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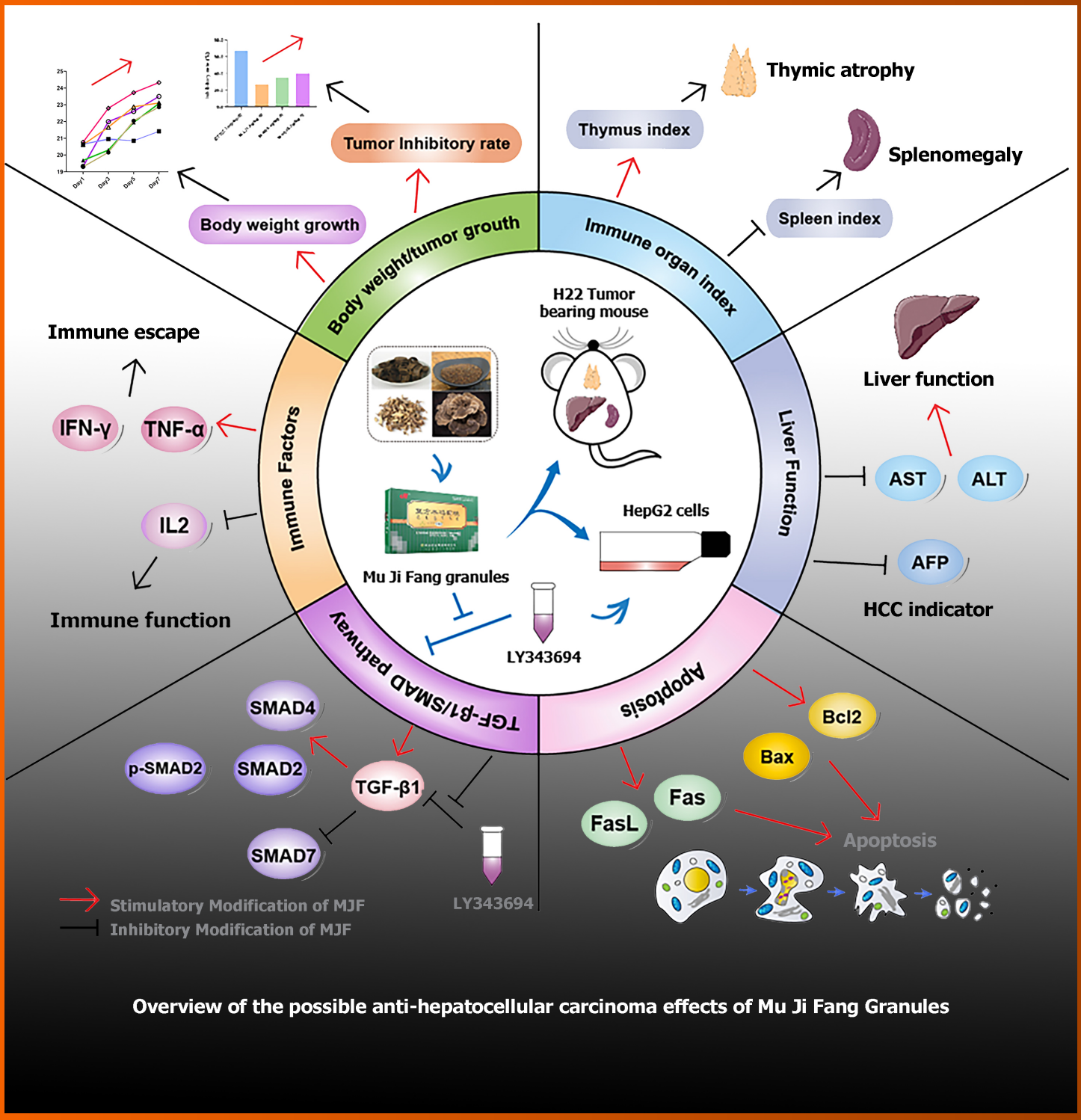

Overview of the possible anti-hepatocellular carcinoma effects of Mu Ji Fang Granules

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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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REVIEW

Immunotherapy for advanced or recurrent hepatocellular carcinoma

Ying-Zhe Luo, Hong Zhu

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Abstract

Hepatocellular carcinoma (HCC) is associated with high morbidity and mortality, and is prone to intra- and extrahepatic metastasis due to the anatomical and functional characteristics of the liver. Due to the complexity and high relapse rate associated with radical surgery or radiofrequency ablation, immune checkpoint inhibitors (ICIs) are increasingly being used to treat HCC. Several immunotherapeutic agents, along with their combinations, have been clinically approved to treat advanced or recurrent HCC. This review discusses the leading ICIs in practice and those currently undergoing randomized phase 1–3 trials as monotherapy or combination therapy. Furthermore, we summarize the rapidly developing alternative strategies such as chimeric antigen receptor-engineered T cell therapy and tumor vaccines. Combination therapy is a promising potential treatment option. These immunotherapies are also summarized in this review, which provides insights into the advantages, limitations, and novel angles for future research in establishing viable and alternative therapies against HCC.

Key Words: Recurrent hepatocellular carcinoma; Immunotherapy; Immune checkpoint inhibitor; Chimeric antigen receptor-engineered T cell; Oncolytic virus; Tumor vaccine

Core Tip: The high recurrence rate of hepatocellular carcinoma (HCC) following radical treatment remains challenging; therefore, immune checkpoint inhibitors (ICIs) are increasingly being used to treat HCC. Herein, we discuss the ICIs in practice and those undergoing trials, and summarize the alternative strategies such as chimeric antigen receptor-engineered T cell therapy and tumor vaccines. Combination therapy is also a promising potential treatment option. We believe our study significantly contributes to the literature as it addresses the current state of immunotherapy against HCC and provides insights into the advantages and limitations, thereby facilitating future research.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy (75%-85% of cases), sixth most diagnosed cancer, and the third most common cause of cancer-related deaths worldwide in 2020[1]. The incidence and main risk factors for HCC vary from area to area. Traditionally, the highest epidemic of HCC is mainly in East and South-East Asia; however, the incidence of HCC has increased in the United States and Europe[2]. The key risk factors of HCC include chronic hepatitis B virus or hepatitis C virus (HCV) infection, aflatoxin-contaminated foods, excessive drinking, obesity, and smoking[3,4].

Hepatic resection is the best method for treating early-stage HCC[5-7]. Radiofrequency ablation (RFA) is also considered a radical treatment in many patients with small HCC and is the recommended treatment for patients with a single tumor < 2 cm or 2–3 nodules of ≤ 3 cm[5-8]. Less than 30% of patients with HCC can be treated with surgery and RFA due to distant metastases, anatomical location limitations, hepatic insufficiency, and neurovascular invasion[9,10]. Besides, patients with HCC who receive radical treatment have a high recurrence rate, typically manifesting as recurrence in liver remnants[11]. The recurrence rate in early HCC patients remains high at 5 years post curable excision [11-13]. Most HCCs (> 70%) are diagnosed at an advanced stage[14]. Radical treatment of recurrent HCC includes repeated hepatic resection and liver transplantation; these radical treatments are complex due to the shortage of donors, small residual areas of liver after hepatectomy, hepatic dysfunction, and multiple metastases. Due to the particularity of advanced and recurrent HCC, radiotherapy alone is not recommended. Systematic chemotherapy is also rarely recommended due to resistance to multiple cytotoxic drugs and abnormal liver function[15]. Therefore, local interventional therapies have been developed to treat recurrence, including transcatheter arterial chemoembolization (TACE)[16] and hepatic artery infusion chemotherapy (HAIC)[17]. Locoregional therapy is, for the most part, not a radical treatment, with recurrence and local disease progression being typical. For patients undergoing these, there is an urgent need to explore new therapies to treat recurrent HCC.

Sorafenib, which was been recommended as a first-line treatment for liver cancer with Child-Pugh type A liver function and Barcelona Clinic Liver Cancer-C in 2007, is a multi- tyrosine kinase inhibitor (TKI) that can extend median overall survival (mOS) and the time to radiologic progression by 3 mo [18]. Lenvatinib, which is an alternative first-line treatment for advanced HCC[19], is not inferior to sorafenib. However, lenvatinib is associated with significant improvements compared with sorafenib in terms of higher objective response rate (ORR), prolonged progression-free survival (PFS), and prolonged time to progression[20,21]. Regorafenib[22], cabozantinib[23], and ramucirumab[24,25] are recommended as second-line treatments for advanced HCC[26]. These licensed systemic multi-TKIs may be poorly tolerated due to their significant side effects, drug resistance, and modest benefits in mOS[21,27-29]. Since nivolumab was approved as a second-line treatment for advanced HCC in 2017, immunotherapy for recurrent or advanced HCC has witnessed rapid development. Nivolumab, pembrolizumab, atezolizumab, durvalumab, ipilimumab, tremelimumab, tislelizumab, sintilimab, and camrelizumab and their combinations have been approved in succession for HCC treatment[8]. The advent of cancer immunotherapy has completely changed the traditional treatment concept for HCC by stimulating the immune system of individuals to kill tumor cells selectively. Other immunotherapy strategies, such as chimeric antigen receptor-engineered T cells (CAR-Ts) and therapeutic cancer vaccines, have matured to the stage of clinical trials, offering new hope for HCC patients[30-32]. This article reviews approved immunotherapies and those in clinical development for HCC treatment.

LIVER AND HCC IMMUNITY

The liver, which receives arterial and venous blood is exposed to pathogens in the systemic circulation (mainly from the gut). Liver immunosurveillance is one of the most critical lines of defense. The liver contains a variety of immune cells, some of which are innate immune cells including neutrophils, macrophages, natural killer cells (NKs), NK T cells (NKTs), dendritic cells (DCs), and Kupffer cells, all of which are essential immune sentinels and antigen-presenting cells (APCs)[33-37]. Kupffer cells can capture antigens under flowing conditions, whereas NKs and NKTs can be activated upon detection of antigens and directly release granulosin and perforase to act on target cells or release large amounts of cytokines (*e.g.*, interferon gamma [IFN-g]) to direct the immune response[38-40]. DCs are the most potent APCs, which can effectively take up, process, and present antigens. As important immune cells, DCs can participate in the development and activation of T and B cells. DCs can also secrete a variety of cytokines (interleukin [IL], IFN, and tumor necrosis factor) and chemokines to participate in the immune function regulation and mediate the chemotaxis of other immune cells[33,41,42]. Neutrophils promote the progression of HCC by interacting with macrophages and regulatory T cells (Tregs). Large numbers of neutrophils predict poor tumor status[43,44]. Conversely, adaptive immune cells include B cells, plasma cells, and effector T cells. A normal liver provides a tolerant microenvironment that inhibits innate and adaptive immunity in homeostasis and prevents inflammation or tissue damage in the liver[45,46].

The immune system of the liver plays a vital role in controlling the occurrence and development of HCC. The interaction between innate and adaptive immunity can lead to effective antitumor immunosurveillance[47]. Tumor cells, Tregs, inhibitory B lymphocytes, and other inhibitory cells mediate the tumor microenvironment by regulating negative costimulatory molecules to achieve immune escape [48]. In addition, myeloid suppressor cells (MDSCs) or M2-polarized tumor-associated macrophages generate an inflammatory microenvironment, which can also serve as a medium for tumor initiation, angiogenesis, and metastasis[49]. Transforming growth factor beta (TGF-β) is the primary mediator for this activity[50] and plays a central role in inflammation, fibrogenesis, and immunomodulation in the HCC microenvironment[51,52]. Therefore, controlling the synthesis and activation of TGF-β during tumor progression is important.

PRINCIPLES OF HEPATOCELLULAR IMMUNOTHERAPY AND IMMUNE CHECKPOINT INHIBITOR

Tumor cells inhibit immune checkpoint overactivation and express corresponding ligands to achieve an immune escape[53]. We previously studied various immunosuppressive receptors, including programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), lymphocyte-activation gene 3, T cell immunoglobulin and mucin domain containing-3, and B- and T-lymphocyte attenuator[54,55]. For example, the inhibitory receptor on T cells, PD-1, can be expressed in various immune cell types and binds to programmed death ligand-1 (PD-L1) of the corresponding target cells to inhibit the effects of T cells. CTLA-4 is expressed on the surface of activated T cells by competing with cluster of differentiation 28 (CD28) and binding to CD80 and CD86 to reduce the co-inhibitory signal of CD28 and induce T cell apoptosis. Meanwhile, CTLA-4, an essential gene in Treg differentiation, development, and maintenance of cell functions is highly expressed in Tregs[56]. The concept of blocking inhibitory immune receptors and activating the antitumor function of reinvigorated immune cells has been experimentally demonstrated and translated into the clinical treatment of many types of tumors[57]. Inhibitors of PD-1, PD-L1, and CTLA-4, known as immune checkpoint inhibitors (ICIs), are an essential part of immunotherapy for many tumors including melanoma, non-small cell lung cancer, and colorectal cancer[58]. ICIs, which can block the influence of negative immune costimulatory molecules, can exhibit antitumor activity and kill tumor cells by promoting and upregulating the activation of T cells, thereby restoring normal physiological functions of the human body[59]. ICIs have shown that effective immune response can exterminate tumor cells. Current approaches of immunotherapy were shown in Figure 1. Some ICIs and their related targets are summarized in Figure 2.

SINGLE IMMUNE AGENT THERAPY

Nivolumab

Nivolumab was approved in 2017 for patients with recurrent HCC who showed no respond to sorafenib treatment[60]. Nivolumab showed noble safety and tolerability in the phase of escalation (0.1-10 mg/kg) in the CheckMate 040 study. Only 12 of 48 patients (25%) experienced grade 3 or 4 AEs, and no deaths linked to nivolumab treatment were confirmed. In the phase of dose expansion (3 mg/kg), ORR, disease control rate (DCR), and mPFS were 20%, 40%, and 4 mo, respectively. Compared with the phase of escalation, the indices of the dose-expansion phase were significantly improved[61]. In the CheckMate

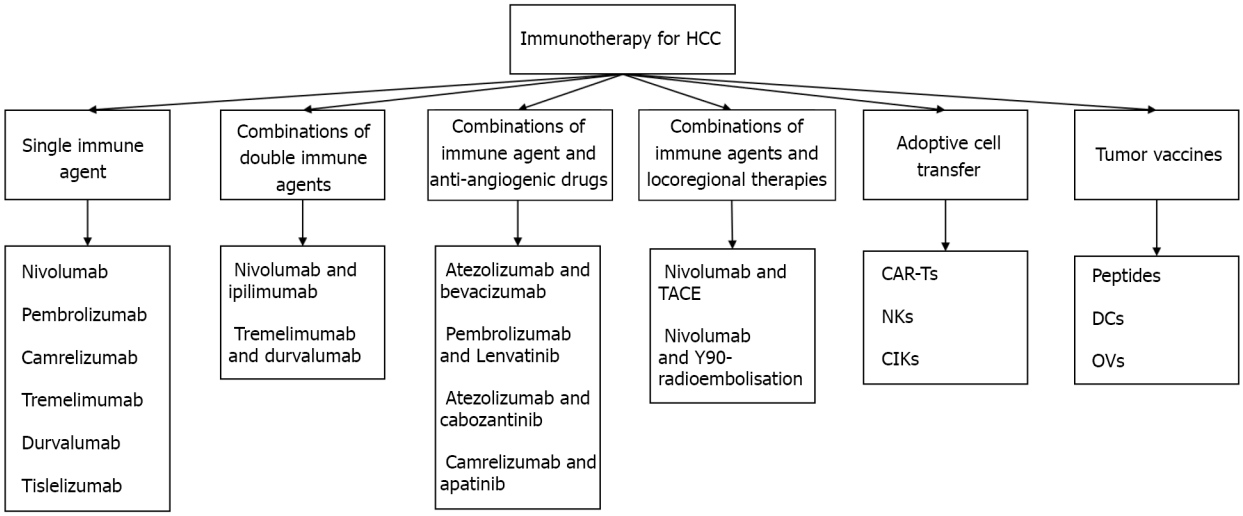

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Figure 1 Current approaches of immunotherapy. CAR-Ts: Chimeric antigen receptor expressing T cells; CIKs: Cytokine-induced killer cells; DCs: Dendritic cells; HCC: Hepatocellular carcinoma; NKs: Natural killer cells; OVs: Oncolytic virus; TACE: Transcatheter arterial chemoembolization.

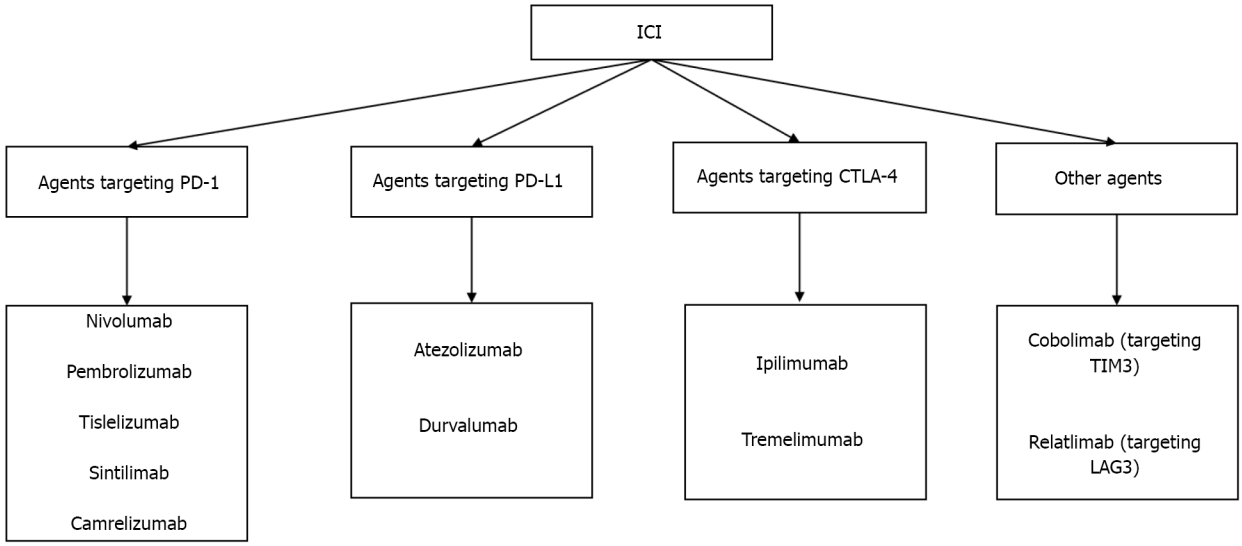

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Figure 2 Immune targets and immune checkpoint inhibitors. CTLA-4: Cytotoxic T lymphocyte-associated antigen 4; ICI: Immune checkpoint inhibitor; LAG3: Lymphocyte-activation gene 3; PD-1: Programmed cell death protein 1; PD-L1: Programmed death ligand 1; TIM3: T cell immunoglobulin and mucin domain containing-3.

040 study (NCT01658878) (Table 1), a single nivolumab showed an enduring response, controlled safety, and satisfactory survival in patients with advanced HCC. As the CheckMate 040 study lacked a randomized control, the CheckMate 459 randomized trial (NCT02576509) (Table 1) was conducted to evaluate the efficacy of nivolumab *vs* sorafenib in a first-line setting. Although nivolumab did not significantly improve mOS (16.4 mo *vs* 14.7 mo, hazard ratio [HR]: 0.85; P = 0.075) compared with sorafenib, a lower proportion of grade 3 or 4 treatment-related adverse events (AEs), persistent response frequency, and clinical activity make nivolumab a broader treatment prospect[62].

Pembrolizumab

Pembrolizumab, an anti-PD-1 monoclonal antibody (mAb), has demonstrated promising antineoplastic effects and safety in a variety of malignant tumors[63]. KEYNOTE-224 study (NCT02702414) (Table 1) was conducted to evaluate the efficacy and safety of pembrolizumab in patients with recurrent HCC with no response to sorafenib. The results included ORR of 17%, DCR of 62%, mPFS of 4.9 mo, mOS of 12.9 mo, and grade 3 or 4 AEs that occurred in 25% of the clinical trial participants. Therefore, the Food and Drug Administration (FDA) approved pembrolizumab for treating unresectable intermediate and advanced HCC in November 2018[64]. Pembrolizumab showed good efficacy and a controllable safety

Table 1 Activity of single immune checkpoint inhibitor from the clinical trials

Drugs (dose)	Other treatment	Targets	Trial identifier	Patient group	*n*	mOS in mo	ORR, %	DCR, %	mPFS in mo	Phase	Setting
Nivolumab (3 mg/kg every 2 wk)	No	PD-1	NCT01658878	Advanced HCC	214	NR	20.0	64.0	4.00	I-II	1L
Nivolumab (240 mg every 2 wk)	*vs* Sorafenib	PD-1	NCT02576509	Advanced HCC	371	16.40	15.0	55.0	3.70	III	1L
Pembrolizumab (200 mg every 3 wk)	No	PD-1	NCT02702414	Advanced HCC	104	12.90	17.0	62.0	4.90	II	2L
Pembrolizumab (200 mg every 3 wk)	*vs* Placebo	PD-1	NCT02702401	Advanced HCC	278	13.90	18.3	62.2	3.00	III	2L
Pembrolizumab (200 mg every 3 wk)	No	PD-1	NCT02658019	Advanced HCC	29	11.00	32.0	46.0	4.50	II	2L
Camrelizumab (200 mg every 2 wk)	*vs* Camrelizumab (200 mg q3w)	PD-1	NCT02989922	Advanced HCC	109	14.20	11.9	47.7	2.30	II	2L
Camrelizumab (200 mg every 3 wk)	*vs* Camrelizumab (200 mg q2w)	PD-1	NCT02989922	Advanced HCC	108	13.20	17.6	44.0	2.00	II	2L
Durvalumab (1500 mg every 4 wk)	*vs* T300+D and tremelimumab	PD-L1	NCT02519348	Unresectable HCC	104	13.60	10.6	37.5	2.07	II	Mix
Durvalumab (1500 mg every 4 wk)	*vs* T300+D and sorafenib	PD-L1	NCT03298451	Unresectable HCC	389	16.56	17.0	54.8	3.65	III	1L
Tremelimumab (750 mg every 4 wk)	*vs* T300+D and durvalumab	CTLA-4	NCT02519348	Unresectable HCC	69	15.10	7.2	49.3	2.69	II	Mix
Tislelizumab (5 mg/kg every 3 wk)	No	PD-1	NCT02407990	Advanced HCC	50		12.2	51.0		Ib	2L

1L: First-line therapy; 2L: Second-line therapy; CTLA-4: Cytotoxic T lymphocyte-associated antigen 4; DCR: Disease control rate; HCC: Hepatocellular carcinoma; mOS: Median overall survival; mPFS: Median progression free survival; NR: Not reached; ORR: Overall response rate; PD-1: Programmed cell death protein 1; PD-L1: Programmed death ligand 1; T300+D: Dose of tremelimumab (300 mg IV, cycle 1) combined with durvalumab (1500 mg IV once every 4 wk).

profile in patients with advanced HCC who had previously received sorafenib; therefore a worldwide phase 3 study of pembrolizumab (KEYNOTE-240) (NCT02702401) (Table 1) was conducted. In the second-line treatment of advanced HCC, mOS of pembrolizumab and placebo were 13.9 mo *vs* 10.6 mo (HR: 0.77), mPFS was 3.3 mo *vs* 2.8 mo (HR: 0.70), and OS and PFS did not meet the specified criteria for statistical significance. Improvements in ORR, DCR, PFS, and OS with pembrolizumab treatment were consistent with the results of the single-cohort KEYNOTE-224 study (Table 1). The difference in ORR (18.4% *vs* 4.4%) favored pembrolizumab[65]. Accelerated FDA approval was acquired for pembrolizumab use for treating advanced HCC in patients who failed to respond to prior sorafenib therapy.

Camrelizumab

Camrelizumab, an immunoglobulin G4 (IgG4) anti-PD-1 mAb, is used to treat several cancers including lymphoma, lung cancer, esophageal cancer, and HCC[66,67]. Camrelizumab showed significant antitumor efficacy and tolerance in patients with advanced solid tumors in phase 1 trials[68-70]. To continue evaluating the activity and safety of camrelizumab as a second-line or higher treatment for advanced or recurrent HCC, a randomized phase 2 trial (NCT02989922) (Table 1) was conducted. A total of 217 patients with advanced HCC were randomly assigned in a 1:1 ratio to two groups, including 2 wk of camrelizumab (3 mg/kg) (n = 109) treatment and 3 wk of camrelizumab (3 mg/kg) (n = 108) treatment. At the end of data cutoff, survival metrics from the 2- or 3-wk group, including mOS (14.2 mo *vs* 13.2 mo), mPFS (2.3 mo *vs* 2 mo), DCR (47.7% *vs* 44 %) and ORR (11.9% *vs* 17.6%) showed good antitumor activity. In terms of safety, grade 3 or 4 AEs occurred in 47 patients (22%)[71].

Compared with other PD-1 inhibitors, camrelizumab experienced a significantly lower DCR (44.2% *vs* 55% with nivolumab[62] in sorafenib-patients and 47.7% *vs* 62% with pembrolizumab[64] in the second-line setting after sorafenib use) and shorter mPFS (2.1 mo *vs* 4.9 mo with pembrolizumab and 3.7 mo

with nivolumab). Overall, camrelizumab demonstrated potential antitumor efficacy and safety. However, the efficacy of single camrelizumab was limited; hence, a combination with targeted agents and other ICIs are needed to improve the efficacy.

In March 2020, camrelizumab was approved by the Chinese Food and Drug Administration for treating patients with advanced HCC who had received sorafenib or chemotherapy with oxaliplatin. Camrelizumab is also the first PD-1 inhibitor with HCC indications approved in China, which is a breakthrough in immunotherapy in China.

Tremelimumab

Tremelimumab is a human IgG2 mAb that blocks the binding of CTLA-4[72]. ORR was 17.6% with a DCR of 76.4% in a clinical trial of tremelimumab in patients with HCC and chronic HCV. Surprisingly, tremelimumab showed satisfactory antitumor activity, antiviral activity, and safety in patients with advanced HCC developed from HCV-induced liver cirrhosis. However, the first trial of tremelimumab for HCC included only 20 patients and therefore could not account for chance results caused by multiple clinical covariates[73]. In a phase 2 clinical trial of tremelimumab in combination with durvalumab for HCC (NCT02519348) (Tables 1 and 2), 326 patients were assigned to four cohorts, namely the tremelimumab monotherapy arm (750 mg once every 4 wk [seven doses] and then once every 12 wk), durvalumab monotherapy arm and T300+D arm (tremelimumab 300 mg plus durvalumab 1500 mg [one dose each during the first cycle] followed by durvalumab 1500 mg once every 4 wk), and T75+D arm (750 mg once every 4 wk [seven doses] and then once every 12 wk). The tremelimumab monotherapy arm represented the first large cohort of HCC patients receiving anti-CTLA-4 monotherapy. The ORR was 7.2%, DCR was 49.3%, mOS was 15.1 mo, and mPFS was 2.69 mo. Although the ORR of this cohort was the lowest (7.2%), the mOS was the second longest, and the median duration of response (mDOR) was prolonged (23.95 mo). However, the grade 1-4 AEs of T300+D were highest (82.4%), whereas that of grade ≥ 3 AEs of tremelimumab monotherapy was the highest (43.5%). Among the four arms, the tremelimumab monotherapy received the highest dose of tremelimumab; therefore, serious AEs were considered to be dose-related to tremelimumab. Compared with tremelimumab monotherapy, the combination of T300+D significantly enhanced antitumor efficacy[74].

Durvalumab

In the phase 2 clinical trial of tremelimumab in combination with durvalumab for HCC (NCT02519348) (Tables 1 and 2) mentioned before, 104 patients with HCC who had progressed on, were intolerant to, or refused sorafenib were randomly assigned to receive durvalumab monotherapy; ORR was 10.6%, DCR was 37.5%, mOS was 13.6 mo, and mPFS was 2.07 mo[74]. Meanwhile, in a phase 3 trial (NCT03298451) (Table 1) of tremelimumab in combination with durvalumab for HCC, the durvalumab monotherapy arm was non-inferior to sorafenib in ORR (17% *vs* 5.1%) and mOS (16.56 mo *vs* 13.77 mo). Compared with durvalumab monotherapy in the phase 2 study, durvalumab in this phase 3 study had significantly increased activity with an ORR of 17%, DCR of 54.8%, mPFS of 3.65 mo, and mOS of 16.56 mo[75].

Tislelizumab

Tislelizumab (BGB-A317) is a humanized IgG4 mAb with high affinity and binding specificity for PD-1. Unlike nivolumab and pembrolizumab, tislelizumab evades the efficacy mediated by Fc gamma R1 (FcγR1) and minimizes the binding of macrophages to FcγR; this may mitigate potential adverse interactions with other immune cells, including macrophages and MDSCs[76-78]. Tislelizumab has demonstrated satisfactory tolerability and significant antitumor activity in patients with advanced HCC. Fifty advanced HCC patients who had previously received other antitumor therapies were reported in the HCC cohort, with an ORR of 12.2% (95% confidence interval [CI]: 4.6-24.8), a DCR of 51% (95%CI: 36.3-65.6), and an average DOR of 15.7 mo. Preliminary safety and antitumor activity support the continued exploration and development of tislelizumab in patients with advanced HCC[79,80]. Therefore, the phase 2 open-label clinical trial of tislelizumab (NCT03419897) further explored the efficacy and safety of Tislelizumab in the second-line treatment of advanced HCC and a phase 3 randomized controlled trial (NCT03412773) is currently evaluating the efficacy and safety of tislelizumab and sorafenib as a first-line treatment for unresectable HCC. These results will provide more options for treating advanced and recurrent HCC.

COMBINATION OF DOUBLE IMMUNE AGENTS THERAPIES

Nivolumab and pembrolizumab have demonstrated antitumor properties in treating advanced HCC. PD-1/PD-L1 inhibitors and CTLA-4 inhibitors influence T cell response through a complementary mechanism to enhance antitumor efficacy[81]. These positive results inspired the study of the combination of PD-1/PD-L1 inhibitors with CTLA-4 inhibitors with an aim of longer survival and higher response rates. Several combinations of ICIs have been tested to prove their efficacy (Table 2), whereas some remain in the experimental research and development stage (Table 3). According to the

Table 2 Activity of combinations of immune checkpoint inhibitors from the clinical trials

Drugs	Targets	Other treatment	Trial identifier	Patient group	*n*	mOS in mo	ORR, %	DCR, %	mPFS in mo	Phase	Setting
Nivolumab + ipilimumab	PD-1; CTLA-4	No	NCT01658878	Advanced HCC	50	22.80	32.0	54.0		I/II	1L
Durvalumab + tremelimumab	PD-L1; CTLA4	*vs* Durvalumab and tremelimumab	NCT02519348	Unresectable HCC	75	18.70	24.0	45.3	2.17	I/II	2L
Durvalumab + tremelimumab	PD-L1; CTLA4	*vs* Durvalumab and sorafenib	NCT03298451	Unresectable HCC	393	16.40	20.1	60.1	3.78	III	1L

1L: First-line therapy; 2L: Second-line therapy; CTLA-4: Cytotoxic T lymphocyte-associated antigen 4; DCR: Disease control rate; HCC: Hepatocellular carcinoma; mOS: Median overall survival; mPFS: Median progression free survival; ORR: Overall response rate; PD-1: Programmed cell death protein 1; PD-L1: Programmed death ligand 1.

Table 3 Activity of combinations of an immune checkpoint inhibitor and a vascular endothelial growth factor inhibitor from clinical trials

Drugs	Other treatment	Targets	Trial identifier	Patient group	*n*	mOS in mo	ORR, %	DCR, %	mPFS in mo	Phase	Setting
Atezolizumab + bevacizumab	*vs* Sorafenib	PD-L1; VEGF	NCT03434379	Unresectable HCC	326	19.20	27.3	74.0	6.90	III	1L
Pembrolizumab + lenvatinib	No	PD-1; VEGFR	NCT03006926	Unresectable HCC	104	22.00	36.0	88.0	8.60	Ib	1L
Sintilimab + IBI305	*vs* Sorafenib	PD-1; VEGF	NCT03794440	Unresectable HCC	380	NR	21.0	72.0	4.60	III	1L
Atezolizumab + cabozantinib	*vs* Sorafenib	PD-L1; VEGFR	NCT03755791	Advanced HCC	432	15.40	11.0	78.0	6.10	III	1L
Camrelizumab + apatinib	No	PD-1; VEGFR	NCT03463876	Advanced HCC	70	NR	34.3	77.1	5.70	II	1L
Camrelizumab + apatinib	No	PD-1; VEGFR	NCT03463876	Advanced HCC	120	NR	22.5	75.8	5.50	II	2L

1L: First-line therapy; 2L: Second-line therapy; CTLA-4: Cytotoxic T lymphocyte-associated antigen 4; DCR: Disease control rate; HCC: Hepatocellular carcinoma; mOS: Median overall survival; mPFS: Median progression free survival; NR: Not reached; ORR: Overall response rate; PD-1: Programmed cell death protein 1; PD-L1: Programmed death ligand 1; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor.

preliminary results of the nivolumab and ipilimumab combination compared with nivolumab monotherapy, the ORR (34%) and mOS (22.8 mo) significantly increased with the combination of PD-1 and CTLA-4[82] (NCT01658878) (Table 2). The rate of AEs was significantly higher with the combination of nivolumab and ipilimumab than with nivolumab monotherapy. More than 50% of patients in the Checkmate 040 study required corticosteroids, and the discontinuation rate was 22%, due to tolerably high immunotoxicity[61]. Similar results that showed the antitumor activity of dual immunoblockers being superior to that of single drug were also observed in tremelimumab and durvalumab for patients with unresectable HCC (NCT02519348). Compared with tremelimumab or durvalumab monotherapy, T300+D showed the most encouraging benefit-risk profile[74], which promotes T300+D to enter into phase 3 clinical trial (NCT03298451). For the 393 patients, the ORR was 20.1%, DCR was 60.1%, mOS was 16.4 mo, and mPFS was 3.7 mo (Table 2). Durvalumab was not inferior to tremelimumab; however, the combination of T300+D showed superior efficacy and a favorable benefit-risk profile compared with durvalumab and tremelimumab monotherapy. Compared with the combination of nivolumab and ipilimumab, the incidence of immunotoxicity requiring systemic corticosteroids in the T300+D regimen was 24.3%. The discontinuation rate was only 10.8% due to AEs[75]. Overall, the results of these two studies demonstrated that PD-1/PD-L1 and CTLA-4 had different and complementary antitumor mechanisms.

COMBINATION OF IMMUNE AGENTS AND ANTI-ANGIOGENIC DRUG THERAPIES

Combination of atezolizumab and bevacizumab

The overexpression of vascular endothelial growth factor (VEGF) is important in the occurrence and development of HCC. Anti-angiogenic drugs, including sorafenib, lenvatinib, and bevacizumab, are capable of targeting platelet-derived growth factor receptor, VEGF receptor (VEGFR), fibroblast growth factor receptor, hepatocyte factor receptor (c-KIT), and other proteins to inhibit tumor angiogenesis. Anti-VEGFR drugs (sorafenib and lenvatinib) effectively reduce VEGFR-mediated immune suppression and promote T cell activity in the tumor environment[83,84]. Sorafenib was the first anti-VEGFR drug used to treat advanced HCC in the past decade. Since then, until the emergence of atezolizumab in combination with bevacizumab, no treatment has surpassed the first-line efficacy of sorafenib[18,85]. In a phase 1b randomized cohort trial comprising 119 patients, atezolizumab in combination with bevacizumab resulted in significantly higher mPFS (7 mo) and ORR (36%) than atezolizumab monotherapy[86]. In the IMbrave150 clinical trial (NCT03434379) (Table 4), compared with sorafenib, the combination of atezolizumab (PD-L1) and bevacizumab (a vascular epidermal growth factor inhibitor) reduced the risk of death by 42% and extended mPFS and mOS by 2.5 and 5.8 mo (median follow-up 15.6 mo), respectively. The results showed an ORR of 27.3%, DCR of 74%, mPFS of 6.9 mo, and mOS of 19.2 mo. Notably, the ORR of this combination even reached more than twice that of sorafenib[85]. With long-term follow-up, to the best of our knowledge, this combination had the longest mOS observed in a phase 3 trial for HCC until now. In terms of safety, the grade ≥ 3 AEs of the combination occurred in 160 patients (49%), which were consistent with the known AEs of each drug [87]. The combination of atezolizumab and bevacizumab was approved by the FDA for treating patients with advanced or recurrent HCC who had not previously received systemic treatment[88].

Combination of pembrolizumab and lenvatinib

Lenvatinib was not statistically inferior to sorafenib in a phase 3 trial comparing lenvatinib with sorafenib as the first-line treatment for unresectable HCC. Compared with sorafenib, lenvatinib showed significant and clinically significant improvements in ORR, PFS, and TTP[21]. However, pembrolizumab also exhibited substantial antitumor activity and safety. Lenvatinib, in combination with pembrolizumab, has received accelerated approval for the treatment of advanced tumors that do not have high microsatellite instability or mismatch repair defects[89]. The encouraging preliminary trial data has led to a phase 1b study for the combinations of lenvatinib and pembrolizumab to treat unresectable HCC (NCT03006926) (Table 4). Surprisingly, the combination achieved an ORR of 46.0% (95%CI: 36.0%–56.3%, mRECIST standard) and a DCR of > 85% (regardless of the RECIST category). mPFS and mOS were 9.3 and 22 mo, respectively. The combination of lenvatinib and pembrolizumab showed no new AEs[90]. Based on the interim data from this study, the FDA granted lenvatinib in combination with pembrolizumab as first-line therapy for advanced HCC. The combination is being studied in a randomized phase 3 trial (NCT03713593) and compared with the first-line treatment of unresectable or metastatic HCC using lenvatinib (Table 3).

Other combination of ICIs and antiangiogenic drugs therapy

ICIs combined with anti-angiogenic agents open a new avenue for treating HCC. In contrast, FDA-approved first-line combination therapies for HCC are only available in a few regions worldwide. Therefore, alternative therapies need to be developed and approved. Currently, PD-1/PD-L1 checkpoint inhibitors, CTLA-4 checkpoint inhibitors, TKI, along with other antitumor agents are undergoing randomized phase 1–3 trials as monotherapy or combination therapy (Table 3). Cabozantinib, approved in 2019 by the FDA as a second-line treatment of sorafenib, has shown promising antitumor activity. COSMIC312 (NCT03755791) evaluated the combination of cabozantinib and atezolizumab *vs* sorafenib as first-line systemic therapy for HCC. Compared with sorafenib, the combination arm significantly improved PFS (HR: 0.63; 99%CI: 0.44–0.91; $P = 0.0012$; mPFS 6.8 mo *vs* 4.2 mo). However, OS was not improved[91] (HR: 0.90; 96%CI: 0.69-1.18; $P = 0.438$). At the end of 2020, the ORIENT-32 trial, which enrolled 571 HCC patients without systemic therapy, reported that combination of sintilizumab (PD-1) and bevacizumab biosimilar (IBI305) was significantly superior to sorafenib in terms of OS and PFS, as shown in Table 4. After a median follow-up of 10 mo, the mOS was not achieved in the combination line (sintilizumab and IBI305), while it was 10.4 mo in the sorafenib group (HR: 0.57; 95%CI: 0.43–0.75; $P < 0.0001$); mPFS (4.6 mo, 95%CI: 4.1–5.7) was significantly prolonged (HR: 0.56, 95%CI: 0.46-0.70; $P < 0.0001$)[92]. In early 2021, camrelizumab (PD-1) in combination with apatinib (a selective VEGFR-2 tyrosine kinase inhibitor) was assessed in phase 2 (NCT03463876) as the first- and second-line treatment for advanced HCC. Significant antitumor activity was achieved in ORR, DOR, and OS for both first- and second-line treatments[93] (Table 4). Encouraging antitumor properties continue to emerge in the new combination therapies with ICIs and TKIs, which will provide options for recurrent HCC treatment.

Table 4 Ongoing phase I-III trials testing immune checkpoint inhibitors in advanced hepatocellular carcinoma

Drugs	Other treatment	Targets	Trial identifier	Patient group	Status	*n*	Estimated completion date	Phase	Setting
Single ICI									
Pembrolizumab	Placebo	PD-1	NCT03062358	Advanced HCC	Active, not recruiting	454	June 30, 2023	III	2L
Tislelizumab	*vs* Sorafenib	PD-1	NCT03412773	Advanced HCC	Active, not recruiting	674	May 1, 2022	III	1L
Durvalumab	No	PD-L1	NCT04294498	Advanced HCC	Recruiting	43	December 31, 2023	II	2L
Tislelizumab	*vs* Sorafenib	PD-1	NCT03419897	Unresectable HCC	Active, not recruiting	249	June 30, 2022	II	2L
Combination of ICIs									
Nivolumab + ipilimumab	*vs* Sorafenib and lenvatinib	CTLA-4, PD-1	NCT04039607	Advanced HCC	Recruiting	728	September 30, 2019	III	1L
Sintilimab + IBI310	*vs* Sorafenib	PD-1, CTLA-4	NCT04720716	Advanced HCC	Recruiting	490	February 7, 2021	III	1L
Combination of ICIs and antiangiogenic drugs									
Nivolumab + regorafenib	No	PD-1, VEGFR	NCT04310709	Unresectable HCC	Recruiting	42	May 30, 2023	II	1L
Pembrolizumab + lenvatinib	Placebo and lenvatinib	PD-1, VEGFR	NCT03713593	Advanced HCC	Recruiting	750	December 31, 2023	III	1L
Pembrolizumab + futibatinib	No	PD-1, FGFR	NCT04828486	Advanced HCC	Recruiting	25	May 6, 2024	II	2L
Pembrolizumab + regorafenib	No	PD-1, VEGFR	NCT03347292	HCC	Active, not recruiting	57	September 26, 2022	I	1L
Pembrolizumab + sorafenib	No	PD-1, VEGFR	NCT03211416	Advanced or metastatic HCC	Recruiting	41	December 7, 2022	I/II	1L
Pembrolizumab + cabozantinib	No	PD-1 VEGFR	NCT04442581	Advanced HCC	Recruiting	29	September 13, 2024	II	1L
Camrelizumab + apatinib	No	PD-1, VEGFR	NCT04826406	HCC	Recruiting	40	August 30, 2023	II	1L
Camrelizumab + lenvatinib	No	PD-1, VEGFR	NCT04443309	Advanced HCC	Recruiting	53	August 1, 2023	I/II	1L
Camrelizumab + apatinib	*vs* Sorafenib	PD-1 VEGFR	NCT03764293	Advanced HCC	Active, not recruiting	543	June 1, 2022	III	1L
Toripalimab + lenvatinib	No	PD-1, VEGFR	NCT04368078	Advanced HCC	Recruiting	76	April 1, 2023	II	2L
Tislelizumab + regorafenib	No	PD-1, VEGFR	NCT04183088	Advanced HCC	Recruiting	125	March 1, 2025	II	1L
Tislelizumab + lenvatinib	No	PD-1, VEGFR	NCT04401800	Locally advanced or Unresectable HCC	Recruiting	66	December 1, 2022	II	1L
Sintilimab + lenvatinib	No	PD-1, VEGFR	NCT04042805	Advanced HCC	Recruiting	36	August 30, 2024	II	1L
Sintilimab + anlotinib	No	PD-1, VEGFR	NCT04052152	Advanced HCC	Recruiting	20	December 30, 2021	II	1L
Sintilimab + IBI305	*vs* Sorafenib	PD-1, VEGFR	NCT03794440	Advanced HCC	Active, not recruiting	595	December 1, 2022	II/III	1L
Sintilimab + regorafenib	*vs* Regorafenib	PD-1, VEGFR	NCT04718909	Unresectable HCC	Recruiting	180	December 31, 2022	II	1L
Sintilimab + donafenib	No	PD-1, VEGFR	NCT05162352	Advanced HCC	Recruiting	30	May 1, 2023	II	1L

Atezolizumab + lenvatinib or sorafenib	*vs* Sorafenib or lenvatinib	PD-L1, VEGFR	NCT04770896	Unresectable HCC	Recruiting	554	October 8, 2024	III	2L
Atezolizumab + bevacizumab	No	PD-L1, VEGFR	NCT04829383	Unresectable HCC	Recruiting	50	July 1, 2024	II	1L
Atezolizumab + bevacizumab	No	PD-L1, VEGFR	NCT04732286	Unresectable HCC	Active, not recruiting	100	September 25, 2023	III	1L
Atezolizumab + bevacizumab	No	PD-L1, VEGFR	NCT04487067	Unresectable HCC	Active, not recruiting	152	July 31, 2023	IIIb	1L
Durvalumab + tivozanib	No	PD-L1, VEGFR	NCT03970616	Advanced HCC	Recruiting	42	August 1, 2022	I/II	Mix
Durvalumab + lenvatinib	No	PD-L1, VEGFR	NCT05312216	Unresectable HCC	Not yet recruiting	25	April 1, 2022	II	1L
Durvalumab + bevacizumab	Placebo	PD-L1, VEGFR	NCT03847428	High risk of recurrence HCC	Active, not recruiting	877	May 31, 2024	III	1L

1L: First-line therapy; 2L: Second-line therapy; CTLA-4: Cytotoxic T lymphocyte-associated antigen 4; FGFR: Fibroblast growth factor receptor; HCC: Hepatocellular carcinoma; ICI: Immune checkpoint inhibitor; NR: Not reached; PD-1: Programmed cell death protein 1; PD-L1: Programmed death ligand 1; VEGFR: Vascular endothelial growth factor receptor.

COMBINATION OF IMMUNE AGENTS AND LOCOREGIONAL THERAPIES

Some locoregional therapies for HCC, including radiotherapy, RFA, TACE and HAIC, can release or produce altering substances from cancer cells to stimulate the aggregation of DCs into tumor tissues. This can upregulate the expression and antigenicity of tumor-associated antigens (TAAs) and trigger injury-related molecular patterns to induce "immunogenic cell death"[94-96]. Locoregional therapies can induce the release of proinflammatory cytokines to activate and expand innate and adaptive immune cells (NK and cytotoxic T cells) and reduce the activity of immunosuppressive cells (Tregs and MDSCs)[97-100]. Meanwhile, immunotherapy can not only improve the hypoxic microenvironment in tumors and enhance the effect of radiotherapy by inducing vascular normalization through a T cell-dependent pathway but also enhance the immune induction effect of radiotherapy to slow the growth of distant tumors (abscopal effect). Radiotherapy and immunotherapy synergize to exert more potent local effects in the irradiated tumors[101,102]. The IMMUTACE trial initially evaluated the efficacy of nivolumab plus TACE in 49 patients with mid-stage HCC; the ORR was 71.4% (95%CI: 56.8%-83.4%), including 16.3% complete responses (CRs) and 55.1% partial responses. Despite the small number of patients in each group, subgroup analyses did not reveal differences in treatment responses[103]. In the CA 209-678 study (NCT03033446) of Y90-radioembolisation followed by nivolumab in 36 patients with advanced HCC, the ORR of 30.6% compared favorably with an ORR of approximately 20% noted with Y90-radioembolisation. Notably, 81% of patients showed regression of radiation-field target lesions. This combination is safe and tolerable with grade 3–4 treatment-related AEs or serious AEs noted in 14% of patients[104]. Many clinical trials of locoregional therapies combined with ICIs are being conducted successively (Table 5). This combination is expected to become the mainstream treatment for HCC in the future.

ADOPTIVE CELL TRANSFER

Adoptive cell transfer is a form of passive therapy in which immune cells are activated and expanded *in vitro* and then reinfused into the patient. These immune cells commonly used include NKs, tumor-infiltrating lymphocytes, lymphokine-activated killer cells, cytokine-induced killer cells (CIKs), and CAR-T cells.

NK cells

NKs can recognize tumor cells based on the expression of ligands for inhibitory and stimulant NK receptors[40]. Encouraging clinical trials results in which autologous lymphocytes containing NK cells were transfused into HCC patients after ablation or resection had shown that extended NKs have significant cytotoxic effects on HCC cells[105]. Furthermore, extended NKs significantly enhanced the anti-HCC cytotoxicity of sorafenib[106]. Multiple phase 2 trials are being conducted to evaluate the use of NKs in patients after hepatectomy (NCT02008929) or TACE (NCT02854839). However, how to cultivate high purity NKs is still a problem to be solved.

Table 5 Ongoing clinical trials that combine locoregional therapies with immune checkpoint inhibitors

Main intervention methods	Comparison arms	Trial identifier	Status	Estimated or actual enrollment	Patient group	Phase
Pembrolizumab + RAF/MWA/brachytherapy/TACE	*vs* Pembrolizumab + RAF/MWA/brachytherapy/TACE	NCT03753659	Active, not recruiting	30	Early-stage HCC	II
Nivolumab + TACE	No	NCT03572582	Active, not recruiting	49	Intermediate-stage HCC	II
Pembrolizumab + TACE	No	NCT03397654	Active, not recruiting	26	HCC	I/II
Durvalumab + tremelimumab + TACE/RAF/cryoablation	*vs* Durvalumab + tremelimumab	NCT02821754	Active, not recruiting	54	Advanced HCC	II
Durvalumab + tremelimumab + TACE	No	NCT03638141	Recruiting	30	Intermediate-stage HCC	II
Durvalumab + tremelimumab + bevacizumab + TACE	No	NCT03937830	Recruiting	22	Advanced HCC	II
Durvalumab + bevacizumab + TACE	*vs* Durvalumab + TACE *vs* TACE	NCT03778957	Active, not recruiting	724	Intermediate-stage HCC	III
Apatinib + camrelizumab + HAIC	No	NCT04191889	Recruiting	84	Advanced HCC	II
Pembrolizumab + SBRT	No	NCT03316872	Recruiting	30	Advanced HCC	II
Durvalumab + tremelimumab + SBRT	No	NCT03482102	Recruiting	70	Advanced HCC	II
Nivolumab + curative resection/RAF	*vs* Curative resection/RAF	NCT03383458	Active, not recruiting	545	Resected HCC	III
Durvalumab + bevacizumab + curative resection/RAF	*vs* Durvalumab + curative resection/RAF *vs* Curative resection/RAF	NCT03847428	Active, not recruiting	877	Resected HCC	III
Ipilimumab + nivolumab + TACE	*vs* Nivolumab + TACE + placebo *vs* TACE + placebo + placebo	NCT04340193	Active, not recruiting	26	Intermediate-stage HCC	III
Lenvatinib + pembrolizumab + TACE	*vs* Placebo + placebo + TACE	NCT04246177	Active, not recruiting	950	Incurable/non-metastatic HCC	III
Nivolumab + DEB TACE	*vs* DEB TACE	NCT04268888	Recruiting	522	Intermediate-stage HCC	II/III

HAIC: Hepatic artery infusion chemotherapy; HCC: Hepatocellular carcinoma; MWA: Microwave ablation; RAF: Radiofrequency ablation; SBRT: Stereotactic body radiation therapy; TACE: Transcatheter arterial chemoembolization.

CIK cells

CIKs are heterogeneous cells with non-major histocompatibility complex-restricted tumor killing activity. After being cultured *in vitro*, CIKs can secrete a variety of cytokines to improve the internal microenvironment of tissues and organs and enhance the killing activity of immune cells[107]. A phase 3 clinical trial (NCT00699816) including 230 patients showed that adjuvant CIK immunotherapy improved PFS and OS in patients with HCC after curable surgical resection, RFA, or percutaneous ethanol injection[105]. CIKs may have a significant impact on adoptive immunotherapy regimens in patients with primary HCC.

CAR-T cell therapy

CAR-T therapy is a developing immunotherapy approach for treating malignant tumors. Due to the great success of CAR-T therapy in the treatment of CD19-positive hematological malignancies, such as a CR rate of up to 90% with anti-CD19 CAR-T cells in B-cell acute lymphoblastic leukemia[108-111], two CAR-T cell therapies, Kymriah® and Yescarta®, were approved by the FDA for lymphoma studies in 2018 and 2017, respectively. Because of this lymphoma breakthrough, CAR-T's application in treating solid tumors, such as HCC, has also been explored. Glypican-3 (GPC-3), a member of the GPC family, is a 70 kDa heparan sulfate proteoglycan overexpressed in HCC and associated with poor diagnosis and prognosis[112-115]. Several clinical trials have evaluated the safety and efficacy of GPC-3 CAR-T cells. Shanghai Renji Hospital combined lymphodepleting chemotherapy with GPC-3 CAR-T cells in 13 patients with GPC3-positive HCC and confirmed the antitumor efficacy and safety of GPC3 CAR-T cells (NCT02395250)[116]. GPC-3 CAR-T cells combined with sorafenib may be a promising option for treating of HCC[117].Chongqing Xinqiao Hospital has attempted to combine TACE with CAR-T to treat

GPC3-positive advanced HCC (NCT03084380). Other clinical trials are recruiting patients to improve the efficacy of intratumoral or intravenous administration of GPC3-CART cells (NCT03130712, NCT02715362, NCT04951141, NCT03198546, and NCT05155189). In conclusion, GPC-3 is a promising target for future therapeutic strategies in HCC. Mucin 1 glycoprotein (MUC-1)[118,119] and epithelial cell adhesion molecule (EpCAM)[120] are two transmembrane glycoproteins that can be overexpressed during the occurrence and development of HCC and can be used as biomarkers and therapeutic targets for HCC. One clinical trial of MUC-1 CAR-T cells (NCT02587689) and two clinical trials of EpCAM CAR-T cells (NCT03013712 and NCT02729493) are ongoing. Alpha-fetoprotein (AFP), which is overexpressed in HCC, is another potential therapeutic target being explored. However, AFP is a glycoprotein of the cellular endocrine system and expression and is therefore considered inappropriate for the CAR. Some researchers have designed a highly specific antibody (Ab) of the (AFP)-MHC complex to be expressed as the CAR and found that CAR-T cells of this Ab had an apparent inhibitory effect on HCC; this provided a promising new approach for HCC immunotherapy[121].

TUMOR VACCINE

Tumor vaccines are active immunotherapies that require the injection of tumor antigens, including viruses, DNA, peptides, and tumor cell-expressed genes, into patients to trigger TAA-specific immune responses and mediate powerful antitumor effects[122]. Therapeutic tumor vaccines include peptides, DCs, whole-cell vaccines, oncolytic viruses, and DNA reagents.

Peptides

Several peptide-based cancer vaccines have been assessed for HCC treatment. As a biomarker of HCC, AFP was constructed as a peptide vaccine, used in 2 patients with AFP-expressing tumors and showed high levels of AFP-specific CD8+T cell expression and apparent safety (NCT00093548). GPC-3 is highly expressed in most malignant tumors and is rarely in normal tissues; therefore, GPC-3 is considered an ideal TAA for developing cancer vaccines[114,123]. The GPC-3 vaccine is well-tolerated and safe[124, 125]. Similarly, multidrug resistance-associated protein 3 (MRP3), a vector-type transporter, highly expressed and associated with various cancers[126], is a great potential candidate for tumor vaccine development. In a phase 1 trial, the MRP3-derived peptides (MRP3765) showed promising safety and antitumor properties in 12 HLA-A24-positive HCC patients. MRP3-specific T-cell responses were induced in 8 patients (72.7%) and the mOS was 14 mo (95%CI: 9.6-18.5)[127]. Other TAAs, including synovial sarcoma X breakpoint 2, NY-ESO-1, human telomerase reverse transcriptase and melanoma-associated antigens family A, can also be valuable targets for HCC immunotherapy, but no clinical trials have verified the clinical response to these antigens in HCC[128]. Although peptide vaccines have achieved some success in terms of safety, tolerability, and mOS improvement, they have fewer clinical benefits and more stringent screening conditions than ICIs.

DC vaccines

DCs as APCs can stimulate T cells and increase the antitumor effect[129]. Peripheral monocytes were isolated *in vitro* and the DC population was expanded by adding cofactors (granulocyte-macrophage colony-stimulating factor or IL-4). Mature DCs are activated with autologous tumor lysates (TLs) or specific TAAs. Finally, these cells are reinfused into the patient to stimulate the adaptive cells to mount an antitumor immune response[36,130,131]. Currently, several clinical trials have confirmed the immunogenicity and safety of DCs. In a phase 1 trial of 17 patients with HCC treated with immunoprimers (ilixadencel), 73% had an increased frequency of tumor-specific CD8+-T cells in their peripheral blood[132]. Meanwhile, a phase 1 clinical trial in Japan injected DCs pulsed with TLs into 10 patients with unresectable HCC. All patients had an excellent immune tolerance; 1 patient experienced significant tumor shrinkage, while two experienced considerable tumor marker decrease[133]. In another phase 2 study, the intravenous administration of mature DCs pulsed with tumor lysate (HepG2) showed promising antitumor properties and safety in 35 patients with HCC[134]. When DCs were combined with TACE, tumor-specific immune responses were enhanced more effectively than when TACE was used alone[135]. Multiple clinical trials on DCs are in progress (NCT01821482, NCT02638857, NCT02882659, NCT03674073, and NCT03203005). A growing body of evidence suggests that DC vaccines have general safety and antitumor properties as primary therapy and adjunct to other established therapies. DC vaccines are promising mainstream immunotherapy for HCC.

Oncolytic viruses

An oncolytic virus (OV) is a specially modified intracellular pathogen that can achieve an antitumor response by massive replication in tumor cells, leading to direct lysis of tumor cells to produce soluble TAAs[136,137]. OVs have been shown to improve ORR and mOS in advanced melanoma (NCT00769704)[138]. Currently, adenovirus and vesicular stomatitis virus are the main oncolytic viruses used to treat HCC, which can preferentially infect HCC tumor cells, followed by the herpes simplex virus and vaccinia virus[139]. In a recent randomized phase 2 trial (NCT00554372), JX-549 (Pexa-Vec)

was injected into the tumors of 30 HCC patients, and mOS was significantly longer in the high-dose group than in the low-dose group (14.1 mo *vs* 6.7 mo) (HR: 0.39; P = 0.020)[140]. Unfortunately, the phase 2b trial (NCT01387555), which compared Pexa-Vec to placebo as second-line therapy in patients with advanced HCC with no response to sorafenib therapy, did not achieve its OS[141]. A phase 3 trial (NCT02562755) is currently underway, which compares the safety and efficacy of sorafenib with Pexa-Vec against sorafenib alone in HCC. Currently, two clinical trials are underway to evaluate the efficacy of the combination of OVs and ICIs in HCC (NCT03647163 and NCT03071094)[142].

CONCLUSION

The rapid development of immunotherapy has changed the traditional treatment modalities for recurrent HCC. Immunotherapy can play a unique role in the comprehensive treatment of HCC, including prolonging and improving quality of life and even curing HCC. Several clinical trials have attempted to evaluate the antitumor properties and safety of ICIs and their combinations in recurrent HCC, and have reported encouraging results. Although ICIs are the leading immunotherapy for recurrent HCC, other immunotherapy modalities including CAR-T cells, DC vaccines, and OVs are rapidly evolving. Among the multiple treatment options for recurrent HCC, achieving satisfactory results with single immunotherapy has become challenging. The development of synergistic immunotherapy may be a promising direction for HCC treatment in the future. In addition, immunosuppression of HCC remains a significant obstacle for immunotherapy drugs in which they must exert their antitumor properties. Another priority is to actively exploring the mechanisms of immunotherapy resistance or overcoming immune drug resistance through multiple antitumor drugs. Immunotherapy can lead to future breakthroughs and progress in treating recurrent HCC.

FOOTNOTES

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