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Chinese Multidisciplinary Expert Consensus on Immune Checkpoint Inhibitor-Based Combination Therapy for Hepatocellular Carcinoma (2023 Edition)

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Abstract

Background: Immune checkpoint inhibitor (ICI)-based combination therapy modalities for hepatocellular carcinoma (HCC) have achieved significant efficacy in clinical research and practice and have become the mainstay for the treatment of unresectable HCC. ***Summary:*** To better help clinicians use combination immunotherapy drugs and regimens rationally, effectively, and safely, the editorial board facilitated a discussion with multidisciplinary experts in the field, adopted the "Delphi" consensus formation method, and finally revised and completed the "*Chinese Multidisciplinary Expert Consensus on the Immune Checkpoint Inhibitors (ICIs)-Based Combination Therapy for Hepatocellular Carcinoma (2023 Edition)*" on the basis of the 2021 edition. ***Key Messages:*** This consensus primarily focuses on the principles and methods of clinical practice of combination therapy based on ICIs, aiming to summarize the recommendations for clinical application based on the latest research and expert experience and provide application guidance for clinicians.

Introduction

Primary liver cancer (PLC) is one of the most common malignancies in China. The latest statistics from the National Cancer Center indicate that the incidence of PLC ranks fourth among Chinese malignancies and second with respect to mortality rate [1]. Hepatocellular carcinoma (HCC) accounts for 75–85% of PLC (HCC only refers to "liver cancer" in this consensus). Cirrhosis caused by hepatitis B virus (HBV) infection is the most important risk factor for HCC in China.

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However, nonalcoholic fatty liver disease has been on the rise as another cause in recent years. At present, radical surgical treatment remains the most effective treatment for liver cancer, and patients in the early phase of disease are candidates for surgical resection, local ablation, liver transplantation, and other radical treatments, with a median survival of more than 5 years. However, due to the occult onset of HCC, more than 70% of Chinese patients with liver cancer are not surgical candidates at the time of first diagnosis. In addition, the postoperative recurrence rate of liver cancer is high, and the total recurrence rate within 5 years is approximately 70%. After relapse, most patients are no longer surgical candidates. Systemic antitumor therapies, especially combination regimens based on immune checkpoint inhibitors (ICIs), have become the most commonly used and most important treatment for patients with unresectable HCC [2].

In 2007, sorafenib became the first approved first-line targeted drug for HCC. Since 2018, more targeted drugs, such as lenvatinib, apatinib, and donafenib, have been introduced. In recent years, with increased understanding of tumor immunology, the clinical application of ICIs has opened up a new era of tumor therapy. ICI-based combination therapy has made consistent breakthroughs in the treatment of HCC, further improving the clinical benefits for HCC patients [3]. ICIs include programmed death-1 (PD-1) antibody, programmed death ligand-1 (PD-L1) antibody, and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibody. Among these therapies, PD-1 antibodies include nivolumab, pembrolizumab, sintilimab, camrelizumab, tislelizumab, toripalimab, and penpulimab; PD-L1 antibodies include atezolizumab, durvalumab, envafolimab, etc.; and CTLA-4 antibodies include ipilimumab and tremelimumab.

Recently, both the "Standard for Diagnosis and Treatment of Primary Liver Cancer" (2022 Edition) [2] and the "Standard for Diagnosis and Treatment of Primary Liver Cancer" (2022 Edition) of the Chinese Society of Clinical Oncology (CSCO) [4] have recommended immunotherapy for HCC. However, due to limited space, the discussion is relatively brief and does not fully meet the needs of clinical practice. This consensus focuses specifically on ICIs and explores the principles and methods of clinical application of ICI combination therapy for HCC, including treatment regimen selection, perioperative application, conversion therapy, selection of appropriate/contraindicated populations, efficacy evaluation, and management of adverse effects. Based on the *Chinese Multidisciplinary Expert Consensus on Combined Immunotherapy Based on Immune Checkpoint Inhibitors for Hepatocellular Carcinoma (2021 Version)* [5] and combined with the latest research progress and expert experience, the *Chinese Multidisciplinary Expert Consensus on Immune Checkpoint Inhibitors (ICIs)-Based Combination Therapy for Hepatocellular Carcinoma (2023 Edition)* was revised to provide a reference for the management of ICIs in the treatment of HCC.

Methodology

This consensus refers to the "Standard for Diagnosis and Treatment of Primary Liver Cancer" (2022 Edition) [2] of the National Health Commission of the People's Republic of China and uses the Grading of Recommendations, Assessment, Development, and Evaluation evidence evaluation and recommendation grading system, which is divided into 5 classes of evidence (classes 1–5) and 3 classes of recommendation strength (strong recommendation [class A], moderate recommendation [class B], and weak recommendation [class C]) (online suppl. Tables S1, S2; for all online suppl. material, see https://doi.org/10.1159/000535496). Additionally, given the lack of clinical research evidence at present and the problems that are often encountered and urgently need to be solved in clinical practice, the Delphi method was used to obtain the strength of expert consensus to determine recommendations. The Delphi method is also known as the expert opinion method and is used to investigate experts' opinions on consensus-related issues in multiple rounds, and then repeatedly consult, summarize, revise, process statistically, and finally summarize the opinions as a result in the form of letter inquiry, according to the systematic procedure, and by the way of anonymous expression of opinions [6]. The process of the Delphi method of this consensus is as follows: (1) the issues that lack clinical evidence in the consensus draft are first summarized; (2) an expert team is then assembled; (3) in the first round of discussion, the controversial issues (by email, etc.) are identified; (4) in the second round of discussion, the summarized issues are reviewed, and a consensus begins to form; the first two rounds of discussions provide a basis for subsequent discussions through qualitative analysis and clarify the issues through open-ended questions or the Likert scale; (5) in the third round of discussion, the expert team is asked to revise/review the judgment and form a consensus after this round of discussion; (6) in the fourth round of discussion (determining whether the issue will be discussed in the fourth round based on the results of the first three rounds of discussion), the expert team is required to make a final judgment on the objections to the previous discussion and give reasons; (7) final conclusions are drawn, an analysis using the standard statistical analysis tools is conducted, and the consensus results are summarized. The effectiveness is affected by the response rate, and the degree of agreement should be ≥75% to form a consensus conclusion [7]. In addition, this consensus has led to supplementary research on the preferences of experts in clinical practice in the form of multiple-choice questions.

ICI Treatment Regimen for HCC

First-Line ICI-Based Combination Regimen

Immunotherapy in Combination with Anti-Angiogenetic Agents

The IMbrave150 study is an international multicenter phase III clinical study. In this study, the median overall survival (mOS) of atezolizumab in combination with

Table 1. Overview of phase III clinical trials of first-line combined immunotherapy for HCC

Regimen category	First-line regimen	Study name	Clinical stage(s)	Dosage and administration	Number of cases in the combination group	Race, %	Overall survival, months	PFS, months	Response rate (RECIST 1.1), %	Response rate (mRECIST), %	Currently approved by FDA or NMPA
Immunotherapy + anti-angiogenic therapy	Atezolizumab + bevacizumab	IMbrave150 [9]	III	Atezolizumab: 1,200 mg, q3w; bevacizumab: 15 mg/kg, q3w	336	White: 37%; Asian: 56% Black or African American: 1.8% Unknown: 6%	19.2	6.9	30%	35%	FDA: 2020.5 NMPA: 2020.10
	Sintilimab + IBI305 (bevacizumab biosimilar)	ORIENT-32 [10]	III	Sintilimab: 200 mg, q3w IBI305: 15 mg/kg, q3w	380	Chinese: 100%	NR	4.6	21% (evaluated by the IRRC) 20% (evaluated by the investigators)	24% (evaluated by the IRRC)	NMPA: 2021.6
Immunotherapy + TKIs	Camrelizumab + apatinib	SHR-1210-III-310 [11]	III	Camrelizumab: 200 mg, q2w Apatinib: 250 mg, once daily	272	White: 16%; Asian: 83% Black or African American: <1% Other: <1%	22.1	5.6	25.4%	33.1%	NMPA: 2023.1
	Pembrolizumab + lenvatinib	Leap-002	III	Pembrolizumab: 200 mg, q3w; lenvatinib: 8 mg (body weight <60 kg) or 12 mg (body weight ≥60 kg), oral, QD	395	/	21.2	8.2	26.1%	40.8%	/
	Atezolizumab + cabozantinib	COSMIC-312 [12]	III	Cabozantinib 40 mg orally once daily plus atezolizumab 1,200 mg intravenously every 3 weeks	432	White: 50%; Asian: 29% Black: 2% Other: 7% Unknown: 12%	15.4	6.8	11%	/	/
Immunotherapy + immunotherapy	Tremelimumab + durvalumab	HIMALAYA [13]	III	Tremelimumab: 300 mg, single dose; durvalumab: 1,500 mg, q4w	393	White: 46.3%; Asian: 49.6% Black or African American: 1.8% Other: 2.1% Unknown: 0.3%	16.4	3.78	20.1%	/	FDA: 2022.10

NR, not reached; FDA, Food and Drug Administration; NMPA, National Medical Products Administration; \, no available data.

bevacizumab was 19.2 months, the median progression-free survival (mPFS) reached 6.9 months, and the objective response rate (ORR) was 30% [8]. The efficacy in the Chinese population subgroup was more favorable, demonstrating that the mOS of the combination group reached 24.0 months (Table 1) [9]. Based on this study, the Food and Drug Administration (FDA) and the National Medical Products Administration (NMPA) of China approved atezolizumab in combination with bevacizumab in May and October 2020, respectively, for the treatment of unresectable HCC not previously treated with systemic therapy. This regimen is currently the preferred first-line systemic therapy recommendation (class 2 evidence, class A recommendation) of various societies and guidelines, including CSCO, the American Association for the Study of Liver Diseases (AASLD), the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and the "Standard for Diagnosis and Treatment of Primary Liver Cancer" (2022 Edition) [2].

The ORIENT-32 study is a multicenter phase III study conducted in China. The mOS of sintilimab in combination with IBI305 (bevacizumab biosimilar) was not reached and was significantly better than that of the sorafenib group; the mPFS reached 4.6 months, and the ORR was 21% (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) [10] (Table 1). Based on this study, NMPA approved sintilimab in combination with IBI305 for the first-line treatment of unresectable or metastatic HCC in June 2021, and the combination therapy regimen was included in the first-line treatment recommendations (class 2 evidence, class A recommendation) in the "Standard for Diagnosis and Treatment of Primary Liver Cancer" (2022 Edition), the "CSCO Immune Checkpoint Inhibitor Clinical Practice" (2022 Edition), and the "CSCO Standard for Diagnosis and Treatment of Primary Liver Cancer" (2022 Edition). At present, there are also a number of ongoing phase III studies of first-line combined immunotherapy for HCC.

Immunotherapy in Combination with Tyrosine Kinase Inhibitors

Multiple immunotherapy therapies in combination with targeted therapy are being clinically explored as first-line treatments for HCC. Study 117 [14] (lenvatinib in combination with nivolumab) and the KEYNOTE-524 [15] (lenvatinib in combination with pembrolizumab) studies both confirmed that ICIs in combination with lenvatinib resulted in a better tumor response in the first-line setting. The results of the KEYNOTE-524 study demonstrated that the ORR was 46.0% per modified RECIST (mRECIST) and 36.0% per RECIST v1.1, mPFS was 9.3 months per mRECIST and 8.6 months per RECIST v1.1, and mOS was 22 months. Based on this study, a further phase III confirmatory exploration of this combination therapy strategy was conducted (Leap-002 study) [16], and the results of Leap-002 at the 2022 ESMO congress were issued, which failed to reach the preset primary study endpoints of OS and PFS. However, the data from the Asian subgroup of the Leap-002 study demonstrated that the benefits of combination regimens compared with lenvatinib alone in Asian populations were more significant than those in the global population, and the difference in efficacy was further widened. According to RECIST v1.1, the mOS was 26.2 months, and the mPFS was 8.3 months in the Asian subgroup [17]. The COSMIC-312 study found that cabozantinib in combination with atezolizumab could significantly prolong the mPFS of HCC patients compared with sorafenib (6.8 months vs. 4.2 months, HR: 0.63, $p = 0.0012$), although there was no statistically significant difference in mOS (HR: 0.90, $p = 0.438$) (class 3 evidence, class C recommendation) [12]. The phase III SHR-1210-III-310 study confirmed that camrelizumab in combination with apatinib met the primary endpoint for the first-line treatment of unresectable or metastatic HCC, with mOS and PFS of 22.1 and 5.6 months, respectively, and ORR of 25.4%, both significantly better than those of the control group, as issued at the 2022 ESMO congress based on RECIST v1.1 assessment [11]. At the same time, relevant indications were applied in China in January 2023 (class 2 evidence, class A recommendation). In the "CSCO Standard for Diagnosis and Treatment of Primary Liver Cancer" (2022 Edition), apatinib in combination with camrelizumab is recommended as first-line treatment for advanced HCC, and lenvatinib in combination with pembrolizumab or nivolumab is a class III expert recommendation [4].

Combined Dual Immunotherapy

The HIMALAYA study is an international, multicenter, open, phase III study of subjects with unresectable HCC who had not received prior systemic therapy. Patients were treated with tremelimumab in combination with durvalumab dual immunotherapy, with a resulting ORR of 20.1% (based on RECIST v1.1), mPFS of 3.78 months, and OS of 16.4 months [13] (Table 1). In the "CSCO Standard for Diagnosis and Treatment of Primary Liver Cancer" (2022 Edition), durvalumab in combination with tremelimumab (STRIDE regimen) is a class I expert recommendation (class 2 evidence, class B recommendation).

Systemic Therapy in Combination with Local Therapy

Local treatment is an important treatment for intermediate-advanced HCC. Many guidelines have recommended local therapy in combination with systemic antitumor therapy, including tyrosine kinase inhibitors (TKIs) [18–20] and immunotherapy, to further improve clinical efficacy. A consensus (89.32%) has been reached that systemic therapy in combination with local therapy is recommended for patients with intermediate to advanced unresectable HCC in the first-line setting. At present, a number of studies based on ICIs in combination with local therapy are ongoing and can be broadly divided into 3 categories: (1) single-agent immunotherapy in combination with local therapy; (2) immunotherapy and TKIs in combination with local therapy; and (3) dual immunotherapy in combination with local therapy.

Consensus Statement 1. ICIs in combination with antiangiogenic agents, such as atezolizumab and bevacizumab/sintilimab and IBI305/camrelizumab and apatinib regimens, can be used as the first-line regimen for unresectable HCC (class 2 evidence, class A recommendation). Dual immunotherapy, such as tremelimumab in combination with durvalumab, can be used as an alternative (class 2 evidence, class B recommendation); pembrolizumab in combination with lenvatinib can be used as an alternative (class 3 evidence, class C recommendation). For patients with intermediate to advanced unresectable HCC, systemic therapy in combination with local therapy can also be used as the first-line treatment [21], such as TACE + systemic therapy (degree of expert consensus: 97.83%) and HAIC + systemic therapy (degree of expert consensus: 83.70%).

Second-Line and Later-Line Regimens of Immunotherapy

Approved Second-Line Regimens for Systemic Therapy of HCC

At present, second-line targeted drugs for HCC that have been approved include regorafenib, cabozantinib, apatinib, and ramucirumab [2]. In the second-line regimen of ICIs, based on phase II clinical studies, camrelizumab has been approved in China for patients with advanced HCC who have previously received sorafenib therapy and/or oxaliplatin-containing systemic chemotherapy (class 4 evidence, class A recommendation) [22]. Based on the RATIONALE-208 study, tislelizumab is approved for the treatment of HCC patients who have received at least one systemic antitumor treatment (class 4 evidence, class A recommendation) [23]. Based on the KEYNOTE-224 study [24], the FDA conditionally approved pembrolizumab for the second-line treatment of patients with advanced HCC in November 2018 (class 3 evidence, class B recommendation). The subsequent confirmatory phase III KEYNOTE-240 [25] study revealed no statistically significant difference in OS or PFS. However, from the perspective of efficacy and safety data, pembrolizumab treatment maintained good consistency in KEYNOTE-240 and KEYNOTE-224, demonstrating clinical significance. The phase III KEYNOTE-394 study [26] confirmed that pembrolizumab could significantly prolong the mOS of patients in Asian populations compared with placebo. Based on the above data, the FDA reinforces the approval decision for the indications of pembrolizumab for the second-line treatment of HCC. At the same time, based on the results of the KEYNOTE-394 study in October 2022, NMPA approved pembrolizumab monotherapy for the treatment of HCC patients who have previously received sorafenib or oxaliplatin-containing chemotherapy (class 3 evidence, class A recommendation). In the CheckMate 040 study, the subgroup data for nivolumab in combination with ipilimumab indicated that the combination regimen brought significant survival benefits for patients with HCC, and the FDA conditionally approved the combination regimen for patients with HCC who have experienced progressive disease (PD) after receiving sorafenib treatment or who are intolerant to sorafenib (class 4 evidence, class B recommendation) [27]. The existing clinical studies of second-line treatment with ICIs are summarized in Table 2.

Investigations of Second-Line Treatment

For patients whose first-line combined immunotherapy regimen failed, there is currently no large sample size phase III clinical trial evidence for the choice of second-line clinical regimen, and the inclusion criteria of the existing clinical studies related to phase I/II second-line systemic therapy are primarily based on patients who have progressed after having received first-line sorafenib or FOLFOX4 therapy. With the development of clinical research and clinical practice of combined immunotherapy and the continuous prolongation of patients' OS, it is necessary to differentiate the patterns of PD and possible immunotypes and implement individualized later-line treatment regimens in the multidisciplinary team (MDT) model. While considering the efficacy of later-line treatment, the safety and toxicity of second-line treatment should also be considered.

There are currently no clear biomarkers for predicting the efficacy of immunotherapy. Some patients with HCC fail to achieve good efficacy or may exhibit hyperprogression (hyperprogression, defined as treatment failure time <2 months, resulted in a 50% increase in tumor burden and a more than 2-fold increase in the rate

of progression compared to pre-immunotherapy imaging) during the first-line treatment. For these patients, the treatment strategy should be adjusted; for patients with hyperprogression, ICI treatment should be avoided in the future and replaced with other regimens. Patients who have received ICIs in combination with TKI regimens may consider choosing systemic chemotherapy; patients who have received ICIs in combination with anti-angiogenetic agents may consider choosing lenvatinib or regorafenib. For cases with slow progression, differentiation of the patterns of progression after treatment is recommended. (1) If the extrahepatic lesion is stable and only the intrahepatic lesion progresses, local therapy for the intrahepatic lesion, including TACE, HAIC, and radiofrequency ablation, is recommended. (2) If a new intrahepatic lesion appears or the extrahepatic lesion progresses, adjustment to the second-line treatment regimen and selection of a combination or single-agent regimen with different mechanisms is recommended. (3) If a new cancer embolus involving the portal vein or hepatic vein appears or the original vessel cancer embolus progresses while other target lesions are stable, radiotherapy is recommended for cancer thrombus involving the portal vein. The evolution of HCC is complex and progresses rapidly; therefore, for patients receiving second-line treatment, the evaluation interval can be shortened, and patients should be followed closely; changes in the patients' symptoms, performance status, liver function indicators, and tumor markers should be carefully monitored. If conditions permit, tumor rebiopsy may be considered for patients after first-line treatment to clarify the change in the tumor microenvironment, which is helpful to determine the cause of failure of front-line treatments and the selection of a second-line regimen.

Consensus Statement 2. For the selection of second-line treatment regimens for HCC, after the failure of first-line combined immunotherapy, it is necessary to differentiate the patterns of PD and the specific application of the first-line regimen. The corresponding new regimens should be selected rationally, taking into account the anticancer mechanism and efficacy evidence as well as the safety and toxicity of second-line regimens (degree of expert consensus: 100%).

Later-Line Treatment

At present, there is no evidence from phase III clinical trials with large sample sizes for later-line treatment of HCC, and there is still a lack of clear treatment strategy recommendations after second-line treatment. Current mechanistic studies suggest that the treatment method and the changes in biological characteristics of the tumor and the immune microenvironment impact one another and mutually evolve. Later-line treatment therefore often represents a more complex treatment challenge. For patients with slow PD, after the failure of second-line combined immunotherapy, it is necessary to differentiate the patterns of PD and the specific composition of first- and second-line regimens; patients can still benefit from a rational later-line treatment strategy in the MDT model, following the synergistic mechanisms of the different treatment methods for HCC. According to the current mechanism of HCC treatment regimens, if immunotherapy in combination with an antiangiogenic therapy strategy or a combined dual immunotherapy strategy is not used in front-line treatment, previously unused combination treatment regimens may be considered. If the front-line treatment has fully concluded, combined immunotherapy, targeted therapy with lenvatinib, sorafenib, or regorafenib (previously unused) or oxaliplatin-dominated systemic chemotherapy (previously unused) may be considered. In addition, for some patients who meet the requirements for later-line treatment, clinical trials of new drugs for HCC may be considered. The goal of later-line treatment of HCC is to maximize the clinical benefits of patients while optimizing patient quality of life.

Consensus Statement 3. Various HCC guidelines lack clear treatment strategy recommendations after second-line treatment. It is necessary to differentiate the patterns of PD and the specific composition of first-line and second-line regimens to reasonably select a later-line treatment strategy according to the synergistic mechanisms of different treatment methods for HCC in the MDT model (degree of expert consensus: 100%).

Immunotherapy in Conversion Therapy

Concept of Conversion Therapy

Conversion therapy refers to converting patients with HCC assessed as unresectable to patients with resectable HCC by interventions, including both the conversion of surgically unresectable HCC to resectable HCC and the conversion of patients with poorer efficacy after resection (China liver cancer staging system [CNLC stage] IIb and stage IIIa) to those with potentially better efficacy after resection (i.e., conversion in the oncological sense) [36].

Controversy Exists in HCC Conversion Therapy

At present, studies on conversion therapy are primarily clinical trials with small sample sizes, and most retrospective studies on conversion therapy have a large selection bias. There is no uniform standard for the definition of unresectable HCC, conversion therapy regimen,

Table 2. Overview of second-line immunotherapy/combined immunotherapy clinical trials for HCC

Regimen category	Study phase	Second-line regimen	Study name	Dosage and administration	Number of cases	Overall survival, months	PFS, months	Response rate, %
Single-agent immunotherapy	III	Pembrolizumab	KEYNOTE-240 [25]	Pembrolizumab: 200 mg, q3w	278	13.9	3	18.3
	III	Pembrolizumab	KEYNOTE-394 [26]	Pembrolizumab: 200 mg, q3w	300	14.6	2.6	13.7
	I/II	Durvalumab	NCT01693562 [28]	Durvalumab: 10 mg/kg, q2w	40	13.2	\	10.3
	II	Tislelizumab	RATIONALE-208 [29]	Tislelizumab: 200 mg, q3w	111	12.4	2.7	13
	II	Camrelizumab	NCT02989922 [22]	Camrelizumab: 3 mg/kg, IV, q2/3w	217	13.8	2.1	14.7
	II	Tremelimumab	NCT01008358 [30]	Tremelimumab: 15 mg/kg, once every 90 days	20	8.2	6.48	17.6
	II	Camrelizumab + apatinib	RESCUE [31]	Camrelizumab: 200 mg (body weight ≥50 kg) or 3 mg/kg (body weight <50 kg), q2w Apatinib: 250 mg, once daily	120	NR	5.5	RECIST 1.1 22.5 (IRC) 7.5 (Investigator) mRECIST 25.0 (IRC)
Immunotherapy + targeted therapy	I/IIa	Nivolumab + regorafenib	GOING NCT04170556 [32]	First 2 cycles: regorafenib – 160 mg/day, dosing for 3 weeks/suspending for 1 week; the third cycle: supplement nivolumab (240 mg, q2w)	51	\	\	\
	I/II	Sitravatinib + tislelizumab	BGB-900-104 NCT03941873 [33]	Sitravatinib: 120 mg, once daily Tislelizumab: 200 mg, q3w	40	NR	Arm B (anti-PD-1/PD-L1 antibody naïve): 6.8 Arm C (R/R): 4.8	Arm B: 9.5 Arm C: 10.5
	Ib	Sintilimab + IBI310 (anti-CTLA4 mAb)	NCT04401813 [34]	Sintilimab: 200 mg, q3w IBI310: 3, 2, or 1 mg/kg, q3w	29	NR	3.9	17.2
Immunotherapy + immunotherapy	I–II	Nivolumab (N) + ipilimumab (I)	CheckMate 040 NCT01658878 [35]	Arm A: N (1 mg/kg) + I (3 mg/kg), q3w (4 doses) Arm B: N (3 mg/kg) + I (1 mg/kg), q3w (4 doses); followed by N (240 mg, q2w) Arm C: N (3 mg/kg) + I (1 mg/kg), q6w	148	Arm A:B:C 22.8: 12.5:12.7	\	Arm A:B:C 32%: 27%:29%

NR, not reached; \, no available data.

conversion therapy cycle, or timing of surgical resection, which affects the comparability of survival data and conversion resection rates. Therefore, further clinical studies will be necessary to the impact of suitable conversion therapy, population conversion therapy methods, the impact of different treatment strategies, and drug combinations on liver safety, risks of subsequent operations, potential complications, risk/benefit ratio, and subsequent treatment regimes.

Conversion Therapy Regimen

According to the "*Chinese Expert Consensus on Conversion Therapy for Hepatocellular Carcinoma*" *(2021 Edition)* [36], relevant evidence and experiences have accumulated in the field of conversion therapy. In clinical practice, conversion therapy can be performed based on the patient's condition. A high-intensity, multimodal antitumor treatment strategy is recommended for the conversion therapy of HCC, and systemic antitumor therapy is one of the primary methods. Some case reports show encouraging conversion resection rates with TKI monotherapy [37–39]. Several retrospective and real-world studies have reported that TKIs in combination with immunotherapy as a conversion therapy method for HCC can achieve a conversion resection rate of 10.2–23.8% [40–43]. In a single-center, single-arm, open-label phase II study, when sintilimab in combination with lenvatinib was used as a conversion therapy regimen, the ORR reached 36.1% (RECIST v1.1), and the conversion resection rate reached 33.3% [44]. Another phase Ib study used cabozantinib in combination with nivolumab as conversion therapy, and the conversion resection rate reached 80% [45].

Systemic therapy in combination with local therapy such as TACE and HAIC can also create potential surgical resection opportunities for patients with initially unresectable HCC and improve patient survival. Systemic antitumor therapy in combination with local therapy is expected to achieve a higher tumor response rate and a higher conversion resection rate. The results of two retrospective studies suggested that the ORRs of systemic antitumor therapy in combination with local therapy reached 59.2% and 84.0% (RECIST v1.1), and the conversion resection rates reached 12.7% and 56.0%, respectively [46, 47]. A prospective multicenter study found that the ORR of lenvatinib and anti-PD-1 antibody in combination with TACE reached 84.2% (mRECIST), and the conversion resection rate reached 50% [48]. At present, a number of immunotherapy-based conversion therapy studies are underway.

Investigations of Conversion Therapy

In clinical practice, the selection of the conversion therapy regimen for patients with potentially resectable HCC remains inconclusive. The current clinical data for first-line HCC systemic therapy indicate that lenvatinib has a higher ORR than sorafenib. Targeted therapy in combination with immunotherapy, including lenvatinib in combination with pembrolizumab, bevacizumab in combination with atezolizumab, bevacizumab analog in combination with sintilimab, and apatinib in combination with camrelizumab, exhibits an ORR >20% for unresectable HCC and exhibits a better conversion potential than monotherapy. Currently, there is a lack of comparative studies between different drug combinations and a lack of comparability of existing studies due to bias in inclusion criteria, timing of surgery, and other factors. When selecting a conversion therapy regimen, both the effect of tumor shrinkage and its characteristics should be considered with respect to safety and accessibility. There is a consensus (99.03%) that conversion therapy is available in patients with potentially resectable HCC.

Consensus Statement 4. For patients with potentially resectable HCC, radical surgery after conversion therapy with an immune combination regimen can provide survival benefits. Conversion therapy is recommended for patients with potentially resectable HCC (degree of expert consensus: 99.03%). Currently, the diagnostic criteria for patients with potentially resectable HCC, potentially advantageous regimens for conversion therapy, selection of surgical timing, and recommendations for subsequent adjuvant therapy need to be discussed and decided by an MDT, with OS as the primary endpoint for rational selection.

Perioperative Regimen of Immunotherapy

Neoadjuvant and Adjuvant Therapy

At present, the high-level evidence for neoadjuvant and adjuvant therapy for HCC is insufficient, and the selection criteria for neoadjuvant and adjuvant therapy for patients with HCC remain controversial. In multiple guidelines, there are no clear recommendations of immunotherapy regimens for neoadjuvant and adjuvant therapy of HCC. A number of preliminary explorations of neoadjuvant and adjuvant therapy have been conducted at this stage.

The goal of neoadjuvant therapy is to reduce the postoperative recurrence rate and prolong postoperative survival. Taking Chinese guidelines and specific national trends into account, neoadjuvant therapy can be considered before surgery for patients with initially resectable HCC (including CNLC stage Ia-IIIa/Barcelona Clinic Liver

Cancer [BCLC] stage A or beyond BCLC criteria but still resectable) and with postoperative high-risk recurrence factors. High-risk recurrence factors include any of the following definitions: (1) two or more of the following characteristics – maximum tumor diameter >5 cm, lesion number ≥3, vascular invasion, poorly differentiated pathology, preoperative alpha-fetoprotein (AFP) ≥400 ng/mL, or (2) presence of tumor thrombus. As the current high-level evidence for HCC neoadjuvant therapy is insufficient, neoadjuvant therapy is not recommended in clinical practice for patients who can directly achieve R0 resection in CNLC stages Ia and Ib and some parts of stage IIa. It remains controversial whether neoadjuvant therapy should be performed in patients with HCC that can be surgically resected but have a high risk of recurrence. A total of 52.43% of experts believe that neoadjuvant therapy should be performed in this group of HCC patients, 45.63% believe that it can be performed according to the selectivity of clinical study results, and 1.94% of experts oppose neoadjuvant therapy in patients with HCC who can be surgically resected but have a high risk of recurrence. Therefore, if neoadjuvant therapy is feasible after the patient's condition is comprehensively considered (taking into account the postoperative high-risk recurrence factors and inability to guarantee R0 resection), it is recommended that clinical trials are performed after ethical review. For CNLC stage IIb and IIIa patients with technically resectable HCC, but there are clear high-risk recurrence factors, surgery is recommended after neoadjuvant therapy to reduce postoperative recurrence. A randomized, open-label phase II study explored the use of nivolumab monotherapy (n = 13) or nivolumab in combination with ipilimumab (n = 14) in the perioperative period (including neoadjuvant and adjuvant therapies) (NCT03222076) with an mPFS of 19.53 months in the combination therapy group and 9.4 months in the monotherapy group. Of the 20 patients who underwent surgical resection, 3 of 9 (33%) patients in the monotherapy group exhibited a major pathological response compared with 3 of 11 (27%) patients in the combination therapy group; these patients had no significantly higher recurrence survival than those without a major pathological response [49].

Adjuvant therapy is typically administered after surgery to destroy any remaining tumor cells in vivo, thus reducing the likelihood of tumor recurrence or metastasis. However, with the failure of the STORM study, recognized treatment of postoperative adjuvant therapy for HCC is lacking. The failure of the STORM study may be because only 53–55% of the patients enrolled in the study were at moderate-to-high risk at baseline, and the recurrence and metastasis rates of early HCC patients were low; thus, it was not surprising that the STORM study yielded comparable recurrence-free survival (RFS) results for sorafenib versus placebo in patients with HCC after radical surgery or ablation [50]. Combined with the current status of diagnosis and treatment of HCC in China, the CSCO guidelines clearly propose that the primary objective of postoperative adjuvant therapy for HCC is to reduce recurrence. For patients with high-risk recurrence factors, close clinical surveillance and active adjuvant therapy measures should be taken. The current consensus (96.12%) is that patients at high risk of recurrence after HCC resection require adjuvant therapy. For patients at a high risk of recurrence, two randomized controlled studies have confirmed that postoperative TACE treatment can reduce recurrence and prolong survival [51, 52]. For HBV-infected patients with HCC, antiviral therapy with a nucleoside analog can not only control the underlying liver disease but also help reduce the postoperative tumor recurrence rate. Postoperative immunotherapy, targeted drugs, immunomodulators, and HAIC alone or in combination with other therapies are being actively explored [2]. The IMbrave050 study is the first phase 3 study of adjuvant treatment for HCC to demonstrate RFS improvement following curative intent resection or ablation. At the prespecified interim analysis, adjuvant atezolizumab + bevacizumab met its primary endpoint and resulted in a statistically significant and clinically meaningful improvement in IRF-assessed RFS versus active surveillance in patients with a high risk of HCC recurrence (HR: 0.72; 95% CI: 0.56, 0.93; p = 0.012) [53].

Consensus Statement 5. The efficacy of neoadjuvant therapies for HCC lacks high-level clinical study evidence, so there is no clear recommendation. Atezolizumab + bevacizumab may be a practice-changing adjuvant treatment option for patients with high-risk HCC that may change the clinical indications for surgical resection or RFA (degree of expert consensus: 96.12%). Ongoing clinical trials of immunotherapy as neoadjuvant/adjuvant therapy for patients with a high-risk recurrence of HCC after surgery are worth exploring.

Management throughout ICI Treatment for HCC

Advantaged Population of ICIs

HBV infection is the most important cause of HCC. Among the causes of HCC worldwide, HBV accounts for 54% of cases, and hepatitis C virus (HCV) accounts for

31%. In China, patients with HBV-related HCC account for approximately 63.9–90.0% of all HCC patients [54, 55]. In clinical studies of systemic therapy for HCC stratified by etiology, many studies have demonstrated that the efficacy of ICI treatment is more favorable in HBV- and/or HCV-infected populations. The OS subgroup analysis of the ORIENT-32 study found that sintilimab in combination with IBI305 treatment exhibited a superior survival benefit in HBV-related populations (HR: 0.58, 95% CI: 0.43–0.76) [10]. OS subgroup analysis of the IMbrave150 study also revealed that the therapeutic strategy of atezolizumab in combination with bevacizumab exhibited superior OS benefits in both HBV (HR: 0.51, 95% CI: 0.32–0.81)- and HCV (HR: 0.43, 95% CI: 0.22–0.87)-related populations [9]. In the HIMALAYA study, the dual immunotherapy strategy of tremelimumab in combination with durvalumab produced a better survival benefit in HBV-related populations (HR: 0.64, 95% CI: 0.48–0.86) [13]. Based on the subgroup analysis of the above studies, the efficacy of ICIs may be more favorable in HBV- or HCV-infected populations, but more clinical data are needed to further verify whether patients with hepatitis virus infection benefit from immunotherapy. At present, many clinical studies on HCC related to hepatitis virus infection have been performed. For HCC patients with combined hepatitis virus infection, regular monitoring of virology indicators is required, and antiviral therapy should be used throughout the treatment process during antitumor treatment. HBV reactivation is a common complication in patients with HBV-related HCC [56]. A retrospective study demonstrated that patients who received TKIs combined with PD-1 inhibitors had a greater risk for HBV reactivation, and those with HBV reactivation had a higher rate of tumor progression and shorter survival time than those receiving TKIs alone [57]. Reasonable antiviral therapy and regular monitoring are also helpful to reduce the risk of HBV reactivation caused by immunotherapy. The OS subgroup analysis of the IMbrave150 study also revealed that atezolizumab in combination with bevacizumab produced better OS benefits in males (HR: 0.64, 95% CI: 0.49–0.83) and related populations with BCLC stage C (HR: 0.63, 95% CI: 0.48–0.82), AFP ˂400 ng/mL (HR: 0.58, 95% CI: 0.42–0.81), large vessel invasion or/and extrahepatic metastasis (HR: 0.64, 95% CI: 0.49–0.85), positive PD-L1 expression (HR: 0.52, 95% CI: 0.32–0.87), or no previous local therapy (HR: 0.61, 95% CI: 0.44–0.86) [9].

At present, as mentioned above, no clear biomarkers have been identified that can predict the efficacy of immunotherapy for HCC. PD-L1 expression, tumor mutation burden, and high-level microsatellite instability/mismatch repair defects have been reported and clinically applied in other types of tumors as the basis for predicting response to ICI treatment. However, HCC studies do not translate well clinically due to a smaller overall volume of research and relative low expression of biomarkers, so further studies and clinical trials exploring the HCC population potentially benefiting from ICI treatment are needed.

Consensus Statement 6. The efficacy of ICIs is more favorable in patients with HBV-infected HCC (degree of expert consensus: 95.15%), and the elucidation of other characteristics, such as HCV infection, male sex, BCLC stage C, AFP <400 ng/mL, large vessel invasion, and/or extrahepatic metastasis, that predict treatment response remains to be further validated by clinical trials.

Suitable Population for ICI Treatment

Currently, ICIs are primarily used in advanced HCC patients without surgical indications. As further explored in clinical trials, immunotherapy may also be used as neoadjuvant or adjuvant therapy in patients with surgically resectable HCC at a high risk of recurrence and as a conversion therapy in patients with potentially resectable HCC. ICIs are also indicated for the later-line treatment of HCC patients, and multiple monotherapies with ICIs have been approved for the second-line treatment of HCC (NMPA or FDA). Combining the inclusion criteria of immunotherapy clinical studies, recent clinical studies and application results, and current guidelines for the diagnosis and treatment of HCC, it is recommended that patients with HCC who plan to be treated with ICIs should meet the following conditions (degree of expert consensus: 90.29%): (1) locally advanced or advanced HCC confirmed by histology/cytology or clinically diagnosed based on medical history, imaging, and blood chemistry examinations; (2) not suitable for radical treatment (e.g., surgery, ablation, or transplantation); (3) high risk of recurrence after hepatectomy with immunotherapy-related neoadjuvant or adjuvant therapy; (4) satisfactory hepatic function and performance status; (5) normal thyroid function before treatment, with thyroid-stimulating hormone (TSH), total tri-iodothyronine (T3), or free T3 and free thyroxine (T4) within or near the normal range; and (6) satisfactory hematologic and organ function (Table 3).

Consensus Statement 7. The clinical application of ICIs is mainly for advanced stage HCC patients without surgical indications but with good hepatic function and performance status. Relevant blood chemistry and cardiopulmonary function testing are required prior to treatment for identifying adverse drug reactions (degree of expert consensus: 95.21%).

Population in Which ICI Treatment Should Be Used with Caution or Contraindicated

According to literature reports and expert experience on the clinical application of ICIs [58–61], combined with data from mechanistic studies, ICIs should be used with caution or should be considered contraindicated in patients with the following conditions:

1. For patients scheduled to receive or who have received an organ or bone marrow transplantation, other therapeutic modalities such as molecular targeted therapy are preferred, and ICIs should be the "last choice." A liver biopsy is recommended to detect the expression of PD-L1 in patients who have received liver transplantation, and PD-1/PD-L1 inhibitors should be contraindicated in patients with high expression [62, 63]. During use, the dosage of immunosuppressants should be gradually reduced, and patients should be closely monitored.
2. Patients with autoimmune diseases, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis, who are active or receiving the treatment are not recommended to use ICIs. Patients with well-controlled disease may use ICIs cautiously under close observation, but ICIs are still not recommended in patients with possible serious consequences in cases of disease recurrence.
3. Patients with untreated or incompletely treated esophageal and gastric varices accompanied by bleeding or at high risk of bleeding must undergo esophagogastroduodenoscopy to assess the condition of gastric varices before immunotherapy in combination with antiangiogenic therapy, and pretreatment is performed according to the diagnostic criteria. ICIs can be used after the condition is stable (degree of expert consensus: 95.15%).
4. Elderly patients are recommended to use CTLA-4 inhibitors with caution for monotherapy or combination therapy; a recent multicenter retrospective study found that there were no statistically significant differences in the incidence of adverse events between patients with advanced or metastatic tumors in different age groups (<65, 65–74, ≥75 years) treated with PD-1 and/or CTLA-4 antibodies. However, the results of a meta-analysis indicated that elderly patients (≥65 years) had fewer survival benefits after treatment with CTLA-4 inhibitors, whereas the survival benefit was comparable in different age groups after treatment with PD-1 and PD-L1 inhibitors [64]. Given that CTLA-4 inhibitors have high-grade 3–4 toxicity, caution is recommended when selecting CTLA-4 inhibitors for treatment in elderly patients [65].
5. Patients with hyperprogression biomarker positivity should use ICIs with caution; MDM2/MDM4 amplification and epidermal growth factor receptor mutations may be potential molecular markers to predict the occurrence of hyperprogression. However, these hyperprogression-related indicators remain under investigation, and a large amount of clinical data are still needed for validation [66].
6. For patients with idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonia or idiopathic pneumonia, or evidence of active pneumonia on recent chest computed tomography (CT), ICIs should be used with caution.
7. For patients with major cardiovascular and cerebrovascular diseases (such as New York Heart Association [NYHA] Class II or greater severe heart disease, myocardial infarction, or cerebrovascular accident within 3 months before starting treatment), unstable arrhythmias, or unstable angina, ICIs should be used with caution.
8. For patients who have experienced severe allergy/hypersensitivity to chimeric or humanized antibodies or fusion proteins, ICIs should be used with caution.
9. Patients with moderate and severe ascites or severe infections should await treatment prior to use of ICIs.
10. For patients infected with human immunodeficiency virus (HIV), recently published data demonstrated that HIV-infected patients have no serious complications and that the efficacy of ICIs is not significantly affected. ICIs may be used with caution and close follow-up [67].
11. Preliminary reports suggest that patients with nonalcoholic fatty liver disease and HCC patients with high Wnt/β-catenin expression may have poor efficacy and should cautiously select this treatment.

Consensus Statement 8. Based on the clinical experience and mechanism of ICIs, special attention should be given to the population in which ICIs are clinically applied. Furthermore, ICIs should be used with caution or may be contraindicated in some patients as described above (degree of expert consensus: 100.00%). The above indications for clinical caution and contraindications of ICIs are a summary of clinical experiences in recent years. The inference that ICIs may lead to potential adverse events requires further research.

Table 3. Blood chemistry indicators and their ranges in patients with HCC suitable for ICI treatment

Test indicator	Recommended range
Hematology	
Hemoglobin (Hb)	≥90 g/L
Absolute neutrophil count (ANC)	≥1.5 × 10^9/L
Platelet count (PLT)	≥50 × 10^9/L
Blood chemistry	
Albumin (Alb)	≥30 g/L
Alanine aminotransferase (ALT)	<5 × ULN
Aspartate aminotransferase (AST)	<5 × ULN
Total bilirubin (TBil)	<3 × ULN
Creatinine (Cr) ≤ 1.5 × ULN, or creatinine clearance (CrCl) ≥50 mL/min (calculate with Cockcroft-Gault formula)	
Coagulation	
International normalized ratio (INR)	≤2 × ULN
Urine protein	< ++; or 24-h urine protein quantification <1.0 g

ULN is the upper limit of normal value.

Assessment and Follow-Up during ICI Treatment

ICIs block the negative regulatory signals of T lymphocytes to release immunosuppression and enhance the antitumor effect of T lymphocytes. However, ICIs may also abnormally amplify their own immune response, resulting in an imbalance between immune tolerance and an autoimmune disease-like inflammatory response when normal tissues are involved; these responses are called immune-related adverse events (irAEs). Before starting ICIs, clinical physicians must perform baseline examinations to assess the susceptibility and possibility of irAEs in patients and educate patients receiving treatment for irAEs. Referring to the "CSCO Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities," baseline examination is recommended for the following items:

1. Medical history: The patient should be asked whether there is a history of autoimmune diseases, endocrine diseases, infectious diseases (HBV, HCV or HIV, etc.), or previous antitumor treatment, as well as documentation of any medications at baseline. Additionally, the patient's smoking history, family medical history, pregnancy status, and bowel evacuation habits should be assessed.
2. Physical examination, including examination of the heart, lung, nervous system, and other important organ systems, should be performed.
3. Imaging examination, including CT examinations of the chest, abdomen, and pelvis, as well as ECG and cardiac color Doppler echocardiography, should be assessed; if symptomatic, specific sites should also be examined, such as pancreatic imaging examination, brain magnetic resonance imaging (MRI), whole-body bone scan, and 24-h dynamic ECG.
4. Hematology examination, including hematology; blood chemistry parameters (blood glucose, blood lipid, myocardial enzyme spectrum, etc.); infectious disease screening (HBV DNA, HCV RNA, HIV antibody and HIV antigen [p24], etc.); cytomegalovirus antibody, T cells, myocardial infarction markers (such as troponin I or T, etc.); and brain natriuretic peptide or NT-Pro-BNP, should be evaluated; if blood glucose is elevated, glycosylated hemoglobin testing should also be performed. At present, genetic testing is conducted at some sites, but the clinical significance of relevant indicators remains unclear. If conditions permit, genetic testing can be performed as a reference for clinical decision-making, which is conducive to the collection of data for clinical studies.
5. Skin and mucosal examination should be assessed, especially for patients with a history of autoimmune skin diseases.
6. Thyroid, pituitary, and adrenal function should be tested, including TSH, T4, T3 and T4, plasma cortisol, adrenocorticotropic hormone, and other pituitary function parameters at 8:00 am (grade I recommendation) and luteinizing hormone, follicle-stimulating hormone, testosterone, and other hormones. If TSH is high, anti-thyroid peroxidase antibodies should be tested; if TSH is low, TSH receptor antibodies should be tested.

7. Pulmonary function: For patients with a history of pulmonary disease, pulmonary function testing, 6-min walk test, and resting or active oxygen saturation tests are recommended.
8. Rheumatoid/skeletal muscle examination: For patients with previous pertinent diseases, joint examination/function assessment should be performed as appropriate; for patients with suspected autoimmune diseases, autoantibodies, erythrocyte sedimentation rate, and other examinations should be performed.

Consensus Statement 9. A relevant medical history, vital signs, blood chemistry, and basic organ function assessment should be performed before each cycle of ICIs. According to the patient's symptoms and signs, regular and irregular re-examinations of laboratory parameters and assessment of organ function are required to avoid the occurrence of adverse reactions (degree of expert consensus: 100%).

9. Hepatitis virus loading monitoring: Most HCC patients in China have chronic liver diseases, of which viral hepatitis is the most common. The vast majority of viral hepatitis cases are caused by HBV infection, and the minority are caused by HCV. Therefore, patients often have both HCC and chronic liver disease, both of which need to be managed during treatment. In addition to antitumor treatment, it is equally important to manage chronic liver diseases, including antiviral treatment for hepatitis patients. For HBsAg-positive patients, antiviral treatment is recommended regardless of HBV DNA testing, and entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide fumarate tablets are preferred. If HBV DNA is >2,000 IU/mL at week 24 of standardized antiviral treatment, hepatologists should be consulted in a timely manner to adjust the antiviral treatment regimen. Patients with negative HBsAg and positive anti-HBc require active antiviral treatment if HBV DNA is positive [56]; if HBV DNA is negative, HBV DNA and HBsAg can be monitored every 1–3 months, and antiviral treatment should be initiated immediately once HBV DNA or HBsAg becomes positive [68–72]. For positive anti-HCV patients, reagents for real-time quantitative PCR with high sensitivity should be used for the HCV RNA testing (lower limit of detection <15 IU/mL). If a high-sensitivity HCV RNA test is unavailable, a nonhigh-sensitivity HCV RNA test (lower limit of detection ≤1,000 IU/mL) can be used. If HCV RNA at baseline is positive, determination of HCV genotyping and use of direct-acting antivirals (DAAs) without interferon under the guidance of a hepatologist is recommended. If conditions permit, initiation of ICI treatment should begin 2 weeks after antiviral treatment or HCV RNA testing negative. HCV RNA and liver function should be periodically monitored during treatment with DAAs, and HCV RNA should be tested at week 4, end of treatment, and 12 or 24 weeks after the end of treatment; if HCV RNA is negative at baseline, HCV RNA testing should be performed every 12 or 24 weeks after initiation of ICIs [73, 74].

Consensus Statement 10. For HCC patients with HBV coinfection who will start ICI treatment, antiviral treatment should ideally be started 1 week before systemic treatment of liver cancer or at the time of ICI initiation. HBV DNA, HBsAg, and anti-HBc should be monitored periodically (degree of expert consensus: 95.15%). HCV RNA should be $< 10^3$ copies/mL for ICI treatment in patients coinfected with HCV, and DAAs or antiviral treatment with interferon should be received concurrently, but HCV RNA levels need to be monitored periodically (degree of expert consensus: 97.09%) (grade I recommendation).

10. Tumor imaging assessment: Tumor imaging should be performed every 6–8 weeks after the start of treatment and then every 12–24 weeks after 1 year until PD occurs, or there is no clinical benefit. During treatment with ICIs, follow-up every 3–6 weeks is recommended to detect and assess adverse drug reactions caused by ICIs in a timely manner [5].

Consensus Statement 11. Monitoring patients after medication initiation is necessary, and follow-up is recommended to facilitate communication about adverse reactions at any time. Routine follow-up examination can be performed every 3–6 weeks, and imaging assessment for treatment efficacy is recommended every 6 weeks.

ICI-Related irAEs and Treatment

ICI-related irAEs are caused by activation of the immune system and often involve the skin, colon, endocrine organs, liver, and lungs. Most irAEs are G1/2, but in rare cases, irAEs are severe and may be life-threatening (<1%), such as interstitial pneumonia and immune-mediated myocarditis.

Common adverse reactions of immunotherapy primarily include the following: (1) skin – rash or mucositis; (2) cardiovascular – hypertension or immune-mediated myocarditis; (3) gastrointestinal – nausea, vomiting, abdominal distension, diarrhea, or enteritis; (4) endocrine abnormalities – thyroiditis, abnormal thyroid function, abnormal adrenal function, or inflammation of the pituitary gland; (5) lung – immune-related pneumonitis; (6) kidney – abnormal renal function or renal insufficiency; and (7) liver – increased transaminases or bilirubin or abnormal hepatic function. The overall incidence of

irAEs after ICI therapy in HCC patients does not significantly differ from that in patients with other tumors, but the incidence of immune-related hepatitis is increased.

Management Principles of irAEs

There are several domestic and foreign guidelines and consensus on the management of immunotherapy-related toxicities, including "CSCO Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities" [61], "Management of Immunotherapy-Related Toxicities" of the NCCN [59, 61], and "Management of Toxicities from Immunotherapy" of the ESMO [75]. For irAEs, according to the involved organs, grade, and severity of adverse events, the dose of ICIs should be adjusted, including dose discontinuation, dose reduction or termination, and corresponding treatment measures should be given.

Glucocorticoids are the primary treatment for most irAEs and should be given early when needed. Delayed use (>5 days) may affect the prognosis of some irAEs. To prevent the recurrence of irAEs, steroid doses should be reduced slowly, generally over a time period >4 weeks, sometimes 6–8 weeks or longer. For cardiac, pulmonary, hepatic, and neurological toxicity, given their morbidity, high-dose glucocorticoids are preferred. For some endocrine toxicities, such as hypothyroidism and diabetes, hormone replacement therapy is used. For skin and endocrine toxicities (G2), ICI treatment can be continued. Other immunosuppressants may be considered in the case of ineffective glucocorticoid treatment, including mycophenolate mofetil, tacrolimus, and anti-thymocyte globulin. Infliximab exhibits potential hepatotoxicity and is not considered for use in patients with immune hepatotoxicity. Clinicians should refer to the guidelines for specific management measures of different types of irAEs, which will not be described in detail here.

Consensus Statement 12. The incidence of adverse reactions to ICIs is high, but most adverse reactions are mild. However, because current commonly used treatment strategies include combination therapy regimens, the incidence of adverse reactions is significantly increased due to drug interactions. In the case of serious adverse reactions, patients should be treated as soon as possible. Consultation with a specialist is also recommended for MDT diagnosis and treatment (degree of expert consensus: 100%). Special irAEs related to HCC treatment with ICIs require close observation and effective treatment.

ICI-Induced Hepatitis

Drug-related hepatotoxicity may occur at any time after the first use of ICIs, with the highest frequency occurring 8–12 weeks after treatment. Before treating HCC patients with ICIs, the patient's liver function should be normalized with effective viral control. Liver function should be monitored routinely and periodically during the treatment. For patients with increased transaminase or bilirubin levels, clarification to determine whether the cause is liver decompensation or tumor progression is important. ICI-related liver injury typically has a good prognosis and rarely causes liver failure and death. After symptomatic treatment and drug discontinuation for 1–3 months, liver function generally recovers to baseline. Hepatotoxicity can be classified into 4 grades according to the "CSCO Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities" [61].

G1: ICIs should be continued, and liver function should be monitored once a week. If liver function is stable, the monitoring frequency can be appropriately reduced.

G2: ICI treatment should be suspended, and patients should be given 0.5–1 mg/kg oral prednisone. If liver function improves, prednisone is slowly reduced to ≤10 mg/day (total course of treatment ≥4 weeks); when hepatotoxicity is ≤ G1, ICIs can be resumed, at which time liver function is measured every 3 days, and liver biopsy is recommended.

G3: ICIs should be discontinued, and oral prednisone or intravenous methylprednisolone (1–2 mg/kg) should be administered, during which liver function is measured every 1–2 days. After hepatotoxicity is reduced to G2, patients can be switched to an equivalent dose of oral prednisone, and the dose continues to be reduced slowly. If liver function does not improve, supplementation with mycophenolate mofetil (500–1,000 mg, 2 times/day) is recommended. If the dose of prednisone is reduced to ≤10 mg/day with hepatotoxicity ≤ G1, ICIs can be initiated again after a discussion with the MDT. If the efficacy of mycophenolate mofetil remains poor, tacrolimus can be supplemented, and hepatologists should be consulted, followed by a CT or ultrasound examination of the liver or a liver biopsy.

G4: ICIs should be permanently discontinued, and patients should be administered intravenous methylprednisolone (1–2 mg/kg). After hepatotoxicity reduces to G2, an equivalent dose of oral prednisone can be substituted, and the dose can be reduced slowly, with a total course of at least 4 weeks. If liver function does not

improve after 3 days, mycophenolate mofetil (500–1,000 mg, 2 times/day) can be supplemented, but infliximab is not recommended. Hospitalization may be considered.

ICI-Induced Pneumonitis

The primary symptoms of ICI-induced pneumonitis (CIP) are newly developed cough, shortness of breath, dyspnea, fever, and chest pain after ICI treatment or exacerbation of preexisting symptoms. Shortness of breath and dyspnea are the most common symptoms, followed by cough, and fever and chest pain are relatively rare. Some patients may not have any symptoms; such cases are typically diagnosed on imaging examination [39]. CIP imaging findings vary, with ground-glass and lattice-like blurred shadows near the periphery common on lung CT, which may also develop into lung consolidation; some patients may also exhibit sarcoid granuloma or pleural effusions. Lesions involving the lower lobe are more common than those involving the middle and upper lobes and are primarily characterized by a mixture of multiple morphologies and multiple sites of involvement. The diagnosis of CIP can be considered if the following 3 criteria are met: (1) the patient has received ICIs; (2) imaging findings reveal new pulmonary shadows; and (3) lung infection, progression of lung tumor, interstitial lung diseases, pulmonary vasculitis, pulmonary embolism, and pulmonary edema due to other causes have been excluded. Clinically, it is necessary to further exclude complicated cases such as CIP coinfection and tumor progression. Pneumonia due to ICIs is classified into 4 grades by severity level:

G1: Asymptomatic, inflammation confined to only one lobe or not more than 25% of the lung parenchyma on chest CT.

Treatment regimen: No treatment is needed, and reexamination of chest CT and pulmonary function should be considered after 3–4 weeks. If imaging results are improved, close follow-up is performed, and patients can resume treatment. If PD occurs upon imaging, the treatment regimen should be updated, and ICI treatment should be suspended. If there is no change on imaging, treatment should be continued, and close follow-up is performed until a new symptom occurs.

G2: New symptoms/or worsening of symptoms, including shortness of breath, cough, chest pain, fever, and hypoxia. Imaging findings involve multiple lobes and involve 25–50% of the lung parenchyma, affecting daily life and requiring drug intervention.

Treatment regimen: Treatment should be paused before patients with a pneumonia risk ≤ G1. Intravenous methylprednisolone at 1–2 mg/kg/day is initiated. After 48–72 h of treatment, if the symptoms are improved, steroid dosing is reduced by 5–10 mg per week for 4–6 weeks. If the symptoms are not improved, treatment should be administered according to G3–G4 reactions. If infection cannot be completely excluded, empirical anti-infective treatment should be considered. After 3–4 weeks, chest CT should be repeated. If clinical symptoms and imaging findings recover to ≤ G1, immunotherapy may be resumed after assessment.

G3: Severe new symptoms; disease involving all lobes or more than 50% of the lung parenchyma; patients incapable of any self-care in daily life and activities; hypoxemia requiring oxygen inhalation and hospitalization.

Treatment regimen: ICIs should be permanently discontinued, and patients should be hospitalized. If infection has not been completely excluded, empirical anti-infective treatment should be initiated, and respiratory or infectious department consultation is recommended. Intravenous methylprednisolone at 2 mg/kg/day and pulmonary ventilation should be administered as appropriate. After 48 h of steroid treatment, if clinical symptoms have improved, treatment should continue until the symptoms improve to ≤ G1, at which time the dose can be gradually reduced over 4–6 weeks. If symptoms are not significantly improved, intravenous infliximab (5 mg/kg) (repeated administration after 14 days), mycophenolate mofetil (1–1.5 g/time, 2 times/day), or immunoglobulin should be considered.

G4: Life-threatening dyspnea or acute respiratory distress syndrome; urgent intervention such as tracheotomy or intubation required.

ICI-Related Myocarditis

The incidence of ICI-related myocarditis is not high, but the prognosis of severe myocarditis is poor, with a high mortality rate. Possible immune-related myocarditis should be diagnosed in any patient who develops signs or symptoms of suspected myocarditis after medication, such as dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis should be distinguished from myocarditis due to viral infection, ischemic events, preexisting arrhythmia, exacerbation of preexisting cardiac conditions, or malignant neoplasm progression. Myocarditis due to ICIs is classified into 4 grades by severity level:

G1: Increased biomarkers of cardiac injury only, with no changes in cardiovascular symptoms, ECG, or echocardiography.

Treatment strategies: Active monitoring, cardiovascular consultation, and trending of cardiac injury markers are necessary. If cardiac injury biomarkers are mildly abnormal and remain stable, ICI treatment can continue. If cardiac injury biomarkers progressively increase, ICI treatment should be suspended, and glucocorticoid treatment can be administered if necessary.

G2: Minor cardiovascular symptoms, with cardiac injury biomarkers and/or ECG abnormalities.

Treatment strategies: ICIs should be immediately discontinued, and bed rest, cardiovascular consultation, ECG monitoring, and trending of cardiac injury markers are necessary. Methylprednisolone (starting dose: 1–4 mg/kg/day) should be administered immediately for 3–5 consecutive days, after which time the dose may be reduced and steroid therapy continued for 2–4 weeks after the condition recovers to baseline level. If the patient does not respond to glucocorticoid treatment, other immunosuppressants can be added as appropriate, and ICIs can be resumed with caution after the patient's condition recovers to baseline levels.

G3–G4: Obvious cardiovascular symptoms or life-threatening conditions requiring urgent hospitalization.

Treatment strategies: ICIs should be permanently discontinued, and bed rest, MDT (cardiovascular department, critical care medicine department, etc.) consultation, ICU-level monitoring, and trending of cardiac injury markers are recommended. Methylprednisolone pulse therapy (500–1,000 mg/day) should be initiated immediately for 3–5 days, followed by gradual dose reduction; glucocorticoid therapy should be continued for approximately 4 weeks after the patient's cardiac function returns to baseline. Pacemakers should be implanted for patients with arrhythmia, and circulatory and respiratory support should be given to critically ill patients in a timely manner.

Autoimmune Pancreatitis and Other Toxicities

Autoimmune pancreatitis is a special type of gastrointestinal adverse event related to immunotherapy. When patients with acute abdominal pain exhibit increased levels of amylase and lipase, the diagnosis of acute pancreatitis should be confirmed as soon as possible. Some patients may experience endocrine toxicity during treatment with ICIs, including abnormal thyroid function and hypophysitis. At this time, intervention should be performed under the guidance of an endocrinologist whenever possible. In addition, the use of ICIs (such as camrelizumab) requires intensive skin examinations, monitoring of skin status, and medication guidance by a dermatologist.

Consensus Statement 13. Because most patients with HCC exhibit hepatic impairment, the use of ICIs often aggravates impaired liver function. Therefore, changes in liver function should be closely monitored. Although the incidence of immune-mediated myocarditis and pneumonia is low, their prognosis is poor with high mortality. Therefore, suspicion of these conditions should raise immediate concern, and careful attention should be given to biomarkers of heart injury and pulmonary imaging changes (degree of expert consensus: 100%).

Rechallenge of ICIs

Rechallenge of ICI refers to restarting ICIs in patients who have experienced irAEs. An observational, cross-sectional, pharmacovigilance cohort study examined individual case safety reports from the WHO database VigiBase, which contains case reports from more than 130 countries. Among 20,471,248 safety events in VigiBase, 24,079 (0.1%) cases were irAEs associated with the use of at least one ICI, of which 6,123 cases (25.4%) were associated with ICI rechallenge. Recurrence status was recorded in 452 (7.4%) cases of 6,123 irAEs associated with ICI rechallenge, including whether it was a recurrence of the same irAE; 130 (28.8%, 95% CI: 24.8–33.1) cases were recurrences of the initial irAEs [58]. Another retrospective study on "retreating with ICIs after discontinuation due to irAEs" systematically reviewed and analyzed 482 patients with advanced non-small cell lung cancer [76] who received ICIs at Memorial Sloan-Kettering Cancer Center (MSKCC) from 2004 to 2011. A total of 168 (14%) of these patients had serious irAEs and required treatment interruption, 38 (56%) of which reinitiated ICIs and 30 (44%) of which discontinued treatment. Most (58%) patients had recurrent/new irAEs of grades 1–2, and 84% of them improved or resolved to grade 1 irAEs. Patients who initially developed irAEs and required hospitalization had a higher possibility of recurrent/new irAEs. Among patients without a partial response observed before the first occurrence of irAEs, the PFS and OS in the reinitiation group were significantly longer than those in the discontinuation group, indicating that patients who did not respond to treatment before the onset of irAEs may benefit from reinitiating treatment. According to the "NCCN Guidelines Insights:

Management of Immunotherapy-Related Toxicities" (2020) [59], the resumption of immunotherapy after the occurrence of severe irAEs requires great caution and close follow-up to monitor for recurrence of irAEs in related organs; if irAEs recur, permanent discontinuation is needed. Tumor status should be assessed before the reinitiation of immunotherapy. If treatment with ICIs achieves an objective response (complete or partial), reinitiation of immunotherapy is not recommended due to the risk of recurrent toxicity, and the physician should discuss with the patient his or her risks/benefits. In addition, patients with serious irAEs caused by one type of immunotherapy require permanent discontinuation of immunotherapy of the same type, and patients with moderate irAEs should be carefully monitored. If the patient has a grade 3/4 irAE due to the use of ipilimumab, PD-1/PD-L1 inhibitor monotherapy may be considered after recovery. With the exception of some special cases, when the toxicity of grade 2 irAEs recovers to ≤ grade 1, immunotherapy can be resumed. If the drug is discontinued due to irAEs, the treatment should be restarted after consultation with relevant organ disease specialists. These guidelines are summarized in the "CSCO Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities" [61]; in some cases, patients cannot completely stop glucocorticoids, and they can restart ICIs as long as the daily dose of prednisone is ≤10 mg (or equivalent dose) and no other immunosuppressants are taken at the same time.

Consensus Statement 14. The criteria for resuming ICIs in patients with previous irAEs are uncertain. If G3 and greater irAEs occur, immunotherapy should be permanently discontinued. If irAEs below G2 occur and resolve to ≤ G1 after treatment, immunotherapy can be resumed after discussion with the MDT (from the perspectives of risk and benefit, in combination with the irAE type, severity level, and efficacy of initial immunotherapy, as well as whether there are other tumor replacement regimens, etc.) under close monitoring and follow-up (degree of expert consensus: 90.5%).

Assessment of ICI Treatment Efficacy

Imaging Assessment

Imaging tests are preferred for assessment of treatment efficacy, and other symptoms, signs, and serology tests should be used as a reference and supporting evidence. Dynamic contrast-enhanced CT or MRI is used to measure the size of HCC and assess treatment efficacy (for accurate assessment of the size of active tumor lesions, high-quality arterial phase and portal venous phase imaging is needed, and delayed phase imaging is not necessary). To avoid missing minor active lesions, thin slice scanning or tumor-specific MRI contrast agents may be performed if necessary (degree of expert consensus: 98.06%). RECIST 1.1 is the common evaluation criterion for the efficacy of solid tumor treatment in clinical practice. However, because the criteria do not distinguish between tumor necrosis and active tumor replication, there are limitations in evaluating the efficacy after comprehensive treatment for some complex tumors, such as HCC. The mRECIST can be applied to contrast-enhanced imaging examination, focusing on the assessment of lesions with arterial phase enhancement (i.e., active tumors), and can more effectively assess the treatment efficacy of HCC than RECIST 1.1, which are valid supplementary criteria for efficacy assessment of HCC treatment (degree of expert consensus: 98.06%). To more accurately measure HCC size and assess activity, flexible selection of reasonable response assessment criteria and target/nontarget lesions is recommended according to the characteristics of imaging findings on HCC. For typical HCC with arterial phase enhancement and clear boundaries, mRECIST can be preferentially recommended as criteria for selecting target lesions and measuring the longest diameter of the active tumor (the longest diameter of the enhanced part should be measured in the arterial phase to avoid the tumor necrosis area; each measurement should assess the longest diameter of the active tumor rather than the longest diameter of the scanning plane at baseline) for efficacy assessment. For HCC with atypical arterial phase enhancement or/and blurred boundary, RECIST 1.1 can be recommended as criteria for selecting nontarget lesions and measuring the longest diameter of the tumor, or mRECIST can be used for nontarget lesions and efficacy assessment. An attempt may be made to use tumor volume instead of tumor diameter as the efficacy assessment criterion. At present, most experts believe that lesions with the following imaging characteristics can be confirmed as new HCC: lesions with an active diameter >1 cm that exhibit a typical "fast in fast out" enhancement pattern on dynamic contrast-enhanced CT/MRI; lesions with a diameter >1 cm but exhibiting an atypical "fast in fast out" pattern on imaging, with a diameter increasing by at least 1 cm during follow-up (after being confirmed as a new lesion, the onset time of the new lesion is the time when it is first discovered) (degree of expert consensus: 99.03%).

As the indications for different immunotherapy regimens for HCC are approved, immune-related efficacy

evaluation becomes increasingly important in HCC. Compared with traditional therapies, immunotherapy has a long smearing effect on its efficacy. In addition, the enlargement of existing lesions and the appearance of new lesions in the early stage of immunotherapy may be pseudoprogression, which is easily misjudged as PD under traditional RECIST 1.1. Therefore, new criteria based on RECIST 1.1 have emerged, such as immune RECIST (iRECIST). At present, iRECIST is widely used, introducing the concepts of PD to be confirmed on the basis of RECIST 1.1, which proposes a model of repeated evaluation to avoid misjudgment of PD by taking atypical response types such as pseudoprogression in immunotherapy into account.

Consensus Statement 15. Imaging examination should prevail in HCC efficacy assessment. For HCC with atypical arterial phase enhancement or/and blurred boundaries, RECIST 1.1 can be recommended as criteria for selecting target lesions and measuring the longest tumor diameter. mRECIST can be used as criteria for efficacy assessment of nontarget lesions. For HCC with typical arterial phase enhancement and clear boundaries, mRECIST is recommended. Due to the possibility of pseudoprogression of HCC immunotherapy, iRECIST can be considered the exploratory evaluation criteria to assess the efficacy of HCC patients based on mRECIST (RECIST 1.1) and combined with iRECIST (degree of expert consensus: 99.03%).

Serology Efficacy Assessment

Serology test results can be used as reference evidence for efficacy evaluation but not as the basis for efficacy evaluation alone. Serum tumor markers are commonly used for screening, diagnosis, monitoring, and follow-up of HCC patients. The most widely used and specific tumor markers in clinical practice are serum AFP, AFP heterogeneity (AFP-L3), and protein induced by vitamin K absence or antagonist-II. Continuous dynamic monitoring during the disease course is necessary when the efficacy is evaluated by tumor marker testing [77–79], and the same test system should be used to ensure the comparability of test results. The test should be repeated once every 1–2 months. Recent studies have demonstrated that the early and rapid decline of markers is a manifestation of significant therapeutic effects.

Consensus Statement 16. In HCC patients with increased AFP, dynamic monitoring results of AFP or/and AFP-L3, protein induced by vitamin K absence or antagonist-II (every 4–8 weeks) should be used as indicators for efficacy. If the AFP level exceeds the upper limit of normal values at baseline, AFP must return to normal levels when used to evaluate a complete response in combination with imaging results (degree of expert consensus: 92.23%).

MDT Management of Therapy with ICIs

The indications, contraindications, medication regimen, efficacy assessment, adverse reaction monitoring, and prevention of ICIs all involve the management of MDTs. MDTs are also a requirement for the National Cancer Center to formulate quality control standards for the diagnosis and treatment of HCC in China. The MDT team should develop the most appropriate treatment strategy in a timely manner based on the latest evidence-based medicine, the patient's condition and wishes, the accessibility of medical resources, oncological assessment, and treatment goals through the full cooperation of relevant clinical professional teams and stratified management. The implementation of the MDT management of HCC immunotherapy not only is an international trend in tumor treatment but also represents an important institutional guarantee for effectively implementing standardized treatment of HCC and guaranteeing medical quality and safety. Therefore, the key points of MDT management in the clinical application of HCC immunotherapy should be emphasized: (1) taking the Departments of Hepatobiliary Surgery, Vascular Intervention, Oncology, Radiology, and Radiotherapy as the core departments, the general condition and tumor stage of patients should be preliminarily assessed, the indications and contraindications for immunotherapy should be investigated, and the basic archives of patients should be established before immunotherapy; (2) taking the Departments of Oncology, Cardiology, Respiratory, Endocrinology, Hepatology, Gastroenterology, Dermatology, ICU, and Pathology as the core departments, drug-related adverse reactions occurring during immunotherapy should be monitored, and treatment measures should be developed; and (3) MDT medical staff are recommended to qualify as good clinical practice, undertake demand-oriented clinical studies, and strengthen the management of off-label applications involving immunotherapy under the framework of MDT.

Consensus Statement 17. In the clinical application of ICIs, the MDT should be fully involved in the medication regimen, efficacy assessment, and adverse reaction monitoring and prevention. The MDT should develop the most appropriate treatment strategy in a timely manner, which should be based on the latest evidence-based medicine, the patient's condition, the accessibility

of medical resources, oncological assessment, and treatment goals through cooperation with relevant clinical professional teams and stratified management (degree of expert consensus: 99.03%).

Prospect

ICIs have attracted significant attention as a cancer therapy in recent years, and many products have been approved for the treatment of HCC in China and abroad. Combination regimens based on ICIs have significantly improved the therapeutic efficacy of HCC patients. However, how to define the population benefiting from different immunotherapy regimens, how to combine ICIs with other systemic and local therapies, and how to prevent and control adverse reactions remain important directions for future exploration. In addition to the treatment of patients with advanced HCC, ICIs have been actively explored in the perioperative period of HCC and may represent an effective treatment. At present, some regimens of combination therapy with novel immunotherapy drugs, such as anti-LAG3 (relatlimab) and TIGIT antibodies, are under clinical exploration. The ICI combination therapy strategy has led to a significant improvement in the ORR of HCC and provides an opportunity for conversion operation of unresectable HCC. However, the correlation between ORR and OS remains controversial, and OS based on quality of life must be the final endpoint of HCC treatment. Immunotherapy breaks the impasse in the systemic treatment of HCC and brings new hope to patients. The treatment of HCC requires cooperation from experts in multidisciplinary fields, and individualized treatment regimens should be developed to achieve precise treatment. Furthermore, while implementing long-term management and improving therapeutic efficacy, strategies to reduce the incidence of adverse reactions and improve patient quality of life will become the direction of continuous exploration in HCC treatment.

Consensus Statement 18. Although combined immunotherapy has significantly improved the survival benefit of HCC patients, the study of HCC-related immunotherapy remains in its infancy, and studies on biomarkers and/or clinicopathological characteristics for efficacy prediction, selection of immune combination regimens, and generation of clinical drug resistance are still being explored. HCC patients are encouraged to actively participate in clinical studies to obtain better survival benefits.

Conflict of Interest Statement

The authors have no relevant financial or nonfinancial interests to disclose.

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Author Contributions

Xiufeng Liu and Yinying Lu contributed equally to the work and were responsible for the provision of study materials and data collection. Xiaoping Chen and Feng Xia contributed to the conception and design. Weiping Zhou, Tao Peng, Huaqiang Bi, and Jie Zhou provided technical and material support. Xiufeng Liu contributed to data analysis, interpretation, and draft writing. All authors read and approved the final manuscript.

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