

Review Article



Current Status and Future Direction of Immunotherapy in Hepatocellular Carcinoma: What Do the Data Suggest?

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Conflict of Interests

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Abbreviations

CI, confidence interval; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HR, hazard ratio; ICI, immune checkpoint inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors

ABSTRACT

Most patients with hepatocellular carcinoma (HCC) are diagnosed at an advanced stage of disease. Until recently, systemic treatment options that showed survival benefits in HCC have been limited to tyrosine kinase inhibitors, antibodies targeting oncogenic signaling pathways or VEGF receptors. The HCC tumor microenvironment is characterized by a dysfunction of the immune system through multiple mechanisms, including accumulation of various immunosuppressive factors, recruitment of regulatory T cells and myeloid-derived suppressor cells, and induction of T cell exhaustion accompanied with the interaction between immune checkpoint ligands and receptors. Immune checkpoint inhibitors (ICIs) have been interfered this interaction and have altered therapeutic landscape of multiple cancer types including HCC. In this review, we discuss the use of anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies in the treatment of advanced HCC. However, ICIs as a single agent do not benefit a significant portion of patients. Therefore, various clinical trials are exploring possible synergistic effects of combinations of different ICIs (anti-PD-1/PD-L1 and anti-CTLA-4 antibodies) or ICIs and target agents. Combinations of ICIs with locoregional therapies may also improve therapeutic responses.

Keywords: Carcinoma, hepatocellular; Immune checkpoint inhibitor; Therapeutics

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most frequently diagnosed cancers and is a leading cause of cancer-related death. Cirrhosis induced by infection, such as by hepatitis B or C virus, is the principal cause of HCC. Other factors, *e.g.*, alcohol, drugs, autoimmune hepatitis, and non-alcoholic fatty liver disease are also associated with HCC development. The incidence of HCC is gradually increasing worldwide despite the development of potent antiviral agents (1-3). Chronic inflammation and subsequent fibrosis can induce the development of HCC; inflammation also results in increased tumor immunogenicity.

In the early stages of HCC, curative treatment is possible. However, 70%–80% of patients are diagnosed with advanced-stage HCC (4). Sorafenib is the first-line systemic therapy for

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patients with Child-Pugh A cirrhosis and Barcelona clinic liver cancer-stage C (5). Sorafenib is an oral multi-tyrosine kinase inhibitor that targets a number of signaling pathways, such as the pathway centered on VEGF (6). Lenvatinib is an alternative first-line therapy and is non-inferior to sorafenib (5,7). Until 2017, there was no second-line treatment for patients in whom sorafenib treatment failed. Regorafenib and cabozantinib are systemic therapies that have recently been used as second-line treatments (8,9). Ramucirumab after sorafenib in patients with advanced HCC and increased α -fetoprotein showed improved overall survival compared with placebo group (10). However, improvements in the overall survival rate have been unsatisfactory. Clearly, new approaches for HCC remain necessary.

Recent advances in molecular and tumor biology have dramatically changed the paradigm of cancer treatment. The development of immune checkpoint inhibitors (ICIs) was clinical breakthrough. Two major targets of immunotherapy are CTLA-4 (also known as CD152) and PD-1 with PD-L1. These molecules inhibit T cell activation and promote a state of T cell dysfunction known as T cell exhaustion (11). ICIs, such as anti-CTLA-4 (e.g., ipilimumab, tremelimumab), anti-PD-1 (e.g., nivolumab, pembrolizumab), and anti-PD-L1 (e.g., durvalumab, atezolizumab) antibodies, are currently approved for several types of hematologic and solid malignancies. HCC occurs in the context of inflammatory environments. Numerous studies have demonstrated the role of immune tolerance in the development of this cancer, suggesting that suppression of ICIs may be an effective treatment strategy (12). In this review, we discuss the current status and future directions of ICIs for HCC (Table 1).

IMMUNOLOGY IN HCC

The liver receives blood from hepatic artery and portal vein, enabling it to detect and initiate immunological responses against viruses, tumors, and parasites (13). However,

Table 1. Clinical trials associated with ICIs in hepatocellular carcinoma

Drug name	Trial name	Phase	Line of therapy	Design	NCT number	Status
Anti-PD-1						
Nivolumab	CheckMate 040	I/II	1L/2L	Nivolumab vs. sorafenib	NCT01658878	Completed
	CheckMate459	III	1L	Nivolumab vs. sorafenib	NCT02576509	Completed
	-	Ib/II	2L	Nivolumab+galunisertib (TGF- β receptor I kinase inhibitor)	NCT02423343	Recruiting
Pembrolizumab	KEYNOTE-224	II	2L	Pembrolizumab	NCT02702414	Completed
	KEYNOTE-240	III	2L	Pembrolizumab vs. placebo	NCT02702401	Recruiting
	-	I	2L	Pemrolizumab+lenvatinib	NCT03006926	Recruiting
Tislelizumab	RATIONALE-301	III	1L	Tislelizumab vs. sorafenib	NCT03412773	Recruiting
Camrelizumab	-	II/III	2L	Camrelizumab	NCT02989922	Recruiting
	-	II	1L/2L	Camrelizumab+apatinib vs. Camrelizumab+FOLFOX4	NCT03092895	Recruiting
Sintilimab	ORIENT-32	III	1L	Sintilimab+bevacizumab (VEGF Ab) vs. sorafenib	NCT03794440	Recruiting
Anti-PD-L1						
Durvalumab	HIMALAYA	III	1L	Durvalumab+tremelimumab (CTLA-4 Ab) vs. durvalumab	NCT03298451	Recruiting
	-	II	1L/2L	Durvalumab; tremelimumab; durvalumab+tremelimumab	NCT02519348	Recruiting
	-	I	2L	Durvalumab+ramucirumab (VEGFR2 inhibitor)	NCT02572687	Recruiting
Atezolizumab	-	I	1L	Atezolizumab+bevacizumab	NCT02715531	Recruiting
	-	III	1L	Atezolizumab+bevacizumab vs. sorafenib	NCT03434379	Recruiting
Avelumab	-	I	1L	Avelumab+axitinib (tyrosine kinase inhibitor)	NCT03289533	Recruiting
Anti-CTLA-4						
Tremelimumab	-	II	2L	Tremelimumab (HCV)	NCT01008358	Completed
Ipilimumab	-	II	Neoadjuvant	Ipilimumab+nivolumab vs. nivolumab	NCT03222076	Recruiting

1L, first line; 2L, second line; HCV, hepatitis C virus.

the inflammatory response causes hepatocellular DNA damage, promotes immune tolerance, and confers transformed hepatocytes to evade host immune surveillance, which cooperatively contribute to initiation and progression of HCC (14,15). Furthermore, the immunosuppressive tumor microenvironment mediates HCC immune tolerance and evasion (16,17). HCC development and progression involves the dysfunction of various human immune components, including immune cells and cytokines involved in HCC proliferation, invasion, and drug resistance (Fig. 1) (18). The infiltrating myeloid-derived suppressor cells and lower numbers of tumor-infiltrating lymphocytes in fibrotic HCC tissue cause damage to effector T cells, reduction of NK cell cytotoxicity, and activation of phenotypes associated with aggressive tumorigenicity (19,20). The recruitment of myeloid-derived suppressor cells by tumor-derived TGF- β selectively suppresses the effector function of T cells, diminishes metabolic fitness for T cells, and eventually leads to T cell apoptosis (21). Moreover, tumor-associated macrophages and neutrophils activated by TGF- β facilitate tumor growth, metastasis, and resistance to sorafenib. In addition, they induce immune tolerance through nuclear factor kappa-light-chain-enhancer of activated B cells signaling (22,23). A positive feedback loop triggering immune evasion occurs when secretion of HCC-derived cytokine (e.g., chemokine C-C motif ligand2, interleukin-4, interleukin-13, and C-X-C motif chemokine 12) induces differentiation of tumor-associated macrophages and activation of tumor-associated neutrophils. These effects result in further recruitment of tumor-associated macrophages and tumor-infiltrating regulatory T cells, as well as apoptosis of cytotoxic T lymphocytes and fatigue of anti-tumor immunity via interleukin-10 (24,25).

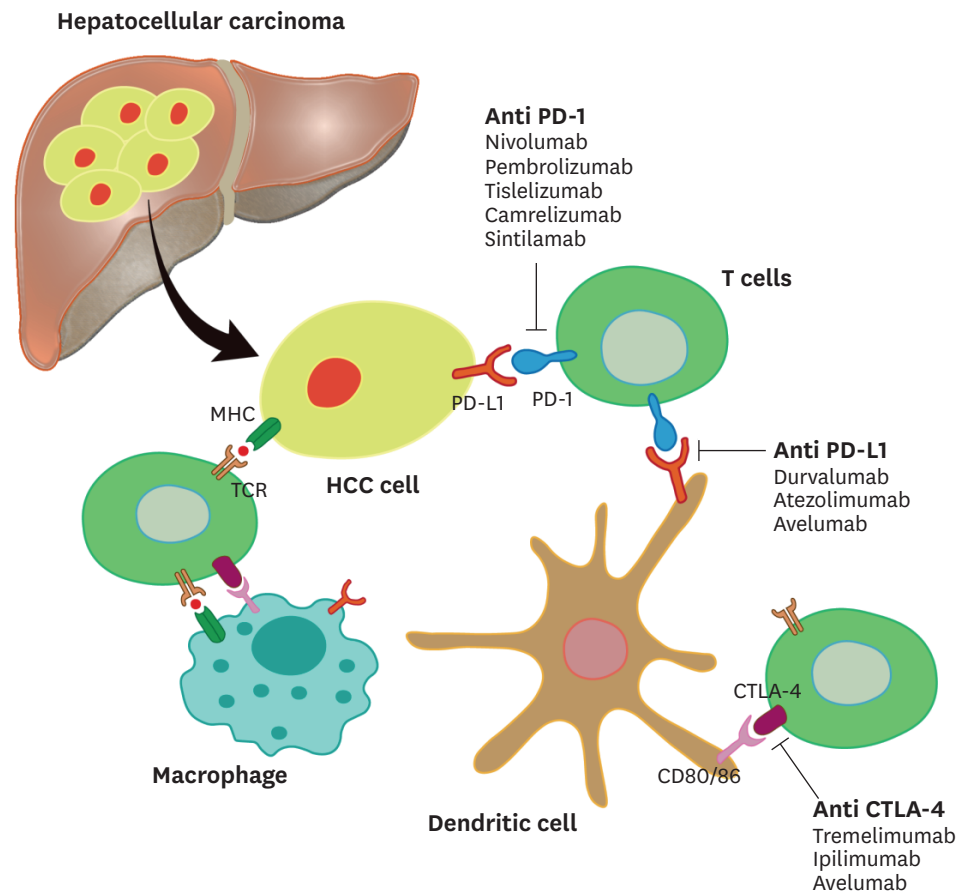


Figure 1. Schematic diagram of T cell Interaction with hepatocellular tumor cells and dendritic cells.

In addition, pro-angiogenic cytokine VEGF is up-regulated by hypoxia inducible factor-dependent pathway in the hypoxic tumor environment, which affects immune suppression in the tumor microenvironment through expressing higher levels of pro-inflammatory cytokines and immunosuppressive mediators (26). NK cells, as modulators of the balance between immune defense and tolerance in the liver, are directly and indirectly affected by the tumor microenvironment. Hypoxic stress and expression of α -fetoprotein in HCC tissue result in suppression of interleukin-12 secretion from dendritic cells, activating receptors on NK cells and causing NK cell dysfunction (27,28). Recent studies also indicate that HCC-associated fibroblast-derived indoleamine-2,3-dioxygenase and prostaglandin E2 inhibit secretion of tumor necrosis factor-alpha and interferon-gamma by NK cells, resulting in persistent fibrosis in HCC and tumor cell immune evasion (29,30). Thus, there are multiple mechanisms by which the intratumoral accumulation of immunosuppressive cells and activation of an inhibitory immune network in the tumor microenvironment induce cancer stem cell-like characteristics and sustain HCC carcinogenesis (31,32).

CURRENT STATUS OF ICIS IN HCC

Anti-PD-1

Nivolumab

Nivolumab (Opdivo®), a fully humanized IgG4 anti-PD-1 monoclonal Ab, was approved by the Food and Drug Administration (FDA) on September 23, 2017, for patients with HCC who experienced sorafenib treatment failure. The CheckMate 040 trial was a phase I/II, open label, noncomparative, dose escalation and expansion trial for patients with advanced HCC and variety of underlying chronic liver diseases (33). The efficacy of nivolumab as a first-line treatment was evaluated in patients with advanced HCC who were treatment-naïve or as a second-line treatment in patients on sorafenib with disease progression. Patients were treated with nivolumab at 0.1–10 mg/kg once every 2 wk (dose-escalating cohort) or at a dose of 3 mg/kg once every 2 wk (expansion cohort). In this trial, 46 (96%) of 48 patients discontinued treatment in the dose-escalation phase, 42 (88%) due to disease progression. The objective response rate was 20% (95% confidence interval [CI], 15%–26%) in patients treated with nivolumab 3 mg/kg in the dose-expansion phase and 15% (95% CI, 6%–28%) in the dose-escalation phase. The most common treatment-related adverse events were fatigue, rash, pruritus, and an increase in liver enzyme levels. Grade 3/4 adverse events (e.g., adrenal insufficiency, diarrhea, hepatitis, and acute kidney injury) occurred in 12 of 48 patients. The baseline tumor cell expression of PD-L1 did not have an obvious effect on the response rate. That study revealed the therapeutic potential of nivolumab, showing favorable efficacy and good safety in patients with HCC who had few treatment options. Regrettably, the CheckMate 459 trial, a randomized phase III study evaluating nivolumab versus sorafenib as a first-line treatment in patients with unresectable HCC, did not achieve significance for its primary endpoint of overall survival as defined in the pre-specified analysis plan (hazard ratio [HR]=0.85; 95% CI=0.72–1.02; p=0.075) (34). Although the results failed to meet the predefined threshold of statistical significance because p-value for overall survival of this trial is borderline, there was a clear trend suggestive of improved overall survival for patients treated with nivolumab compared to sorafenib. A phase I/II trial of nivolumab, ipilimumab, and their combination at different doses and intervals is ongoing (35).

Pembrolizumab

Pembrolizumab (Keytruda®) is an IgG4/ κ isotype humanized monoclonal Ab targeting the PD-1 receptor in immune cells. Pembrolizumab was first approved for the treatment

of metastatic melanoma, metastatic non-small-cell lung cancer, recurrent or metastatic squamous cell carcinoma of the head and neck, recurrent locally advanced or metastatic gastric cancer, locally advanced or metastatic urothelial cancer and classical Hodgkin lymphoma (36). The results of the KEYNOTE-224 trial led the FDA to approve pembrolizumab as a second-line agent for treatment of HCC after sorafenib therapy on November 10, 2018 (37). The KEYNOTE-224 study was a non-randomized, open-label, multicenter phase II trial in which 104 patients were treated with intravenous pembrolizumab (200 mg) at 3-wk intervals for 2 years or until disease progression, or any other reason to stop treatment. The trial enrolled sorafenib-refractory or -intolerant patients (cohort 1) and patients with no history of systemic treatment (cohort 2) (37). The objective response rate was 17% (complete, 1%; partial, 16%). Forty-six (44%) patients had stable disease, while 34 (33%) had progressive disease. However, serious adverse events occurred in 15% of patients. One died due to treatment-related ulcerative esophagitis.

The phase III KEYNOTE-240 trial is a confirmatory trial for pembrolizumab. Pembrolizumab was granted an accelerated approval in November 2018 for use in patients with HCC who were previously treated with sorafenib, based on data from the phase II KEYNOTE-224 trial. A total of 413 patients with advanced HCC who had previously received systemic therapy were randomized to receive pembrolizumab plus best supportive care or placebo plus best supportive care (38). Although results from the final analysis showed that improved overall survival when compared with placebo, the differences did not reach statistical significance per predefined criteria (HR=0.781; 95% CI=0.611–0.998; p=0.0238). In addition, patients treated with pembrolizumab exhibited improvement in progression-free survival, but this difference also failed to meet predefined threshold for significance. A phase III trial involving 5 Asian countries is underway (KEYNOTE-394, NCT03062358) (39).

Tislelizumab

Tislelizumab (BGB-A317) is an anti-PD-1 Ab undergoing development by BeiGene (Beijing, China). Its safety was confirmed in a phase I trial involving 61 patients with cancers, including HCC. The RATIONALE-301 randomized phase III trial of tislelizumab versus sorafenib as the first-line regimen is ongoing (NCT03412773) (40). Patients were treated with tislelizumab 200 mg intravenously every 3 wk. The primary endpoint is overall survival and the secondary endpoint is non-inferiority of tislelizumab compared to sorafenib.

Camrelizumab

Camrelizumab (SHR-1210) is a fully humanized anti-PD1 IgG4 monoclonal Ab undergoing development by Incyte (Wilmington, DE, USA) and Jiangsu HengRui (Lianyungang, China). A phase I trial confirmed its safety in 58 patients with solid cancers (41). A phase II/III trial is underway, and involves patients who failed to respond or were intolerant to prior systemic treatment (NCT02989922) (42). Camrelizumab was administered intravenously at 3 mg/kg on day 1 every 2 wk (cohort 1) with the same dose every 3 wk (cohort 2). According to the interim results of the phase II trial, the objective response rate was 13.8% (95% CI, 9.5%–19.1%) and 6-month overall survival rate was 74.7% (95% CI, 68.3%–79.9%).

Sintilimab

The anti-PD1 Ab, sintilimab, is undergoing a phase III trial. The ORIENT-32 study (NCT03794440) is a randomized, open-label, multicenter trial in China of sintilimab and bevacizumab (anti-VEGF Ab, IBI-305) versus sorafenib as a first-line treatment. Patients are treated with sintilimab (200 mg) and bevacizumab (15 mg/kg) intravenously on day 1 every 3 wk.

Anti-PD-L1

Durvalumab

Durvalumab (MEDI4736) is an anti-PD-L1 Ab undergoing development by MedImmune/AstraZeneca (Cambridge, UK). Durvalumab has been approved for locally advanced or metastatic urothelial carcinoma. A phase I/II trial of durvalumab monotherapy for solid cancers, including HCC, showed a 10% response rate and a median survival duration of 13.2 months in patients with HCC (43). A phase I/II study evaluating a combination of durvalumab, and tremelimumab (an anti-CTLA-4 Ab) confirmed its safety (44). No unexpected side effects of durvalumab and tremelimumab were observed in patients with unresectable HCC. A phase III trial of durvalumab plus tremelimumab combination therapy as a first-line regimen is ongoing (HIMALAYA study, NCT03298451) (45). The trial is a 4-arm comparing patients receiving durvalumab monotherapy, durvalumab plus tremelimumab combination therapy (regimens 1 and 2), and sorafenib monotherapy. The primary endpoint of the study is overall survival; study completion is anticipated in 2020.

Atezolizumab

Atezolizumab (MPDL3280A) is an anti-PD-L1 Ab undergoing development by Roche (Basel, Switzerland). Atezolizumab has been proven effective for locally advanced or metastatic urothelial carcinoma and metastatic non-small-cell lung cancer. A phase I trial of atezolizumab plus bevacizumab (anti-VEGF Ab) therapy is ongoing (46). According to the interim results, the response rate at presentation was 32%, based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Recently, the phase III IMbrave150 study found that combined treatment with atezolizumab and bevacizumab was associated with statistically significant improvements in both overall survival and progression-free survival, compared with sorafenib, in patients with unresectable HCC who had not received previous systemic therapy. Bevacizumab presumably enhances the ability of the PD-L1 inhibitor to restore antitumor immunity. An open-label, randomized phase III trial focusing on survival in patients receiving atezolizumab plus bevacizumab therapy and sorafenib monotherapy as first-line regimens is underway (NCT03434379) (47). Patients receive 1,200 mg atezolizumab plus 15 mg/kg bevacizumab, both administered intravenously, on day 1 of each 21-day cycle. FDA grants breakthrough therapy designation for atezolizumab/bevacizumab combination as the first-line treatment for advanced or metastatic HCC last year.

Avelumab

Avelumab (MSB0010718C) is an anti-PD-L1 Ab undergoing development by Merck KGaA (Darmstadt, Germany), Pfizer (New York, NY, USA) and Eli Lilly (Indianapolis, IN, USA). Avelumab plus axitinib (AG-013736) is undergoing a phase I trial of safety and tolerability (NCT03289533). Patients will receive avelumab 10 mg/kg every 2 wk in combination with axitinib 5 mg twice a day.

Anti-CTLA-4

Tremelimumab

Tremelimumab (CP 675206) is a CTLA-4 blocking monoclonal Ab undergoing development by MedImmune/AstraZeneca. The first small phase II clinical trial of tremelimumab monotherapy for patients with HCC and chronic hepatitis C virus infection has been conducted (48). Tremelimumab at 15 mg/kg intravenously every 90 days was administered until tumor progression or severe toxicity; partial response rate was 17.6%, disease control rate was 76.4%, and the time to progression was 6.48 months (95% CI, 3.95–9.14 months). Although a significant proportion (42.9%) of patients in Child-Pugh stage B were included

in the study, the safety profile of treatment was also acceptable. As mentioned above, a phase III study of efficacy and safety of durvalumab (anti-PD-L1) plus tremelimumab combination therapy and durvalumab monotherapy versus sorafenib is ongoing.

Tremelimumab combined with tumor ablation was evaluated in a second small pilot study (49). Locoregional therapy was expected to have a synergistic effect by inducing immunogenic tumor cell death. A confirmed partial response was achieved in 26.3% of patients. This proof-of-concept study demonstrated that immunotherapy in combination with tumor ablation could be used as treatment for patients with advanced HCC.

Ipilimumab

Ipilimumab (YERVOY®) is an anti-CTLA-4 Ab undergoing development by Bristol-Myers Squibb (New York, NY, USA)/Ono (Osaka, Japan). The CheckMate 040 study includes evaluation of nivolumab plus ipilimumab in a subcohort of sorafenib-treated patients (NCT01658878). Preliminary results showed an objective response rate of 31%, with a median duration of response of 17 months. Two other clinical studies of nivolumab plus ipilimumab as a neoadjuvant therapy are ongoing. One is a randomized phase II trial in the US comparing nivolumab monotherapy with nivolumab plus ipilimumab combination therapy (NCT03222076); the other is a planned phase II trial in Taiwan and will evaluate the combination therapy alone (NCT03510871).

OTHER IMMUNOTHERAPIES

T cell immunoglobulin and mucin-domain containing-3 is a transmembrane protein expressed by CT4⁺ Th1 cells and CD8⁺ Tc1 (cytotoxic) cells (50). A phase II trial of an anti-T cell immunoglobulin and mucin-domain containing-3 Ab (TSR-022) and anti-PD-1 (TSR-042) Ab for HCC is planned (NCT03680508). TGF- β is involved in induction of maintenance of regulatory T cells. A phase I trial of anti-TGF- β monoclonal Ab NIS793 and PD-1 inhibitor spartalizumab for advanced malignancies, including HCC, is underway (NCT02947165). Anti-TGF- β Ab is administered every 2 or 3 wk and anti-PD-1 Ab is administered every 3 or 4 wk.

Cellular immunotherapies, such as chimeric antigen receptor T cells, reportedly benefit patients with hematologic malignancies (51). Few studies have evaluated the efficacies of cellular immunotherapies against solid cancers, such as HCC. In the recent phase 3 trial, adjuvant immunotherapy with activated cytokine-induced killer cells prolonged recurrence-free and overall survival of patients who underwent curative treatment for HCC (52). clinical trial of autologous T cell receptor-engineered T cells that recognize alpha-fetoprotein, involving patients with HCC and lung cancer, is underway (NCT03441100). Finally, a trial involving T cells that recognize glypican-3 (glypican-3-specific chimeric antigen receptor expressing T cells) is now recruiting patients (NCT02905188). Glypican-3 is a membrane factor expressed by most HCC cells.

ICIS-BASED COMBINATION THERAPY

Because HCC has various causes and uses numerous mechanisms to evade the immune system, an attractive therapeutic approach involves combining different treatment mechanisms. Potential synergistic combinations include two ICIs and ICIs with conventional

Table 2. Summary of clinical trials of ICIs-based combination treatment in hepatocellular carcinoma

Characteristic	Phase	Line of therapy	Treatment	No. of patients	Results
Combination of 2 ICIs					
Nivolumab+ipilimumab (62)	II	2L	(A) Nivolumab 1 mg/kg+ipilimumab 3 mg/kg Q3W (4 doses) or (B) nivolumab 3 mg/kg+ipilimumab 1 mg/kg Q3W (4 doses), each followed by nivolumab 240 mg Q2W, or (C) nivolumab 3 mg/kg Q2W+ipilimumab 1 mg/kg Q6W	148	(A) ORR: 32%, CR: 8%, PR: 8%, DCR: 54%, mOS: 23 months or (B) ORR: 32%, CR: 6%, PR: 24%, DCR: 43%, mOS: 12 months or (C) ORR: 31%, CR: 0%, PR: 31%, DCR: 49%, mOS: 13 months
Durvalumab+tremelimumab (44)	I/II	1L/2L	11 HBV positive, 9 HCV positive, 20 uninfected	40	ORR: 15%, CR+PR: 20%, DCR16: 57.5%
ICIs+angiogenesis inhibitors					
Atezolizumab+bevacizumab (63)	III	1L	(A) Atezolizumab 1,200 mg IV Q3W+bevacizumab 15 mg/kg IV Q3W or (B) sorafenib 400 mg BID	501	(A) mOS: NA, mPFS: 6.8 months (B) mOS: 13.2 months, mPFS: 4.3 months
Pembrolizumab+lenvatinib (64)	Ib	1L	Lenvatinib (BW >60 kg: 12 mg/day; <60 kg: 8 mg/day QD) and pembrolizumab (200 mg IV Q3W)	67	ORR: 44.8%, CR: 6.0%, PR: 26%, SD: 37.3%, PD: 9.0%
Avelumab+axitinib (56)	I	1L	Avelumab 10 mg/kg IV Q2W+axitinib 5 mg orally BID	22	ORR: 31.8%, mPFS: 3.8 months, 6-month PFS: 30.9% (mRECIST)
Camrelizumab+apatinib (57)	Ib	2L	Camrelizumab 200 mg every 2 wk and apatinib 125–500 mg once daily	16	PR: 44.4%, ORR: 50%, DCR: 93.8%, mPFS: 5.8 months
ICIs+locoregional therapy					
Tremelimumab+tumor ablation (49)	III	1L/2L	Tremelimumab (3.5 and 10 mg/kg IV) every 4 wk for 6 doses, followed by 3-monthly infusions. On day 36, patients underwent ablation	32	6-month PFS: 57.1%, 12-month PFS: 33.1%, mTTP: 7.4 months, mOS: 12.3 months
ICIs+yttrium-90 radioembolization (65)	NA	1L/2L	Nivolumab alone or ipilimumab and nivolumab or ipilimumab and nivolumab following nivolumab	26	TTP: 5.7 months, PFS: 5.7 months

1L, first line; 2L, second line; Q3W, every 3 weeks; Q2W, every 2 weeks; Q6W, every 6 weeks; ORR, objective response rate; CR, complete response; PR, partial response; DCR, disease control rate; mOS, median overall survival; HBV, hepatitis B virus; HCV, hepatitis C virus; IV, intravenously; PFS, progression free survival; mPFS, median progression free survival; TTP, time to tumor progression; mTTP, median time to tumor progression; NA, not available; mRECIST, median Response Evaluation Criteria in Solid Tumors; BID, twice a day; SD, standard deviation; BW, body weight; QD, once daily.

therapies (e.g., transarterial chemoembolization, transarterial radioembolization, radiation therapy, and targeted therapies). **Table 2** summarizes the results of studies associated with ICI-based combination therapies.

Combinations of two ICIs

Combinations of two ICIs are considered promising because they can target multiple mechanisms. The high efficacy of combination therapy has been proven in other solid tumors (53). Targeting the PD-1/PD-L1 pathway alone might not inhibit development of the immunosuppressive microenvironment if the required CD8⁺ T cells are not adequately represented in the tumor microenvironment. However, simultaneous inhibition of the CTLA-4 pathway might increase the number of activated CD8⁺ T cells in lymph nodes; this would be followed by an increase in the number of activated CD8⁺ T cells infiltrating tumor tissue and an enhancement of their antitumor effects. As stated above, combinations of durvalumab plus tremelimumab (NCT03298451) and nivolumab plus ipilimumab (NCT01658878, NCT03222076, NCT03510871) are examples of possible therapies.

ICIs and angiogenesis inhibitors

HCC is a highly vascularized tumor with predominantly arterial blood flow. Thus, angiogenesis inhibitors are good options for combination treatment of HCC. Proangiogenic growth factors, which are mainly produced by tumor cells, tumor-associated macrophages, and tumor-associated fibroblasts, include VEGF-A, platelet-derived growth factor, IGF-1, and TGF- β (54). Atezolizumab plus bevacizumab (NCT03434379), pembrolizumab plus lenvatinib, camrelizumab plus apatinib, and avelumab plus axitinib are representative combinations of ICIs and angiogenesis inhibitors. Atezolizumab plus bevacizumab was discussed earlier in this review. A phase I trial for pembrolizumab plus lenvatinib

is underway. Preliminary results showed that 46% of patients with HCC exhibited a radiological response (55). Consequently, a phase 3 study was initiated to compare lenvatinib to pembrolizumab plus lenvatinib in treatment-naive patients with advanced HCC (NCT03713593). A phase Ib trial of avelumab plus axitinib in 22 naive patients with HCC showed 13.6% and 31.8% objective response rates according to RECIST and mRECIST criteria, respectively (56). Camrelizumab plus apatinib showed that 50% of patients with HCC achieved a partial response (57). Trials of nivolumab plus bevacizumab (NCT03382886), nivolumab plus lenvatinib (NCT03418922), and pembrolizumab plus lenvatinib (NCT03713593) are underway.

Combinations of ICIs and locoregional therapy

Several trials are evaluating ICIs as (neo)adjuvant setting following by curative resection or ablation, such as nivolumab versus placebo following resection or ablation (NCT03343458) and the MK-3475-937/KEYNOTE-937 trial with pembrolizumab (NCT03867084). Tremelimumab combined with tumor ablation is a potential treatment option for patients with advanced HCC (49).

Transarterial chemoembolization is associated with enhanced spread of tumor-associated antigens and an increase in VEGF. A study of transarterial chemoembolization plus nivolumab is underway (NCT03143270). More complex approaches have recently been proposed, including those used in the LEAP-01 study (chemoembolization combined with pembrolizumab and lenvatinib, NCT03713593) and the EMERALD-1 study (chemoembolization combined with durvalumab and bevacizumab, NCT03778957). Transarterial radioembolization also promotes radiation-induced tumor damage similar to that induced by stereotactic radiation therapy (58). Several phase I and II studies combining locoregional therapy with ICIs are expected to begin soon (NCT02837029, NCT03033446, NCT03099564, and NCT03380130).

CONCLUSIONS AND FUTURE PERSPECTIVES

Sorafenib and lenvatinib are currently the first-line agents for advanced HCC. However, the prognosis for advanced HCC remains unsatisfactory. ICIs might improve the prognosis of patients with advanced HCC. Recent data have shown that immunotherapies enhance survival and are safe, but their effects are limited. Combination therapies using ICIs with other agents are expected to overcome tumor-induced immunosuppression. Various combinations of immunotherapies are undergoing trials; the results are eagerly anticipated.

In addition, it is not yet possible to determine which patients can be treated effectively with immunotherapy. High expression of PD-L1 is reportedly associated with poor outcome in patients with HCC (59). However, the predictive role of PD-L1 expression in HCC patients treated with ICIs is unclear. In addition, investigating noninvasive biomarkers predicting response to ICIs is warranted (60,61).

In conclusion, advances in immunotherapy have opened a new chapter in the treatment of HCC. However, further investigation of the immune biology of HCC is needed to facilitate development of more effective therapies for patients with HCC. In addition, overcoming issues such as the lack of biomarkers and combination therapies will improve the prognosis of patients with advanced HCC.

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