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ABOUT COVER

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REVIEW

Immunotherapy in hepatocellular carcinoma: Combination strategies

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Abstract

Liver cancer is one of the most common causes of cancer death globally, and its incidence in the United States is increasing. Patients with advanced hepatocellular carcinoma (HCC) who are not candidates for surgical resection, liver transplant, or locoregional therapies can be treated with systemic therapies. Multiple agents, including sorafenib, lenvatinib, and regorafenib are approved for use as either first- or second-line therapy in this patient population, but all have relatively modest survival benefits. HCC is potentially susceptible to therapy with checkpoint inhibitors, including agents such as nivolumab and pembrolizumab, which are both approved by the Food and Drug Administration for patients previously treated with sorafenib but have not demonstrated superior overall survival in phase III trials. It is clear that more effective approaches are needed to potentiate the effects of checkpoint inhibitors in patients with HCC. This review will outline and appraise the current literature on the use of checkpoint inhibitors in HCC as part of a combination treatment involving an additional mode of therapy. The list of agents that can be paired with checkpoint inhibitors includes an additional checkpoint inhibitor, vascular endothelial growth factor or vascular endothelial growth factor receptor inhibitors, tyrosine kinase inhibitors, OX-40 agonists, and PT-112 inhibitors. The main non-pharmacologic therapies currently being studied for inclusion in a combination strategy include radiation therapy, trans-arterial chemoembolization, and ablation.

Key words: Hepatocellular carcinoma; Liver neoplasms; Antineoplastic agents; Immunological; Protein kinase inhibitors; Angiogenesis inhibitors

Core tip: Immunotherapy remains a viable option for the systemic treatment of patients

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with unresectable hepatocellular carcinoma, although nivolumab and pembrolizumab failed to meet their endpoints in phase III studies. Combining immunotherapy with other treatment modalities may improve treatment responses. Multiple clinical trials are evaluating the safety and efficacy of these new combination strategies, which involve pairing PD-1 or PD-L1 inhibitors with CTLA-4 inhibitors, or pairing checkpoint inhibitors with alternative agents or non-pharmacologic therapies.

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INTRODUCTION

Worldwide, liver cancer is the fourth leading cause of cancer death and the seventh most common cancer in terms of incidence[1]. The most common liver cancer subtype is hepatocellular carcinoma[1]. Over the last 40 years, hepatocellular carcinoma (HCC) incidence has risen by approximately three-fold in the United States[2]. Between 2000 and 2009, the incidence rose by approximately 4.5% per year and 0.7% per year from 2010 to 2012[3]. Between the years 2018 and 2040, global liver cancer incidence is expected to rise by approximately 62%, while the number of liver cancer deaths worldwide will rise by 64%[2]. If HCC is detected at an early stage (Barcelona Clinic Liver Cancer stage 0 or A), surgical resection or ablation can be performed in select groups of patients[4]. Approximately 70% of patients will develop evidence of recurrence following resection[4,5]. If patients are not candidates for surgical resection, liver transplantation is offered to patients who meet the Milan criteria and provides a possibility of cure[4,5]. Patients who are not eligible for surgery or liver transplantation are candidates for locoregional therapies, including trans-arterial chemoembolization (TACE) and ablation, if they have early- or intermediate-stage disease (Barcelona Clinic Liver Cancer stage 0-B), or systemic therapies if they have advanced disease (Barcelona Clinic Liver Cancer stage C)[4]. Multiple options for systemic therapy exist (Table 1). The tyrosine kinase inhibitors sorafenib and lenvatinib are approved for use as first-line therapy[6]. Ramucirumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF) receptor 2, and the tyrosine kinase inhibitors regorafenib and cabozantinib are approved for patients previously treated with sorafenib, however, candidates for ramucirumab therapy must also have an alpha-fetoprotein (AFP) level of 400 ng/mL or greater[6,7]. With the exception of lenvatinib, which produced an objective response rate (ORR) of 24.1%, the rest of the approved systemic therapies could only achieve an ORR in the range of 2 to 11%[8-12]. Sorafenib, ramucirumab, regorafenib and cabozantinib were directly compared to placebo and increased overall survival by only 1.2 to 2.8 months[8,10-12].

In hopes of discovering therapies that could produce greater responses, investigators began to utilize checkpoint inhibitors in HCC patients, given their success in other malignancies and the contribution of the PD-1/PD-L1 and CTLA4 pathways to creating an immunosuppressive tumor microenvironment[13-15](Table 2). Nivolumab demonstrated an ORR of 15% and 20% in the dose-escalation and dose-expansion phases of the CheckMate 040 trial, respectively, while pembrolizumab produced an ORR of 17% in the KEYNOTE-224 trial[13,14]. Both agents were then Food and Drug Administration (FDA)-approved for use in patients who had previously received sorafenib[16,17]. However, neither nivolumab or pembrolizumab demonstrated a statistically significant improvement in overall survival (OS) in patients with unresectable HCC when compared to sorafenib or placebo in phase III trials, respectively[18,19]. Other checkpoint inhibitors studied in HCC patients in completed phase II trials include the PD-1 inhibitors camrelizumab, the PD-L1 inhibitor durvalumab, and the CTLA4 inhibitor tremelimumab[20-22]. In a phase II multicenter study (NCT02989922) involving 217 patients from Chinese medical centers with HCC who had failed or could not tolerate prior systemic therapy who were treated with camrelizumab, the ORR was 13.8%, with a six-month OS rate of 74.7%[20]. Durvalumab demonstrated an ORR of 10.3% with a median OS of 13.2 months in a multi-center phase I/II study in a cohort of 40 patients with HCC, most of whom had received prior sorafenib[21]. In a phase II study of tremelimumab in 21 patients from Spanish medical

Table 1 List of systemic therapies utilized in combination therapy

Drug class	List of agents	Mechanism of action
PD-1 inhibitors	Nivolumab, Pembrolizumab, Camrelizumab, Tislelizumab	Inhibits PD-1 receptor from binding to PD-L1
PD-L1 inhibitors	Atezolizumab, Durvalumab, Avelumab	Inhibits PD-L1 ligand from binding to PD-1 receptor
CTLA-4 inhibitors	Ipilimumab, Tremelimumab	Inhibits CTLA-4 receptor from binding to CD80 or CD86
OX40 agonists	INCAGN01876, INCAGN01949	Activates OX40 receptor *via* direct binding
Multiple tyrosine kinase inhibitors	Sorafenib, Cabozantinib, Lenvatinib, Regorafenib, Apatinib	Inhibits signaling from multiple tyrosine kinases
VEGF or VEGFR inhibitors	Ramucirumab, Bevacizumab	Inhibits VEGF interaction with VEGFR
Phosphaplatins	PT-112	Activates tumor cell apoptosis, inhibits angiogenesis

VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor.

centers with advanced HCC and chronic hepatitis C virus (HCV) infection, the ORR was 17.6% with a median OS of 8.2 months[22]. Tremelimumab caused a decrease in AFP levels of more than 50% in slightly more than one-third of all patients, and a reduction in HCV viral load in most patients[22].

The relatively modest benefits of currently-available systemic therapies for patients with advanced or unresectable HCC underscore the need for novel and improved therapies. Although nivolumab and pembrolizumab did not reach their endpoints in phase III trials, checkpoint inhibitors in general remain the focus of multiple active trials[18,19] (Tables 3-6). Updated results from the KEYNOTE-224 trial demonstrated that median OS was much greater in patients who responded to pembrolizumab compared to non-responders at the time of the first post-treatment scan, and that 30.8% of patients were alive at a median follow-up of 31.2 months[23]. These results suggest that patients who respond to checkpoint inhibitors may have a durable response. Combination therapies involving the use of both a checkpoint inhibitor and another therapy may provide a greater benefit than single-agent immunotherapy if they can substantially improve overall response rates. This review will outline the main types of combination therapies currently under investigation, discuss the rationale behind their design, and summarize the main clinical trials evaluating their safety and efficacy in HCC patients.

COMBINATION THERAPY WITH PD-1/PD-L1 INHIBITORS PLUS CTLA-4 INHIBITORS

The combination of nivolumab plus ipilimumab has proven successful in improving treatment responses in multiple malignancies when compared to standard-of-care therapy[24-27]. As a first line regimen, the combination of nivolumab and ipilimumab has demonstrated superior ORR, OS, and progression-free survival (PFS) when compared to either agent alone in patients with metastatic melanoma, even after 48 months of median follow-up[24,28]. Given what is known regarding the immune microenvironment of HCC, these results raised the question about whether or not the combination of a PD-1 inhibitor and CTLA-4 inhibitor can demonstrate durable clinical responses in advanced HCC patients that are superior to those seen with single-agent checkpoint inhibitors or targeted therapies in HCC patients.

Nivolumab plus ipilimumab

The CheckMate 040 study (NCT01658878) randomized 148 HCC patients who were previously treated with sorafenib to three separate arms comparing various treatment regimens utilizing ipilimumab and nivolumab[29,30]. Patients in Arm A received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every three weeks for four doses followed by nivolumab 240 mg every two weeks, patients in Arm B received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every three weeks for four doses followed by nivolumab 240 mg every two weeks, and patients in Arm C received nivolumab 3 mg/kg every two weeks plus ipilimumab 1 mg/kg given every six weeks[29]. Initial results indicated that 37% of patients developed grade 3 or 4 toxicity, with rash and pruritus being the most frequently reported adverse effect[29]. The ORR

Table 2 Reported results of successful clinical trials evaluating immunotherapy in hepatocellular carcinoma patients

Therapy	Comparator	Therapy indication	Phase	Approximate data collection period	Patients enrolled	Primary endpoints	Trial identifier
Nivolumab	None	Not specified	I/II	November 26, 2012-August 8, 2016	214 (dose-escalation), 48 (dose-expansion)	ORR (dose-escalation phase - 15%), (dose-expansion phase – 20%)	NCT01658878 (CheckMate 040)
Pembrolizumab	None	Second-line	II	June 22, 2016- February 20, 2017	104	ORR – 18.3%, median OS 13.2 mo	NCT02702414 (KEYNOTE-224)
Camrelizumab	Camrelizumab (regimen 1) *vs* camrelizumab (regimen 2)	Second-line	II	November 15, 2016–November 16, 2017	220	ORR 13.8%, median OS not reached	NCT02989922
Durvalumab	None	Not specified	I/II	August 29, 2012-October 24, 2016	40	ORR – 10.3%, median OS 13.2 mo	NCT01693562
Tremelimumab	None	Not specified	II	December 2008-May 2012	21	ORR - 17.6%, DCR 76.4%	NCT01008358
Pembrolizumab	Placebo	Second-line	III	May 31, 2016-November 23, 2017	413	Median OS 13.9 *vs* 10.6 months – HR: 0.781; 95%CI: 0.611 to 0.998; P = 0.0238, PFS 3.0 *vs* 2.8 months – HR: 0.718; 95%CI, 0.570 to 0.904; P = 0.0022 (pembrolizumab *vs* placebo)	NCT02702401
Nivolumab plus ipilimumab	Nivolumab plus ipilimumab (regimen 1 *vs* regimen 2 *vs* regimen 3)	Second-line	I/II	Minimum follow-up-28 months at time of data cutoff	148	ORR – (32 - Arm A, 31- Arm B, 31 - Arm C), median DOR (17.5 - Arm A, 22.2 - Arm B, 16.6 - Arm C)	NCT01658878 (CheckMate 040)
Durvalumab plus tremelimumab	None	Second-line	I/II	October 19, 2015-January 10, 2017	40	ORR – 15%	NCT02519348
Atezolizumab plus bevacizumab	Sorafenib	First-line	III	March 15, 2018-November 2019	501	OS HR: 0.58 (95%CI: 0.42- 0.79; P = 0.0006), PFS 6.8 *vs* 4.3 mo, P < 0.0001 (atezolizumab plus bevacizumab *vs* sorafenib)	NCT03434379(IMbrave 150)

ORR: Overall response rate; OS: Overall survival; DCR: Disease control rate; PFS: Progression-free survival; DOR: Duration of response; OS HR: Overall survival hazard rate.

was 31%, and after 24 months of follow-up, the OS rate was 40%[29]. This study was updated at the International Liver Cancer Association Conference in Sep 2019[31]. All 3 arms achieved a similar ORR (Arm A - 32%, Arm B - 31% and Arm C - 31%), while Arm A achieved the longest median OS (22.8 months *vs* 12.5 months for Arm B and 12.7 months for Arm C) and the highest OS rate at 30 months (44%)[31](Table 2). The study remains active[30].

The rather innovative study design allowed investigators to compare the impact of various doses of nivolumab and ipilimumab on treatment response[29-31]. The dosing schedule in Arms A and B was similar, however, the dose of ipilimumab was three times higher in Arm A, and patients in Arm C received ipilimumab less frequently than the other two arms[29]. The higher dose of ipilimumab received by patients in Arm A compared to patients in Arms B or C may have been responsible for the improved median overall survival[29]. Unsurprisingly, Arm A also had the highest number of treatment-related adverse effects, possibly due to the larger doses of ipilimumab the

Table 3 Summary of active clinical trials evaluating checkpoint inhibitor combination therapy

Therapy	Comparator	Therapy indication	Phase	Estimated study duration	Estimated patient enrollment	Primary endpoints	Trial identifier
Nivolumab plus ipilimumab	None	Neoadjuvant	I/II	March 1, 2019-September 1, 2022	32	Delay to surgery, incidence of treatment-related adverse events	NCT03682276 (PRIME-HCC)
Nivolumab plus ipilimumab	Nivolumab *vs* nivolumab plus ipilimumab (regimen 1) *vs* nivolumab plus ipilimumab (regimen 2)	Neoadjuvant	II	September 28, 2017-September 30, 2022	45	Incidence of adverse events	NCT03222076
Nivolumab plus ipilimumab	None	Neoadjuvant	II	June 1, 2018-December 31, 2022	40	Percentage of subjects with tumor shrinkage after therapy	NCT03510871
Nivolumab and ipilimumab plus INCAGN01876 (OX-40 Agonist)	Nivolumab plus INCAGN01876 *vs* ipilimumab plus INCAGN01876	Not specified	I/II	April 13, 2017-October 28, 2021	285	Safety and tolerability, ORR	NCT03126110
Nivolumab plus ipilimumab	Sorafenib or lenvatinib	First-line	III	September 16, 2019 – September 16, 2023	1084	OS	NCT04039607 (CheckMate 9DW)
Durvalumab plus tremelimumab	Durvalumab *vs* tremelimumab *vs* durvalumab plus tremelimumab (regimen 1) *vs* durvalumab plus tremelimumab (regimen 2) *vs* durvalumab plus bevacizumab	Second-line (first-line for patients receiving durvalumab plus bevacizumab)	II	October 19, 2015-January 6, 2021	433	Number patients experiencing adverse events and dose-limiting toxicities	NCT02519348
Durvalumab plus tremelimumab	Durvalumab *vs* durvalumab plus tremelimumab (regimen 1) *vs* durvalumab plus tremelimumab (regimen 2) *vs* sorafenib	First-line	III	October 11, 2017-October 30, 2020	1310	OS	NCT03298451 (HIMALAYA)

HCC: Hepatocellular carcinoma; ORR: Overall response rate; OS: Overall survival.

patients received, highlighting the inherent toxicity of this combination[31]. Twenty-two percent of patients discontinued the combination due to drug-related adverse events, compared to 6% and 2% of patients in Arms B and C, respectively[31]. Based on the results of CheckMate 040, the FDA has granted a priority review for nivolumab plus ipilimumab in the treatment of patients with advanced HCC who progressed on sorafenib as of November 2019[32].

There are multiple active clinical trials in addition to CheckMate 040 evaluating nivolumab plus ipilimumab for various treatment indications in HCC patients (Table 3). These include the phase III CheckMate 9DW clinical trial (NCT04039607) evaluating nivolumab plus ipilimumab as first-line therapy in comparison to sorafenib or lenvatinib in patients with advanced HCC[33]. The primary endpoint is overall survival[33]. If the combination of nivolumab and ipilimumab demonstrates significantly improved OS compared to standard-of-care sorafenib or lenvatinib, it may become the new standard-of-care first-line therapy. However, the increased

Table 4 Summary of active clinical trials evaluating combination therapy of checkpoint inhibitors plus vascular endothelial growth factor/factor receptor inhibitors

Therapy	Comparator	Therapy indication	Phase	Estimated study duration	Estimated patient enrollment	Primary endpoints	Trial identifier
Atezolizumab plus bevacizumab	None	First-line	II	January 1, 2020-June 30, 2022	48	Best overall response rate	NCT04180072
Atezolizumab plus bevacizumab	Sorafenib	First-line	III	March 15, 2018-June 29, 2022	480	OS, PFS	NCT03434379 (IMbrave 150)
Atezolizumab plus bevacizumab	Active surveillance	Adjuvant	III	December 31, 2019-July 12, 2027	662	RFS	NCT04102098 (IMbrave 150)
Durvalumab plus bevacizumab	Durvalumab alone *vs* tremelimumab alone *vs* durvalumab plus tremelimumab (regimen 1 *vs* regimen 2) *vs* durvalumab plus bevacizumab	First-line	II	October 19, 2015-January 6, 2021	433	Number patients experiencing adverse events and dose-limiting toxicities	NCT02519348
Durvalumab plus bevacizumab	Durvalumab plus placebo *vs* placebo alone	Adjuvant	III	April 29, 2019-June 16, 2023	888	RFS	NCT03847428 (EMERALD-2)
Camrelizumab plus apatinib	None	Second-line	II	June 1, 2019 – October 1, 2020	40	ORR	NCT04014101
Camrelizumab plus apatinib	Hepatic arterial infusion of chemotherapy	Adjuvant	II	February 15, 2019-February 28, 2023	200	RFS	NCT03839550
Camrelizumab plus apatinib and hepatic arterial infusion of FOLFOX chemotherapy regimen	None	Not specified	II	April 13, 2020-December 31, 2025	84	ORR	NCT04191889
Camrelizumab plus apatinib	Sorafenib	First-line	III	June 10, 2019-June 2022	510	OS, PFS	NCT03764293

OS: Overall survival; PFS: Progression-free survival; RFS: Recurrence-free survival; ORR: Overall response rate.

toxicity seen with this combination, especially if doses are similar to those used in Arm A of the CheckMate 040 trial, may lead to higher rates of therapy discontinuation[29]. At least three separate studies will evaluate the safety and feasibility of neoadjuvant nivolumab plus ipilimumab administered prior to surgical resection[34-36]. The phase II study (NCT03222076) sponsored by Anderson Cancer Center will randomize 45 patients with resectable HCC to receive adjuvant nivolumab or nivolumab plus ipilimumab prior to resection[34]. If successful, further studies may explore whether neoadjuvant nivolumab plus ipilimumab can decrease the high recurrence rates observed after surgical resection[4,5].

Durvalumab plus tremelimumab

The combination of durvalumab and tremelimumab was studied in a phase I/II trial (NCT02519348) in patients with unresectable HCC[37]. The safety profile was deemed

Table 5 Summary of active clinical trials evaluating combination therapy of checkpoint inhibitors plus tyrosine kinase inhibitors

Therapy	Comparator	Therapy indication	Phase	Estimated study duration	Estimated patient enrollment	Primary endpoints	Trial identifier
Nivolumab plus sorafenib	Nivolumab plus sorafenib (regimen 1 *vs* regimen 2)	First-line	II	April 16, 2018-May 31, 2020	40	MTD, ORR	NCT03439891
Pembrolizumab plus sorafenib	None	First-line	Ib/II	September 13, 2017-September 13, 2021	27	ORR	NCT03211416
Nivolumab plus lenvatinib	None	First-line	II	June 12, 2019-October 2021	50	ORR, safety/tolerability	NCT03841201
Pembrolizumab plus lenvatinib	Placebo plus lenvatinib	First-line	III	December 31, 2018-May 13, 2022	750	PFS, OS	NCT03713593 (LEAP-002)
Nivolumab plus cabozantinib	Nivolumab plus Ipilimumab plus cabozantinib	Not Specified	I/II	September 26, 2012-April 29, 2022	1097	Safety and tolerability	NCT01658878 (CheckMate 040)
Nivolumab plus Ipilimumab plus cabozantinib	Nivolumab plus cabozantinib	Not Specified	I/II	September 26, 2012-April 29, 2022	1097	Safety and tolerability	NCT01658878 (CheckMate 040)
Atezolizumab plus cabozantinib	Sorafenib *vs* cabozantinib	First-line	III	December 10, 2018-December 1, 2021	740	Duration of PFS, duration of OS	NCT03755791 (COSMIC-312)
Nivolumab plus regorafenib	None	Second-line	I/II	March 16 2020-December 2022	60	Rate of adverse events, rate of death	NCT04170556 (GOING)
Nivolumab plus regorafenib	None	First-line	II	May 30, 2020-May 30, 2023	42	Response rate	NCT04310709 (RENOBATE)

MTD: Maximum tolerated dose; ORR: Overall response rate; PFS: Progression-free survival; OS: Overall survival.

tolerable and an ORR of 15% was noted, according to results from the phase I portion of the study[37](Table 2). Common adverse effects included pruritus, fatigue, and elevated transaminases, which are similar to those noted in patients treated with durvalumab in phase II studies[21,37]. The phase II portion of the study seeks to evaluate the safety and feasibility of durvalumab plus tremelimumab as second-line therapy[38] (Table 3). This study will randomize 433 patients into five separate arms, in which patients with advanced HCC will receive either durvalumab or tremelimumab alone, durvalumab plus tremelimumab, or durvalumab plus bevacizumab[38]. Two arms of the study will compare different regimens of durvalumab plus tremelimumab[38]. Additional active studies involving this combination include the phase III HIMALAYA clinical trial (NCT03298451) which will compare durvalumab plus tremelimumab to sorafenib or durvalumab alone as first-line therapy in approximately 1310 advanced HCC patients from multiple countries[39](Table 3). Overall survival is the primary endpoint[39].

It remains to be seen whether the combination of durvalumab plus tremelimumab will have a similar toxicity profile as nivolumab plus ipilimumab. If durvalumab plus tremelimumab can demonstrate a high ORR with a comparatively lower rate of immune-related adverse effects, then it may become a viable alternative for HCC patients who have failed prior systemic therapies and cannot tolerate nivolumab plus ipilimumab due to adverse effects. If the dosing schedule utilized in the phase I/II clinical trial (NCT02519348) is adopted, this may minimize toxicity given the relatively infrequent dosing schedule of every four weeks[37]. Although the most common side-effects seen in patients treated with either combination include liver function test abnormalities and skin ailments such as pruritus or rash, the CheckMate 040 study demonstrated that 22% of patients discontinued therapy with nivolumab and ipilimumab due to treatment-related toxicity, compared to 7.5% of patients receiving durvalumab and tremelimumab in the NCT02519348 trial[31,37]. Given the ability of tremelimumab to reduce HCV viral loads, this combination may be preferred for patients with chronic hepatitis C infections[22].

Table 6 Summary of active clinical trials evaluating combination therapy of checkpoint inhibitors plus ablation, trans-arterial chemoembolization, or radiation

Therapy	Comparator	Therapy indication	Phase	Estimated study duration	Estimated patient enrollment	Primary endpoints	Trial identifier
Pembrolizumab plus RFA or MWA	None	First-line	II	May 9, 2019-September 2022	30	ORR	NCT03753659 (IMMULAB)
Durvalumab plus tremelimumab plus RFA	Durvalumab plus tremelimuumab, durvalumab plus tremelimumab plus TACE, or durvalumab plus tremelimumab plus cryoablation	Second-line	II	July 5, 2016, December 31, 2021	90	PFS	NCT02821754
Nivolumab plus TACE	None	First-line	II	June 14, 2018-September 2022	49	ORR	NCT03572582 (IMMUTACE)
Pembrolizumab plus TACE	None	First-line	I/II	January 28, 2018-December 31, 2020	26	Incidence of adverse events	NCT03397654 (PETAL)
Durvalumab plus tremelimumab plus TACE	Durvalumab plus tremelimuumab, durvalumab plus tremelimumab plus RFA, or durvalumab plus tremelimumab plus cryoablation	Second-line	II	July 5, 2016-December 31, 2021	90	PFS	NCT02821754
Durvalumab plus tremelimumab plus DEB-TACE	Durvalumab plus tremelimumab plus DEB-TACE (regimen 1 *vs* regimen 2)	Not Specified	II	June 12, 2019-November 2020	30	ORR	NCT03638141
Durvalumab plus bevacizumab plus TACE	Durvalumab plus bevacizumab plus TACE (one TACE procedure *vs* possibility of multiple procedures)	Second-line	II	April 27, 2020-December 31, 2022	22	PFS	NCT03937830
Durvalumab and bevacizumab plus TACE	Durvalumab plus placebo plus TACE *vs* placebo plus TACE	Not specified	III	November 30, 2018-November 29, 2023	600	PFS	NCT03778957 (EMERALD-1)
Pembrolizumab plus SBRT	None	Second-line	II	February 15, 2018-April 2, 2022	30	ORR	NCT03316872
Durvalumab plus tremelimumab and radiation	None	Second-line	II	May 14, 2018-October 31, 2025	70	ORR	NCT03482102

RFA: Radiofrequency ablation; MWA: Microwave ablation; ORR: Overall response rate; TACE: Transarterial chemoembolization; PFS: Progression-free survival; DEB-TACE: Drug-eluting bead transarterial chemoembolization; SBRT: Stereotactic body radiotherapy.

COMBINATION THERAPY WITH CHECKPOINT INHIBITORS PLUS OX40 AGONISTS

OX40 is a co-stimulatory receptor that is expressed by CD4 and CD8+ T-cells after antigen stimulation[40]. Treg cells can also express OX40[40]. OX40 agonists, which are monoclonal antibodies that bind OX40, induce T-cell expansion and persistence and may be able to suppress Treg activity[40]. The clinical use of a monoclonal antibody targeting OX40 was deemed safe following a phase I study (NCT01644968) in 30 patients with various malignancies, with the most common adverse effects including fatigue, rash, lymphopenia, fever, and pruritus[41]. Twelve patients in demonstrated a reduction in the size of at least one individual metastasis[41].

A combination strategy utilizing OX-40 agonists in conjunction with checkpoint inhibitors may be a viable option in the treatment of HCC. PD-1/PDL1 or CTLA4 blockade and OX40 agonism administered together may produce a greater activation of the immune system due to the targeting of distinct pathways. The use of an OX-40 monoclonal antibody in conjunction with an anti-PD-1 monoclonal antibody in mice models of ovarian cancer produced responses that were superior than those from either agent alone[42]. A phase I/II clinical trial (NCT03241173) was performed to determine whether this form of combination therapy is safe and effective in patients with solid malignancies including HCC[43]. The study contained three separate arms, including two arms where nivolumab or ipilimumab alone were given with the OX-40 inhibitor INCAGN01949, and another arm where both checkpoint inhibitors and INCAGN01949 were administered together[43]. Results are pending[43]. An additional

phase I/II trial sponsored by Incyte Biosciences (NCT03126110) is active and is similarly designed to the first trial, but is employing the OX40 agonist INCAGN01876 in patients with solid malignancies, including HCC[43,44](Table 3).

COMBINATION THERAPY WITH CHECKPOINT INHIBITORS PLUS VASCULAR ENDOTHELIAL GROWTH FACTOR OR VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR INHIBITORS

Anti-angiogenic agents have been a focus of research in HCC due to the relatively high vascularity of HCC tumors, however, studies suggest they may also have beneficial effects on the immune system[45-47]. VEGF expression can modulate the immune system *via* various mechanisms, leading to immunosuppression[46,47]. VEGF molecules can inhibit leukocyte adherence to the endothelium, inhibit the development of dendritic cells, and promote Treg proliferation[46,47]. The combination of checkpoint inhibitors and VEGF or vascular endothelial growth factor receptor (VEGFR) inhibitors may cause a greater net activation of the immune system than checkpoint inhibitors alone due to the added effect of VEGF inhibition.

Atezolizumab plus bevacizumab

Bevacizumab, a VEGF inhibitor, is currently approved for the treatment of multiple malignancies, including metastatic colorectal cancer, non-squamous non-small cell lung cancer, and ovarian cancer[48]. Bevacizumab was studied in a phase II trial in 46 patients with unresectable HCC and treatment resulted in a median PFS of 6.9 months and an OS rate of 53% at 1 year, 28% at 2 years, and 23% at 3 years[49]. However, 11% of patients developed clinically significant bleeding, including one patient who suffered a variceal bleed that was ultimately fatal[49]. Another phase II study evaluating single-agent bevacizumab in advanced HCC patients found that 9% of patients developed gastrointestinal bleeding[45]. Atezolizumab is a humanized monoclonal antibody that targets PD-L1 and prevents its binding to the PD-1 receptor and the B7.1 molecule[50]. It has been approved either as a single agent or in combination with chemotherapy for the treatment of patients with non-small cell lung cancer, small-cell lung cancer, urothelial carcinoma, and breast cancer[51]. The combination of atezolizumab plus bevacizumab demonstrated prolonged progression-free survival in metastatic renal cell carcinoma patients in a phase III trial with an acceptable safety profile[52].

Initial data testing this combination in HCC patients originates from a phase Ib study (NCT02645531) evaluating this combination as first-line therapy in 26 patients with advanced HCC[53]. Approximately 35% of patients developed grade 3-4 toxicities with hypertension being the most frequently reported adverse event, with an ORR of 62%[53]. In late 2019, the study authors reported that patients who received the combination therapy in Arm F demonstrated significantly better median progression-free survival (5.6 *vs* 3.4 months, $P = 0.0108$) when compared to atezolizumab alone[54]. The most common side effects seen in the patients randomized to combination therapy included proteinuria, fatigue and rash[55]. Patients in Arm A had a median overall survival of 17.1 months[55]. Initial phase III data has been reported from the IMBRAVE 150 trial that randomized approximately 501 systemic treatment-naïve patients with unresectable HCC to receive atezolizumab plus bevacizumab or sorafenib alone[56]. Preliminary data published in November 2019 demonstrated an improved PFS (6.8 *vs* 4.3) and OS hazard ratio (0.58) with the combination *vs* sorafenib alone[56](Table 2). Recent quality-of-life data from IMbrave150 presented in January 2020 revealed that patients taking atezolizumab plus bevacizumab had delayed time to deterioration of quality-of-life[57]. Patients in the combination arm reported greater time to deterioration of physical functioning, diarrhea, loss of appetite, fatigue, and pain[57](Table 4).

These data suggest that atezolizumab plus bevacizumab may become an alternative regimen for patients with advanced HCC due to its relatively acceptable toxicity profile when compared to a dual checkpoint inhibitor regimen, and improved efficacy when compared to sorafenib alone. The study remains active[58].

Other active clinical trials evaluating this combination include the NCT04102098 phase III trial, a part of the IMbrave 150 study, which will randomize 662 patients with resectable HCC and a high risk of recurrence to receive atezolizumab plus bevacizumab or surveillance as adjuvant therapy[59](Table 4). Given the significant improvement in PFS seen when this combination is used as first-line therapy, it may also be successful as adjuvant therapy and reduce the high recurrence rates often seen post-resection[4-5,56,59]. A single-arm phase II trial (NCT04180072) will enroll 48 patients

with advanced HCC and chronic HBV infection, allowing the investigators to determine whether HBV infection has any significant effect on the safety and effectiveness of atezolizumab plus bevacizumab[60](Table 4).

Durvalumab plus bevacizumab

The results of the studies testing atezolizumab and bevacizumab may be generalizable to other checkpoint inhibitors, such as durvalumab, if used in combination with bevacizumab or other VEGF inhibitors given similar mechanisms of action. The combination of durvalumab plus bevacizumab is being studied in multiple different trials, including the aforementioned phase II study (NCT02519348) in patients with advanced HCC as first-line therapy[38](Table 3). The phase III EMERALD-2 trial (NCT03847428) will compare durvalumab plus bevacizumab to either durvalumab alone or placebo as adjuvant therapy after either ablation or resection in HCC patients with a high risk of recurrence[61](Table 4).

Durvalumab plus ramucirumab

A phase I trial (NCT02572687) is evaluating the safety of the combination of ramucirumab and durvalumab in patients with advanced gastrointestinal or thoracic malignancies including hepatocellular carcinoma[62]. Although no reported phase II or III trials are currently active, if this combination proves to be safe with a tolerable side-effect profile, further study is warranted based on the results of the REACH-2 trial to determine if this combination is most effective in patients with an AFP greater than 400[10].

Camrelizumab plus apatinib

Apatinib is a tyrosine kinase inhibitor of VEGFR2 that binds to its target with ten-fold more affinity than sorafenib, and is currently approved in China for use in advanced gastric cancer patients[63,64]. Apatinib has demonstrated a tolerable safety profile with evidence of anti-tumor activity in HCC patients as single-agent therapy[64]. In a murine model of lung cancer, the combination of apatinib and an anti-PD-L1 monoclonal antibody inhibited tumor growth in a synergistic fashion with a notable increase in tumor-infiltrating lymphocytes[65]. The combination of apatinib and camrelizumab was studied in a phase Ia and Ib trial (NCT02942329) that enrolled 43 Chinese patients with various gastrointestinal malignancies, including gastric cancer, esophagogastric junction cancer, and advanced hepatocellular carcinoma[63]. This combination was thought to have a tolerable safety profile, with the most common side-effects being hypertension and an elevated AST[63]. Half of all HCC patients demonstrated a partial response, a response similar in magnitude to results from the initial Phase 1b trial (NCT02715531) testing first-line atezolizumab and bevacizumab[53,63]. Multiple studies are evaluating this combination in distinct HCC patient populations[66-69](Table 4). A phase II study (NCT04014101) seeks to determine whether camrelizumab plus apatinib is safe and effective in patients with advanced HCC as second-line therapy[66]. Another phase II study (NCT03839550) will determine whether this combination is superior to hepatic arterial infusion of chemotherapy in the adjuvant setting, with recurrence-free survival as the primary endpoint[67]. The phase II TRIPLET study (NCT04191889) will evaluate the safety and efficacy of the combination of FOLFOX chemotherapy infused directly into an artery perfusing the tumors, followed by camrelizumab and apatinib in 84 patients with advanced HCC[68]. A phase III study (NCT03764293) evaluating camrelizumab and apatinib as first-line therapy in advanced HCC patients will report both OS and PFS as primary endpoints[69]. The aforementioned studies are primarily being carried out in Chinese medical centers, which will limit the external validity of the results and require additional studies before their findings can be generalized to other patient populations[66-69].

COMBINATION THERAPY WITH CHECKPOINT INHIBITORS PLUS MULTI-TARGETED TYROSINE KINASE INHIBITORS

Sorafenib, lenvatinib, cabozantinib, and regorafenib all have activity against VEGF receptors and may mitigate the immunosuppressive activity of VEGF[6]. Although the exact mechanisms of action are unclear, TKIs can modulate the immune system[70-72]. Sorafenib decreased the populations of Tregs and CD8+ T cells that expressed PD-1 in the tumors of mice models of HCC[70]. An *in-vitro* study demonstrated that sorafenib could increase effector-T cell activation and inhibit Treg suppression of effector-T cells,

albeit at sub-pharmacologic doses[71]. Sorafenib has also been shown to restore the ability of dendritic cells to activate T cells *in vitro*[72]. In mouse models of HCC, lenvatinib demonstrated greater antitumor activity in immunocompetent mice when compared to sorafenib but not in immunodeficient mice, suggesting that the increase in activity may be related to immunomodulatory effects[73].

Given that the mechanism of action of TKIs differs from that of checkpoint inhibitors, pairing a TKI with a checkpoint inhibitor may produce responses that are either additive or synergistic. Additionally, responses to combination therapy with checkpoint inhibitors and TKIs may be more effective than responses to VEGF or VEGFR inhibitors alone because TKIs inhibit multiple distinct signaling pathways. If these combination therapies are proven effective, their safety may be of concern. Common toxicities observed with the various TKIs include diarrhea, skin rashes, fatigue, nausea, elevated aspartate aminotransferase levels, and rash[8,9,11,12]. The side-effect profiles of checkpoint inhibitors partially overlap with those of the TKIs, and it is unclear whether this may lead to greater toxicity when compared to single-agent regimens[13,14,24,31].

Sorafenib plus checkpoint inhibitors

The safety and effectiveness of sorafenib plus pembrolizumab as first-line therapy will be evaluated in 27 patients with advanced or metastatic HCC participating in a phase Ib/II study (NCT03211416) by the Roswell Park Cancer Institute[74](Table 5). One phase II trial (NCT03439891) will study the combination of nivolumab plus sorafenib as first-line therapy in patients with advanced HCC[75](Table 5). ORR is one of the primary endpoints for both studies[74,75].

Cabozantinib plus checkpoint inhibitors

Studies testing treatment regimens involving cabozantinib plus immunotherapy include the aforementioned CheckMate 040 study (NCT01658878), which contains two separate arms in which patients are receiving nivolumab plus cabozantinib and nivolumab and ipilimumab plus cabozantinib[30](Table 2). Initial data from this portion of the CheckMate 040 study has been reported[76]. Seventy-one patients with advanced HCC who were sorafenib-naïve or who had previously been treated with sorafenib were randomized to receive nivolumab plus cabozantinib or nivolumab plus ipilimumab and cabozantinib[76]. The ORR was 26% *vs* 17% for those who received all three drugs or nivolumab plus cabozantinib, respectively[76](Table 2). Median PFS was 6.8 for the three-drug regimen arm and 5.5 for the two-drug regimen arm[76](Table 2). The three-drug regimen caused significantly more toxicity, with 71% of patients in that arm reporting grade 3-4 adverse effects, *vs* 42% of patients in the two-drug arm[76]. Approximately 20% of patients in the three-drug arm discontinued the drug secondary to toxicity, compared with 3% of the patients in the two-drug arm[76]. Although the three-drug regimen demonstrates promise based on these early results, its high rate of toxicity may prohibit widespread adoption as standard-of-care therapy. Other checkpoint inhibitors, such as atezolizumab, are being studied as part of combination regimens involving cabozantinib[76](Table 5). The phase III COSMIC-312 trial (NCT03755791) will study the combination of cabozantinib and atezolizumab *vs* sorafenib as first-line therapy in a multi-national group of patients with advanced HCC[77](Table 5).

Lenvatinib plus checkpoint inhibitors

A phase 1b trial (NCT03006926) in which 18 patients were given a combination of lenvatinib and pembrolizumab demonstrated an acceptable safety profile, with hypertension and poor appetite reported as the most common adverse effects[78]. One phase II study (NCT03841201) will test the combination of lenvatinib and nivolumab in a cohort of patients from a German medical center with ORR and safety and tolerability measures as the primary endpoints[79](Table 5). A phase III study (NCT03713593) sponsored by Merck will test the combination of lenvatinib plus pembrolizumab in an international cohort of approximately 750 patients with advanced HCC with PFS and OS as the primary endpoints[80]. Patients will be randomized to receive either lenvatinib plus pembrolizumab or lenvatinib plus placebo[80](Table 5).

Regorafenib plus checkpoint inhibitors

Multiple studies evaluating regorafenib in conjunction with PD-1 inhibitors are active. They include a phase Ib trial sponsored by Bayer[81] that will elucidate the safety profile of regorafenib plus pembrolizumab. Recent results were presented at the American

Society of Clinical Oncology Gastrointestinal Cancers Symposium in January 2020[82]. Thirty-five patients had been treated, with 29 in the dose-defining cohort and 6 in the dose-expansion cohort[82]. Fifteen patients had discontinued treatment, with either clinical or radiologic disease progression as the most common reason[82]. Eighty-nine percent of patients experienced grade 3 or 4 treatment-emergent adverse events[82]. The multi-center phase II (GOING) trial (NCT04170556) and the single-center phase II (RENOBATE) trial from South Korea will evaluate the combination of regorafenib and nivolumab as second-line and first-line therapy, respectively[83,84](Table 5).

COMBINATION THERAPY WITH CHECKPOINT INHIBITORS PLUS LOCOREGIONAL THERAPIES

Locoregional therapies can activate the immune system through various mechanisms[85-87].

Treatment with either radiofrequency ablation (RFA) or TACE can stimulate the expansion of T-cells recognizing tumor-associated antigens, while RFA can lead to natural killer cell activation[85-87]. The ability of locoregional therapies to stimulate the immune system makes them potential candidates for an effective combination strategy with checkpoint inhibitors[85-87]. The side-effect profiles of immunotherapy and these locoregional therapies differ significantly, which may lead to relatively low toxicity compared to other combination regimens previously discussed[14,15,31,88,89].

Checkpoint inhibitors plus ablation

Patients who will likely be eligible for combination therapies involving ablation will have tumors 3 cm or less with early-stage, BCLC class 0 or A disease who are not candidates for surgical resection[4,5]. Although multiple types of ablation exist, RFA is the usual standard of care and adverse events may include intraperitoneal bleeding, intrahepatic abscess, grounding pad burns, bile duct injury, thermal damage to organs in close proximity to the tumor, pneumothorax, pain, and tumor seeding of tissues[4,88]. RFA is not optimal for tumors that are larger than 5 cm, numerous with 3 or more lesions, poorly visible *via* ultrasound, or adjacent to structures such as the biliary tree, bowel, and vital organs such as the heart[4,5,90].

Multiple studies evaluating combinations of radiofrequency ablation and immunotherapy are ongoing[91-93](Table 6). Patients with unresectable HCC underwent treatment with tremelimumab and radiofrequency ablation or chemoablation in a phase I study in which 32 patients were enrolled[91]. A partial response was noted in 5 out of 19 patients, and 12 out of 14 patients with confirmed HCV infection were noted to have a decrease in their viral load, consistent with prior studies involving tremelimumab[22,91]. The phase II clinical trial (NCT02821754) sponsored by the National Cancer Institute (NCI) includes an arm where patients with advanced HCC will receive durvalumab plus tremelimumab and RFA, and another where patients will receive cryoablation in conjunction with the checkpoint inhibitors as second-line therapy[92]. Progression-free survival is the primary outcome[92]. Studies involving pembrolizumab include the IMMULAB phase II study (NCT03753659), which will test the combination of RFA or microwave ablation plus pembrolizumab in 30 patients who had not received prior systemic therapy and report ORR as the primary outcome[93].

Checkpoint inhibitors plus TACE

TACE plus immunotherapy may be appropriate for patients with intermediate-stage disease, including those with BCLC class B disease based on current indications for TACE[4]. Some patients who are ineligible for RFA, such as those with larger tumors, multiple lesions, or smaller tumors which cannot be safely ablated may be candidates for TACE[4]. Potential adverse events of TACE therapy include damage to the hepatic artery, bile duct injury, acute liver failure, variceal bleeding, and cholecystitis[89,94]. Specific protocols for performing TACE may differ, and the types of chemotherapy, embolic agents, and schedule of TACE sessions may vary between institutions, among other factors[89]. This variation in how TACE is performed may lead to variation in side-effect profiles, and could affect the efficacy of combination therapies when compared across medical centers[89].

Multiple studies testing the safety of treatment combinations involving checkpoint inhibitors and TACE are active[95-99](Table 6). The phase II, single-arm IMMUTACE study from Germany (NCT03572582) will study the effectiveness and safety of

nivolumab plus TACE for patients with intermediate-stage HCC who have not received prior systemic therapy or TACE, with ORR as the primary endpoint[95]. The combination of TACE and pembrolizumab will be studied as first-line therapy in the phase I/II, single-arm PETAL trial (NCT03397654), which will report the incidence of adverse effects as the primary outcome measure[96]. A phase II clinical trial (NCT03638141) will evaluate the combination of durvalumab plus tremelimumab and drug-eluting bead TACE (deb-TACE) in approximately 90 patients with advanced HCC[97]. Patients with active HCV infection will be excluded, which may hinder the ability to detect any effects of the combination therapy on HCV viral load possibly due to tremelimumab[22,97]. The previously mentioned NCT02821754 phase II trial sponsored by the NCI contains an arm in which patients will receive durvalumab plus tremelimumab and TACE[92]. The combination of durvalumab plus bevacizumab and TACE will be evaluated as second-line therapy in a phase II trial (NCT03937830) sponsored by the NCI in 22 patients with advanced HCC[98]. The combination of durvalumab, bevacizumab and TACE will be compared to TACE alone or TACE plus durvalumab in the phase III, multi-center EMERALD-1 clinical trial (NCT03778957) which will report PFS as a primary outcome measure[99]. Secondary outcome measures include overall survival[99].

COMBINATION THERAPY WITH CHECKPOINT INHIBITORS PLUS RADIATION

The effect of checkpoint inhibitors on T-cells can be amplified by radiation[100]. Radiation therapy (RT) has been shown to induce antitumor immune responses through the formation of antitumor antibodies[100]. RT directed at one tumor site can induce responses in other tumor sites not directly targeted, a phenomenon known as the abscopal effect, which is related to immune system activation[100,102,103]. In mouse models of melanoma, radiation therapy can increase both antigen presentation to T-cells recognizing tumor antigens and infiltration of tumors by those T-cells[101]. RT can increase the expression of MHC-1 (major histocompatibility complex-1) molecules in tumors and increase T-cell and natural killer cell tumor infiltration[102,103]. Stereotactic body radiotherapy (SBRT) can be used to treat early-stage, BCLC A disease that is not amenable to treatment with RFA, and can achieve local control rates of approximately 80% or greater[90]. SBRT is a possible alternative treatment option after TACE has been unsuccessful, with local control rates of approximately 87%-99% in multiple studies[90]. Adverse events as a result of SBRT may include upper gastrointestinal bleeding from esophageal varices or gastric and duodenal ulcers, and biliary strictures[104]. SBRT generally has a more tolerable side-effect profile when compared to TACE, with rates of grade 3 or higher toxicity estimated at 6% to 27% in patients with unresectable HCC who receive SBRT[90,104]. If proven safe, SBRT plus immunotherapy could become a reasonable treatment option for HCC patients who are not candidates for RFA or who have failed TACE.

Multiple studies testing the combination of ionizing radiation and immunotherapy are ongoing in patients with unresectable HCC[105-107](Table 6). One phase I study (NCT03203304) will enroll 50 participants with advanced HCC who will first receive SBRT[105]. Patients will be randomized into two arms, one of which will receive nivolumab alone after SBRT, while the second will receive nivolumab and ipilimumab[105]. If the results from this study suggest that administering nivolumab plus ipilimumab after SBRT is safe, better responses may be seen with that combination than with nivolumab alone given after SBRT due to the synergistic effects of nivolumab plus ipilimumab[24,28,105]. A phase II study (NCT03482102) sponsored by Massachusetts General Hospital will evaluate the safety and efficacy of durvalumab and tremelimumab administered in combination with radiation as second-line therapy[106]. As with prior studies examining durvalumab plus tremelimumab, a central question of the NCT03482102 study is whether this combination will be less toxic than those utilizing nivolumab plus ipilimumab in addition to SBRT, and whether tremelimumab will lower the viral load in patients infected with HCV[22,31,106]. Another phase II study will report the overall response rate after enrolling approximately 30 patients, and treating them with pembrolizumab and SBRT in the second-line setting[107]. Both radiation dosing and the time intervals between radiation treatment and immunotherapy treatment may affect the efficacy of combination therapies, and should be considered when the results of these various studies are available[108].

FUTURE DIRECTIONS

PD-1 and PT-112 inhibitors

PT-112 is a platinum-based drug of the phosphaplatin class currently under development by Phosphaplatin Therapeutics with reported anti-tumor effects both *in-vivo* and *in-vitro*[109-111]. It promotes apoptosis in tumor cells and may have anti-angiogenic effects[110]. An *in-vitro* study demonstrated that PT-112 treatment led to increased phosphorylation of a wide variety of targets, including VGFR1, EGFR, and CDC2, suggesting it may have activity against multiple distinct pathways[111]. Tumor cells may not be able to evade the drug's antitumor effects through traditional drug resistance pathways because it binds to transmembrane proteins rather than DNA[110,112]. An *in-vitro* study in ovarian cancer cells demonstrated that cisplatin enters cells more readily than phosphaplatins, and may suggest that phosphaplatin treatment may produce fewer side-effects when compared to cisplatin therapy due to reduced intracellular accumulation[113]. A phase I clinical trial involving 62 patients receiving PT-112 (NCT2266745) demonstrated no maximum tolerated dose, with fatigue as the most frequently-reported adverse event[114]. A patient with small cell lung cancer who progressed after prior treatment with both a CTLA-4 inhibitor and PD-1 inhibitor was progression-free at 7.5 months, while a patient with non-small cell lung cancer who progressed on a PD-1 inhibitor was progression-free at 6 months, indicating the potential benefit of PT-112 therapy[114]. The ORR was approximately 10.7%[114]. A phase I/II trial testing PT-112 in patients with advanced solid tumors, including patients with advanced HCC, remains active[115]. The safety and efficacy of combining PD-1 therapy and PT-112 is being explored in a multi-center, non-randomized, phase I/II trial (NCT03409458) by Phosphaplatin Therapeutics that will administer PT-112 in combination with avelumab in patients with solid tumors, not including HCC[116]. If combination therapy involving PT-112 and immunotherapy is safe and effective, the natural properties of phosphaplatins may prevent drug resistance, leading to more durable responses. If these regimens are truly less toxic than other combination regimens due to low levels of intracellular accumulation of phosphaplatins, PT-112-based combination therapy may become an alternative option for HCC patients who cannot tolerate other regimens due to adverse effects if it is proven safe[113].

CONCLUSION

Although immunotherapy remains a promising strategy for HCC patients with unresectable disease, checkpoint inhibitors used as single-agent therapy produce relatively modest overall response rates without significant improvements in survival[18,19]. As we have outlined in this review, a combination treatment strategy pairing checkpoint inhibitors with additional pharmacologic agents, locoregional therapy or radiation therapy may produce greater responses than single-agent immunotherapy. Multiple active clinical trials are underway to determine which combination strategies can safely produce durable clinical responses, ideally with significant improvements in overall survival and overall response rates.

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