and there are no reports of HBV-related hepatitis in these trials [4, 11, 12, 14, 16]. In the ORIENT-32 trial, the baseline HBV DNA was ≤2,000 IU/mL or 10^4 copies/mL [6]. A phase II clinical trial of camrelizumab for liver cancer (baseline HBV DNA <500 IU/mL) reported that among 180 patients receiving antiviral therapy, 46 had increased HBV DNA, without causing treatment interruption or termination [14].

Recommendation 9:

For HBV-related HCC, as long as HBV DNA can be detected, antiviral therapy should be applied. In HBsAg-positive HCC cases, even in case of no HBV DNA detection, nucleos(t)ide analogues antiviral therapy should be administered. In patients with excessive viral load, antiviral therapy should be performed before immunotherapy to reduce the viral load, and HBV DNA should be less than 2,000 IU/mL before treatment. During immunotherapy, HBV DNA should be redetected every 3–6 months (IIb, A).

Principles for the Management of irAEs

Regarding the management of immunotherapy-related toxicity, there are currently many domestic and foreign guidelines and consensuses, including the *Guidelines for the Management of Toxicities Related to Immune Checkpoint Inhibitors* by the Chinese Society of Clinical Oncology (CSCO), the *Management of Immunotherapy-related Toxicities* by the National Comprehensive Cancer Network (NCCN), and the *Management of Toxicities from Immunotherapy* by the European Society for Medical Oncology (ESMO). The *Guidelines for the Management of Toxicities Related to Immune Checkpoint Inhibitors* (2019) of CSCO generally manage irAEs by classifying their toxicities into 4 grades, as shown in Table 7 [38]. Glucocorticoid is the main means to manage most irAEs and should be given early when needed. Delayed use (>5 days) may affect the outcome of some irAEs. To prevent the recurrence of irAEs, hormone reduction needs to be carried out slowly, usually lasting for >4 weeks, and sometimes 6–8 weeks or longer. The toxicities in the heart, lungs, liver, and nervous system are sometimes very dangerous, so high-dose glucocorticoid administration is the first choice. For some endocrine toxicities causing hypothyroidism and diabetes, replacement hormone therapy should be used instead of glucocorticoid therapy. In case of G2 skin and endocrine toxicities, ICI treatment can be

continued. If glucocorticoid therapy is ineffective, other immunosuppressive agents can be considered, including infliximab, mycophenolate mofetil, tacrolimus, and antithymocyte globulins. Infliximab has potential hepatotoxicity and should not be considered for use in patients with immune hepatotoxicity. The specific management of different types of irAEs can be found in the guidelines and will not be described in detail here.

Rechallenge of ICIs

Rechallenge refers to restarting ICI treatment after discontinuation due to irAEs, which leads to an incidence of irAEs ranging between 18% and 52% [39–42], including the recurrence of the original irAEs or the emergence of new irAEs. It has been reported that in patients with immune hepatitis, pneumonia, and colitis, restarting ICI treatment and rechallenging to use CTLA-4 inhibitors may lead to a higher incidence of irAEs [39, 42]. Except for a few cases, when G2 irAEs are degraded to ≤G1 after treatment with a dose of prednisone ≤10 mg/day (or equivalent dose), ICI treatment may be restarted. In case of severe and life-threatening irAEs, especially G3/4 cardiac, pulmonary, and neural toxicities, ICI treatment must be withdrawn permanently. For patients who respond to the initial ICI treatment, in view of the persistence of efficacy and the risk of toxicity, restarting ICI administration may not be recommended. To restart treatment with ICIs, different types of ICIs should be selected, e.g., changing CTLA-4 inhibitors to PD-1/PD-L1 inhibitors. Indications for restarting ICI treatment may vary according to irAEs of different organs, so recommendations in the guidelines should be followed. Regarding the restarting of ICI treatment against hepatotoxicity from immunotherapy, there are differences in the recommendations of rechallenge for G3 toxicity in domestic and foreign guidelines. For G3 immune hepatotoxicity (ALT/AST = 5–20 times the normal upper limit or total bilirubin 3–10 times the normal upper limit), especially with elevated bilirubin, rechallenge of ICIs should be done with special caution.

Recommendation 10:

The rechallenge of ICI treatment needs to be considered from the perspectives of risk and benefit, in combination with the type and severity of irAEs and the efficacy of initial immunotherapy, and whether there are other alternative treatment methods for tumors (III, A).

Application of Immunotherapy in Special Populations

The treatment of special HCC populations is still difficult. Most clinical studies have not solved these medical needs, such as in organ transplantation, decompensated liver cirrhosis, fibrolamellar HCC, active autoimmune diseases (ADs), and infection with HIV. In addition, the evidence of immunotherapy for HCC combined with PVTT is relatively limited. This consensus summarizes the current status, contraindications, challenges, and unresolved problems of immunotherapy in special populations with HCC.

Organ Transplantation

For organ transplantation, both CTLA-4 and PD-1 signaling pathways are involved in the induction of transplant immune tolerance, so the use of ICIs may lead to immune rejection after transplantation and increased risk of lethality. Organ transplantation is usually the exclusion criterion in clinical trials examining ICIs. At present, most of the relevant reports are retrospective analyses and individual cases. In a retrospective analysis, the mortality rate from transplant rejection was 40.4% in 57 patients administered organ transplantation after ICI treatment; while the mortality rate of liver transplantation was as high as 76.5% (13/17), the mortality rate from immune rejection after liver transplantation was higher than that of kidney transplantation (OR = 3.1, $p = 0.04$) [43]. A domestic prospective trial reported that 5 patients with recurrence of malignant tumors after liver transplantation and negative PD-L1 expression in the transplant showed no transplant rejection after anti-PD-1 treatment, of which 3 cases had objective response, and 1 patient showing positive expression of PD-L1 had transplant rejection and died after treatment with a PD-1 inhibitor [44]. It may be the direction of future exploration to identify patients with tumor recurrence after liver transplantation who may benefit from immunotherapy through clinicopathological characteristics and biomarkers.

Recommendation 11:

Considering the high risk of transplant rejection and lethality, ICI treatment is not routinely recommended for the treatment of patients with tumor recurrence after liver transplantation (III, D). If there are no other treatment options, physicians should fully communicate with the patient and the transplant surgeon about whether to start the ICI treatment.

Child-Pugh Class B and Class C

Almost all previous prospective clinical studies assessing targeted therapy or immunotherapy for HCC have included patients with Child-Pugh Class A liver function, and only a few included patients with B7 liver function. CheckMate 040 trial-cohort 5 included patients with Child-Pugh B7-8 and found that the ORR of nivolumab for HCC untreated or treated with sorafenib was 10.2%, for a DCR of 55.1% and an mOS of 7.6 months. The safety was similar to that of the Child-Pugh Class A cohorts, with 25 patients (51%) reporting TRAEs and 2 with discontinuation due to TRAEs [45].

Recommendation 12:

In HCC patients with relatively good liver function of Child-Pugh Class B, ICI treatment can be considered with caution (IIb, B), and the best supportive treatment is recommended for patients of Child-Pugh Class C.

Fibrolamellar HCC and Combined Hepatocellular-Cholangiocellular Carcinoma

Fibrolamellar HCC and combined liver cancer (hepatocellular and cholangiocellular) are rare and special subtypes of liver cancer, which are usually excluded by randomized controlled clinical studies. The clinical prognosis and treatments remain unclear and ununified, with very few case reports on ICI treatment. A small sample of data shows that fibrolamellar HCC may be less sensitive to chemotherapy; sorafenib had limited efficacy, and median OS in patients with unresectable tumors was 10 months [46]. The molecular variation characteristics of combined hepatocellular-cholangiocellular carcinoma remain unclear. Retrospective studies have shown that platinum-containing chemotherapy may be the most effective palliative treatment, and sorafenib seems to be much less effective for this subtype [47].

Recommendation 13:

There is a lack of evidence-based medicine evidence for the systemic treatment of fibrolamellar HCC and combined liver cancer, including immunotherapy (III, I). In the future, basket or umbrella trials can be used to explore targeted therapy and immunotherapy regimens for these rare pathological types of liver cancer.

Autoimmune Diseases

Due to concerns about the increased toxicity of ICIs, tumor patients with ADs are usually excluded from clinical studies. Most patients reported in retrospective studies had mildly active ADs or ADs requiring no treatment, and ICI treatment still seemed to have good efficacy and relatively controllable safety. Despite the increase in the occurrence of immune toxicity, the main performance was mild to moderate toxicity [48, 49]. A meta-analysis included retrospective data of 619 tumor patients with AD, and the results showed that 60% of patients had worsening of the original AD and/or new irAEs after ICI treatment, accounting for 35% and 33%, respectively; G1/2 irAEs accounted for 80% and 68%, respectively, while the ORR was 30%, and the use of baseline immunosuppressants tended to reduce the ORR [49]. There are still many unclear issues, such as the impact of the type of AD on ICI treatment, including the risk of immunotherapy for HCC combined with autoimmune liver diseases; the lack of immunotherapy data for moderate to severe active AD; how to use selective and non-selective immunosuppressive agents to reduce the effect on the efficacy of ICI treatment. More detailed and in-depth studies are required.

Recommendation 14:

For patients with mild active ADs or ADs requiring no treatment, ICI treatment is not an absolute contraindication but should be used with caution (III, C). Patients with autoimmune neurological diseases or life-threatening ADs, especially those whose condition cannot be controlled by immunosuppressive agents or can be controlled only with large doses, are not suitable for ICI treatment.

Chronic Kidney Disease

Anti-PD-1, PD-L1, and CTLA-4 monoclonal antibodies are macromolecular drugs, which are not metabolized by the liver and kidney, but are catabolized into peptides and amino acids through the dissimilation of proteolytic enzymes and eliminated through internalization after binding to the target; renal insufficiency has no significant effect on their clearance [50]. Previous clinical studies of immunotherapy in HCC had inclusion criteria of creatinine ≤1.5 times the normal value or creatinine clearance ≥60 mL/min or >40 mL/min and excluded patients with severe renal dysfunction [12, 13]. A retrospective study reported that 17 tumor patients with creatinine ≥2 mg/dL or glomerular filtration rate ≤30 mL/min had no increase in the incidence of irAEs after PD-1 inhibitor treatment [51], with no further deterioration of organ function; another 18 patients with renal carcinoma under hemodialysis received nivolumab treatment, and hemodialysis did not seem to change the expected efficacy and safety [52]. However, HCC patients with end-stage renal disease often have a more complicated condition in clin-

ical practice, with high incidence of complications such as diabetes, hypertension, heart failure, and gout and a poor prognosis.

Recommendation 15:

Due to the lack of data from large sample studies and sufficient clinical application experience, immunotherapy should be used with caution for patients with severe renal impairment (III, C).

Combined HIV Infection

Among individuals infected with HIV, the high infection rates of HBV and HCV increase the incidence and mortality of HCC in this population [53]. Liver damage caused by HIV infection and antiretroviral therapy is common, and the patient's underlying immune status may also affect the safety of systemic drug therapy. A retrospective study of patients with tumors combined with HIV infection administered PD-1/PD-L1 inhibitor treatment (including 3 cases of HCC) [54, 55], and a prospective phase II trial (20 cases, excluding HCC cases) [56] showed that the efficacy and safety of immunotherapy are comparable to those found in HIV-negative patients, with no significant effect on HIV viral load.

Recommendation 16:

Under antiretroviral therapy, it may be possible for HIV-infected patients with tumors to receive ICI treatment, but there are very few reports assessing HCC patients. Therefore, more clinical data and experience are still needed, and ICI treatment should be used with caution (IIb, C).

Combined PVTT

PVTT is an important prognostic factor of HCC. In clinical studies for the marketing of immunotherapeutic drugs, PVTT patients account for about 10–40%, and major PVTT is often excluded, so data on immunotherapy in PVTT patients are relatively limited. Analysis of the large-vessel invasion subgroup of the IMbrave150 trial showed that atezolizumab combined with bevacizumab still had improved PFS and OS [4], but mOS in the VP4 type was only 7.6 months, and the incidence of varicose vein bleeding (14%) and G5 gastrointestinal bleeding (5%) increased [57]. In patients with severe esophageal varices and high risk of bleeding, ICIs combined with bevacizumab should be used with caution, and endoscopic varicose ligation before treatment can be considered to reduce the risk of bleeding.

Recommendation 17:

In patients with PVTT, immunotherapy combined with anti-angiogenesis-targeted therapy is preferred for systemic therapy. Because of the great heterogeneity among PVTT patients, caused by the difference in the involved scope of PVTT and intrahepatic tumor burden, the existence of extrahepatic metastasis, and the status of liver function, it is recommended to participate in multidisciplinary discussions (Ib, A).

Outlook

In recent years, ICIs have opened a new direction for systemic therapy in HCC. China has the largest population of HCC patients in the world, and most of them are diagnosed at an advanced stage. For such a large group of patients, other guidelines just tell us that ICIs should be used. However, more detailed guidance is needed on how to use these ICIS and how to deal with irAEs for different subgroups of HCC patients. Additionally, advanced HCC has other treatments in our country and other guidelines also do not tell us how immunotherapy combined with other treatments, which may be more beneficial to advanced HCC patients. Lastly, the ICIs approved by NMPA are different from FDA or other countries, so it is necessary to formulate a consensus in line with China's reality and China's experience in advanced HCC treatment should also be shared with other countries. Since the approval of multiple PD-1 inhibitors at home and abroad for second-line treatment of HCC, atezolizumab combined with bevacizumab and sintilimab combined with IBI305 (bevacizumab biosimilar) also demonstrated the success of immunotherapy combined with anti-angiogenesis therapy in advanced HCC. At present, there are many ongoing phase III clinical trials examining immunotherapy combined with TKI drugs or systemic chemotherapy and double immunotherapy, and studies on immunotherapy combined with local treatments such as radiotherapy and interventional therapy are also ongoing. While progress has been made in the systemic treatment of advanced HCC, the following questions and challenges remain. What is the best combination immunotherapy regimen? What are the treatment options after progress has been made in immunotherapy combined with anti-angiogenesis therapy? With the great heterogeneity of advanced HCC, how can the treatment regimen be optimized for different clinical features? At the same time, the progress of immunotherapy also provides important support for the conversion therapy of unresectable HCCs.

Phase III clinical trials of multiple postoperative adjuvant treatments of immunotherapy are also expected to fill the gap in drug therapy in this field.

Conclusion

Immunotherapy has made a breakthrough in the systemic treatment of HCC. With the successive approval of ICI drugs for HCC indications, and the inclusion of some drugs into the national medical insurance, more HCC patients receive immunotherapy in clinic. Based on the data from important clinical trials in HCC immunotherapy, as well as the experience of experts and scholars in clinical practice, this consensus provides opinions and suggestions about population selection for treatment, therapeutic regimen determination, efficacy evaluation, AE management, and special population application and serves as a reference for clinical drug use. For immunotherapy, an emerging treatment for HCC, new drugs and treatment methods are still being explored, and more experience is needed for the management of irAEs. With the continuous emergence of new evidence in evidence-based medicine, this consensus still needs to be updated and completed by peers.

Conflict of Interest Statement

The authors have no conflicts of interest to declare. Prof. Jia Fan is an Associate Editor of *Liver Cancer*.

Funding Sources

This research received no external funding.

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