Immuno-oncology for Hepatocellular Carcinoma

The Present and the Future

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KEYWORDS

• Hepatocellular carcinoma • Immunotherapy • Checkpoint inhibitor

KEY POINTS

- Systemic immunotherapy is expanding and changing the landscape of treatment for advanced-stage hepatocellular carcinoma.
- Frontline combination immunotherapy using synergistic mechanisms is proving to extend patient lives by bringing about increased and prolonged antitumor response.
- The role of immunotherapy in the setting of liver transplant remains uncertain; resolution of the potential lack of response and risk of adverse events leading to graft failure requires further investigation.

INTRODUCTION

Hepatocellular carcinoma (HCC), which arises from a background of chronic liver disease, is a highly lethal malignancy, with 42,810 new diagnoses and 30,160 cancer-related deaths estimated in the United States during 2020.[1] Worldwide, HCC is the fifth most common cancer and the third most common cause of cancer death.[2] Risk factors predisposing patients to HCC include hepatitis B virus (HBV), hepatitis C virus (HCV), hereditary hemochromatosis, and alcoholic as well as nonalcoholic cirrhosis.[3] Through research, we now have a better understanding of the molecular mechanisms of HCC, but there is still a paucity of therapeutic options, and local surgical resection still poses a significant risk of recurrence owing to underlying cirrhosis.[4] Liver transplantation has the lowest recurrence rates of 10% to 20%, but only in patients with early stage HCC.[5]

Sorafenib, an oral tyrosine kinase inhibitor (TKI), was the first systemic therapy for advanced HCC approved by the US Food and Drug Administration (FDA). Sorafenib was found to prolong median overall survival by approximately 3 months.[6,7] Sorafenib

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remained the only FDA approved systemic therapy for 10 years until regorafenib and nivolumab were approved in 2017, closely followed by pembrolizumab in 2018 and cabozantinib and ramucirumab in 2019, for patients previously treated with sorafenib. In 2018, a sorafenib competitor, lenvatinib, was approved for first-line treatment of patients with HCC. By the end of 2019, 7 systemic therapeutic agents were available for the treatment of patients with HCC, but there are limited data on how to sequence these treatments for maximum survival benefit to patients. Five of the 7 approved treatments—namely, sorafenib, regorafenib, lenvatinib, cabozantinib, and ramucirumab—were shown to prolong patient survival by targeting tumor angiogenesis and signaling pathways for tumor proliferation. Nivolumab and pembrolizumab are immune checkpoint inhibitors that overcome tumor immune evasion. The novel mechanism of action of immune checkpoint inhibitors and their durable response has reshaped the treatment landscape for HCC.

IMMUNOTHERAPY RATIONALE

HCC is a potentially highly immune-responsive tumor, given its origins from an inflammatory background, making immunotherapy more likely to be effective. There have been cases of spontaneous remission of HCC after removal of patients from therapy, indicating a delayed antitumor immune response, occurring only after removal of immunosuppression.[8–10] A strong relationship between HCC and the patient's immune system is seen for cases that have a high tumor proinflammatory T-cell infiltrate, a high tumor CD4:CD8 ratio, a decreased risk of recurrence, and improved disease-free survival and overall survival.[11–14]

The liver has a natural immune tolerance—through upregulation of cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death protein-1 (PD-1)—to avoid unnecessary inflammation from antigens in the portal venous system. This may lead to impaired antitumor response in HCC. Superior disease-free survival and overall survival are seen in HCC tumors with lower levels of PD-1 and programmed death-ligand 1 and 2 (PD-L1 and PD-L2)[15,16]; hence, immune checkpoint blockade is hypothesized to overcome immune tolerance in the liver leading to a robust antitumor response where other treatments have failed.

Immune Checkpoint Inhibitor Monotherapy in Hepatocellular Carcinoma

Durable response to anti–programmed cell death protein-1 therapy

An early signal of the antitumor activity of immune checkpoint inhibitors in HCC was demonstrated in a phase II study of tremelimumab in patients with advanced disease.[17] Tremelimumab is a monoclonal antibody that binds to CTLA-4 expressed on the surface of activated T lymphocytes, resulting in inhibition of B7-CTLA-4–mediated downregulation of T-cell activation. Study investigators evaluated 21 patients treated with 15 mg/kg intravenous (IV) tremelimumab every 90 days for about 2 cycles. Tumor burden was decreased in 2 patients, and disease stabilization was observed in 11 patients, which lasted for more than 1 year. Concerns about liver toxicity and/or reactivation of viral hepatitis led to additional testing of immune checkpoint inhibitors in patients with HCC; however, the anti–PD-1 agent nivolumab was used for this testing owing to its better safety profile. The BMS-initiated dose escalation and expansion trial (CheckMate 040) tested nivolumab in adults ($\geq$18 years) with histologically confirmed advanced HCC with or without HCV or HBV infection (NCT01658878). Patients received IV nivolumab at doses of 0.1 to 10 mg/kg every 2 weeks in the dose-escalation phase (3 + 3 design) of this trial. Then, in the dose expansion phase, 3 mg/kg nivolumab was administered every

2 weeks to 4 different patient cohorts: sorafenib untreated or intolerant without viral hepatitis, sorafenib progressors without viral hepatitis, HCV infected, and HBV infected. The primary end points were safety and tolerability and objective response rate (Response Evaluation Criteria In Solid Tumors version 1.1). The objective response rate was 20% (95% confidence interval [CI], 15–26) in patients treated with nivolumab in the dose expansion phase and 15% (95% CI 6–28) in the dose-escalation phase. The median duration of response was 17 months and the median overall survival was 15 months. The adverse events (AEs) were comparable with those experienced in patients with other types of cancer receiving nivolumab treatment.[18–20] Based on data from this trial, the FDA granted accelerated approval of nivolumab for patients with advanced HCC who have progressed or are intolerable to sorafenib treatment, pending confirmation of survival benefit in a randomized phase III study.

The CheckMate 040 study details are outlined in **Fig. 1**.

Negative phase III studies of nivolumab and pembrolizumab

In CheckMate 459, an international, multicenter, randomized phase III trial, 743 treatment-naïve patients with HCC were randomized to standard sorafenib (400 mg twice daily) or nivolumab (240 mg every 2 weeks).[21] Although study results did not meet statistical significance, the overall survival was improved with nivolumab over sorafenib (16.4 months vs 14.7 months; hazard ratio [HR], 0.85; 95% CI, 0.72–1.02; $P = .0752$).[21] The median progression-free survival was similar between the 2 groups, but the response rate for nivolumab was higher than sorafenib at (15% vs 7%).[21]

Investigators in the phase III KEYNOTE-240 trial randomized 408 patients at a 2:1 ratio to pembrolizumab (200 mg IV every 3 weeks) + best supportive care versus placebo (every 3 weeks) + best supportive care for up to 35 cycles or until disease progression or unacceptable toxicity. The objective response rate was 16.9% (95% CI, 12.7%–21.8%) for pembrolizumab versus 2.2% (95% CI, 0.5%–6.4%) for placebo (nominal one-sided $P = .00001$). Pembrolizumab responses were durable (median duration of response, 13.8 months [95% CI, 1.5–23.6+]), and although overall survival and progression-free survival were improved, prespecified statistical criteria were such that significance was not reached (overall survival, 13.6 vs 10.6 months [hazard ratio, 0.78; 1-sided $P = .0238$]; progression-free survival, 4.2 vs 3.8 months [hazard ratio, 0.78; 1-sided $P = .0209$]).[22]

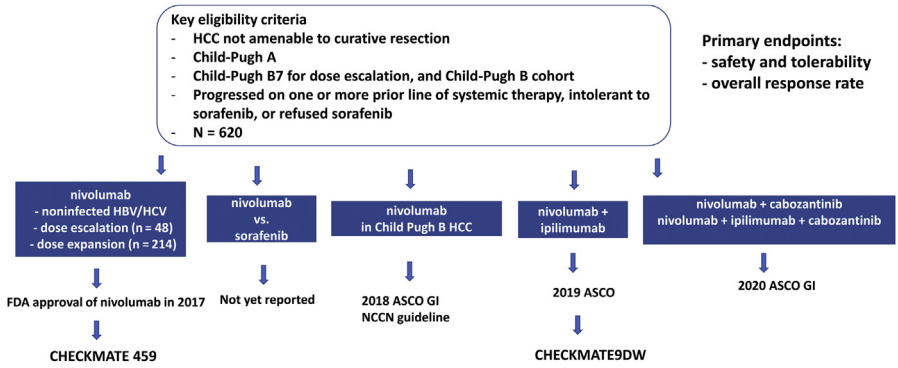

Fig. 1. CHECKMATE 040 phase I/II study of nivolumab in HCC.

Interestingly, the overall survival was higher in the control arms of both of these negative studies compared with the control arms from other earlier studies. Taking the CheckMate 459 study (2019), the median overall survival was 14.7 months in the sorafenib control arm, which is higher than the 10.2 months observed in the original SHARP study (2007).[6] Taking the KEYNOTE-240 trial, the median overall survival for patients receiving best supportive care after first-line sorafenib treatment was higher (10.6 months) than that in the RESOURCE study of second-line regorafenib (7.8 months)—the study that led to the approval of regorafenib in this setting.

Patient demographics (key prognostic parameters) were similar between the CheckMate 459 and SHARP trials. However, the quantity and quality of second-line therapies have changed from supportive care or continuation of sorafenib treatment to an additional TKI as well as immune therapy. In studies, it follows that these second-line treatments may significantly build on overall survival measures from first-line treatments.

Also, considering the KEYNOTE 240 study and its negative findings, the use of dual co-primary study end points of progression-free survival and overall survival, and 2 interim analyses resulted in stricter prespecified *P* values compared with a single primary study end point and fewer interim analyses. Hence, these phase III studies likely still demonstrate meaningful clinical benefit from experimental treatment, even though they do not statistically meet the primary study end points.

Immune Checkpoint Inhibitor Combination Therapy in Hepatocellular Carcinoma

Early promising results from anti–cytotoxic T-lymphocyte-associated protein-4 and anti–programmed cell death protein-1 combined therapy

After it was found that the anti–CTLA-4 and anti–PD-1 therapies acted synergistically and increased response rates in patients with metastatic melanoma, advanced renal cell carcinoma, and metastatic colorectal cancer with deficient mismatch repair/microsatellite instability—high, studies of this type of combination therapy ensued in patients with HCC,[23–25] with the hope of improving on monotherapy results. Two combinations, nivolumab plus ipilimumab and durvalumab plus tremelimumab, were evaluated in HCC with promising results. Ipilimumab is another anti–CTLA-4 antibody and durvalumab is an antibody raised against PD-L1. The safety and efficacy of the durvalumab plus tremelimumab combination compared with either drug alone was evaluated in a phase I/II study.[26] Forty patients with HCC were enrolled (11 HBV positive, 9 HCV positive, 20 uninfected); 30% had no prior systemic therapy and 93% were Child-Pugh class A. The confirmed response rate was 15%. The most common ($\geq$15%) treatment-related AEs were fatigue (20%), increased alanine aminotransferase (18%), pruritus (18%), and increased aspartate aminotransferase (15%). The most common grade 3 or higher related AE was asymptomatic increased aspartate aminotransferase (10%). The combination is being investigated in the phase III HIMALAYA trial (NCT03298451), which is enrolling patients with unresectable, advanced HCC who have not previously received systemic treatment and are ineligible for locoregional therapy. The HIMALAYA trial is comparing sorafenib to durvalumab alone and in combination with tremelimumab (in 2 different combination regimens) with a primary end point of overall survival (NCT03298451).

The Checkmate 040 trial opened a nivolumab plus ipilimumab treatment cohort.[27] Patients with advanced stage HCC (n = 148) who had been treated with sorafenib were randomized to 3 nivolumab and ipilimumab dose and schedule variation arms. The objective response rate was found to be around 30%, with any ipilimumab plus nivolumab regimen—twice that of nivolumab monotherapy at comparable doses.[27] A median overall survival of 23 months was seen in patients who received nivolumab

(1mg/kg) plus ipilumumab (3mg/kg) every 3 weeks for 4 doses followed by nivolumab 240mg every 2 weeks (arm A), with a rate of 61% median overall survival at 12 months and 48% median overall survival at 24 months.[27] The reported treatment-related AEs were consistent with the known safety profiles of the individual components of the combination treatments and were reversible.

The doubled response rate and prolonged median overall survival in patients receiving second-line systemic therapy for advanced HCC supports the FDA approval of the combination of nivolumab and ipilimumab in patients with HCC who have been treated with sorafenib. Moreover, the ongoing, randomized, phase III CheckMate 9DW trial is treating patients with the combination of ipilimumab (1 mg/kg) plus nivolumab (3 mg/kg) every 3 weeks for 4 doses followed by maintenance nivolumab at a straight dose of 480 mg every 4 weeks and comparing the response of these patients with those receiving sorafenib or lenvatinib in the frontline setting. The primary end point is overall survival (NCT04039607) (**Table 1**).

Combinations of immunotherapy and antiangiogenesis inhibitors

Strong scientific rationale and emerging clinical data suggest that the combined vascular endothelial growth factor (VEGF)/PD-L1 blockade may be clinically beneficial in patients with HCC.

Bevacizumab and atezolizumab combination

It is known that HCC is a highly vascularized tumor and that several proangiogenic factors play a role in HCC pathogenesis. For example, in HCC, increased VEGF correlates with vascular density, tumor invasiveness, metastasis, and poor prognosis.[28–30] The VEGF pathway also plays a crucial role in exerting and maintaining an immunosuppressive tumor microenvironment through several mechanisms. The VEGF inhibitor bevacizumab can restore and/or maintain the antigen presentation capacity of dendritic cells, leading to enhanced T-cell infiltration in tumors.[31,32] In addition to increased trafficking of T cells into tumors,[33] several publications have illustrated that anti-VEGF therapies can also decrease the frequency of myeloid-derived suppressor cells, decrease production of suppressive cytokines, and lower expression of inhibitory checkpoints on $CD8^+$ T cells in tumors.[34,35] Therefore, the immunomodulatory effect of bevacizumab is expected to increase CD8-positive T-cell recruitment, and relieve intratumoral immunosuppression, thereby boosting the effects of immune checkpoint inhibitors.

The combination of bevacizumab and atezolizumab, an anti–PD-L1 antibody, was first tested in patients with HCC in a phase I multicenter study GO30140. In this study, systemic treatment-naïve patients with locally advanced or metastatic HCC received 1200 mg of atezolizumab plus 15 mg/kg of bevacizumab every 3 weeks. Investigators found that 23 of the 73 efficacy-evaluable patients (31.5%; 95% CI, 21.1–43.4) achieved confirmed objective responses, and 1 patient (1.4%) achieved a durable complete response. The median progression-free survival was 14.9 months (95% CI, 7.4–NE). No new safety signals related to the combination therapy were identified beyond the established safety profile for each individual agent.[36]

The follow-up phase III, open-label, randomized IMbrave 150 trial is comparing combination atezolizumab (1200 mg IV every 3 weeks) plus bevacizumab (15 mg/kg IV every 3 weeks) to oral sorafenib (400 mg twice a day) in patients with unresectable advanced HCC (NCT03434379). The primary end points include overall survival and progression-free survival, and the trial completed enrollment in December 2018. All primary end points were reportedly met at a median of 8.6 months of follow-up: the median overall survival was 13.2 months in the sorafenib arm but not yet met in the

Table 1
Clinical trials on HCC treatment approved by FDA or pending FDA approval

Trial	Phase	Therapy	Mechanism	Lines of Therapy	Outcome
SHARP NCT00105443	3	Sorafenib	Inhibitor of VEGFR, PDGFR, and RAF kinases	First	Overall survival of 10.7 mo vs overall survival of 7.9 mo for placebo
REFLECT NCT01761266	3	Lenvatinib	Inhibitor of VEGFR1, 2 and 3, fibroblast growth factor 1, 2, 3 and 4, PDGFR alpha, c-Kit, and the RET proto-oncogene	First	Overall survival of 13.6 mo vs overall survival of 12.3 mo for Sorafenib
RESORCE NCT01774344	3	Regorafenib	Inhibitor of VEGFR2-TIE2 tyrosine kinase	Second	Overall survival of 10.6 mo vs overall survival of 7.8 mo for placebo
CELESTIAL NCT01908426	3	Cabozantinib	Inhibitor of c-Met, VEGFR2, AXL, and RET	Second	Overall survival of 10.2 mo vs overall survival of 8.0 mo for placebo
REACH-2 NCT02435433	3	Ramucirumab	Inhibitor of VEGFR2	Second	Overall survival of 8.5 mo vs overall survival of 7.3 mo for placebo
CHECKMATE 040 NCT01658878	1/2	Nivolumab	Immune checkpoint inhibitor	Second	Response rate of 15%, 4% complete response
KEYNOTE 224 NCT02702414	2	Pembrolizumab	Immune checkpoint inhibitor	Second	Response rate of 17%, 1% complete response
CHECKMATE 040 NCT01658878	1/2	Nivolumab + ipilimumab	Immune checkpoint inhibitor	Second	Response rate of 32%, 8% complete response; median overall survival of 23 mo
IMBRAVE 150 NCT03434379	3	Bevacizumab + atezolizumab	Immune checkpoint inhibitor	First	Median overall survival not estimable (NE) compared with 13.2 mo with sorafenib (P = .0006). Median progression-free survival 6.8 mo vs 4.5 mo with sorafenib (P<.0001).

Abbreviations: PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

experimental arm (HR, 0.58; 95% CI, 0.42–0.79; $P = .0006$); the median progression-free survival was 4.5 months versus 6.8 months (HR, 0.59; 95% CI, 0.47–0.76; $P<.0001$).[37] Response rates from the combination therapy were double that of sorafenib (objective response rate, 27% vs 12%; $P<.0001$). There were no new safety signals identified and overall this novel combination has the potential to be practice changing.

Tyrosine kinase inhibitors and immune checkpoint inhibitor combination

Multitargeted TKIs such as lenvatinib can inhibit cancer cell proliferation and modulate the tumor immune environment. There lies a rationale for the combination of lenvatinib with immune checkpoint inhibitors for the management of HCC.

Multi-TKI lenvatinib inhibits VEGF receptors 1, 2, and 3; fibroblast growth factors 1, 2, 3, and 4; platelet-derived growth factor-α; c-Kit; and RET. The REFLECT trial found that in patients with advanced HCC, lenvatinib provides a similar overall survival improvement to sorafenib, leading to FDA approval of lenvatinib in systemic treatment-naïve patients with advanced HCC. The phase I trial of lenvatinib plus pembrolizumab revealed grade 3 or higher treatment-related AEs in 60% of patients, with only 5% requiring discontinuation of therapy, and a preliminary response rate of 42%.[38] The combination of lenvatinib and pembrolizumab is being compared with first-line lenvatinib monotherapy in the double-blind, randomized LEAP002 study. The primary end points are progression-free survival and overall survival (NCT03713593).

Multi-TKI cabozantinib inhibits c-Met, VEGF receptor 2, AXL, and RET, showing prolongation of overall survival in patients with advanced HCC who had received sorafenib or additional systemic therapy in the Celestrial study. The phase III COSMIC-312 trial is now investigating the benefits of cabozantinib with and without atezolizumab compared with sorafenib in patients with advanced untreated HCC (NCT03755791).

The expanding landscape of immunotherapy use in HCC is reviewed in **Fig. 2**.

Triple combination

A CHECKMATE 040 study cohort enrolled 35 patients to receive nivolumab (3 mg/kg every 2 weeks), ipilimumab (1 mg/kg every 6 weeks), and cabozantinib (40 mg daily).[39] Early promising efficacy data are as follows: response rate, 29%; disease control rate, 80%; progression-free survival, 6.8 months; and median duration of response and median overall survival, not yet reached at 19 months follow-up. The rate of treatment-related grade 3 or 4 AEs was 71% and manageable (17% hypertension, 23% increase in aspartate aminotransferase, 17% increase in alanine aminotransferase, and 17% increase in lipase).

Management of adverse event of immune checkpoint inhibitors

Immune checkpoint inhibitors are well-tolerated by patients with HCC. When nivolumab was compared with sorafenib in the randomized phase III study (Keynote 459 study), grade 3 and 4 treatment-related AEs were reported in 81 patients (22%) in the nivolumab arm compared with 179 (49%) in the sorafenib arm.[21] Treatment discontinuation owing to an AE was reported for 16 patients (4%) receiving nivolumab versus 29 (8%) patients receiving sorafenib. Patient-reported findings suggest that those in the nivolumab arm experienced a better quality of life.

Immune-mediated AEs from pembrolizumab therapy were reported at a rate of 18.3%, and the most commonly observed toxicities were hypothyroidism, hyperthyroidism, and pneumonitis.[40] These events were grade 3 or higher in 7.2% of patients, and approximately 90% of these were resolved. Just over 8% of patients received steroids for possible immune-mediated AEs.

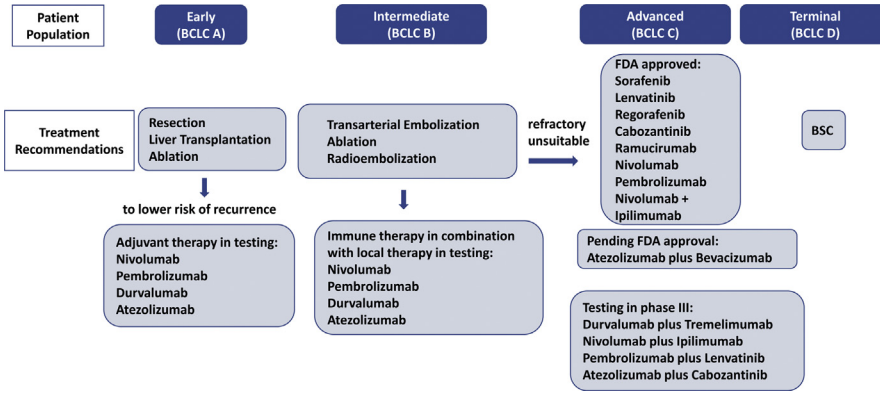

Fig. 2. The expanding landscape of immunotherapy use in patients with HCC.

The improved efficacy observed from the combination of nivolumab and ipilimumab is at the apparent cost of increased toxicity compared with single-agent immune checkpoint inhibitor therapy. As shown in Checkmate 040 study (Nivolumab package inset, Princeton NJ, Bristol Myers Squibb Company, 2020), 59% of patients receiving nivolumab and ipilimumab experienced grade 3 or higher AEs. Of these AEs, the following occurred at a rate of 4% or more: pyrexia, diarrhea, anemia, increased aspartate aminotransferase, adrenal insufficiency, ascites, esophageal variceal hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis. Adverse reactions led to treatment delay in 65% of patients and treatment discontinuation in 29%. A handful of patients (8.2%) received high-dose corticosteroids for a median of 1.6 weeks (range, 0.4–147.6 weeks). Most of the immune-mediated AEs could be resolved, including 80% of pneumonitis, 100% of colitis, 90% of hepatitis, and 82% of rashes. It was concluded that adverse reactions from the combination of nivolumab and ipilimumab are common but manageable. Physicians and other medical staff taking care of patients with HCC receiving immune checkpoint inhibitors need to be vigilant about monitoring for and managing patient AEs in an efficient and timely manner, especially if combination therapy is the chosen treatment.

Expanding on immune checkpoint treatment combinations

Local therapies including radiofrequency ablation, transarterial chemoembolization, transarterial radioembolization, and microwave embolization stimulate tumor destruction, the release of tumor antigens, and ultimately increase the production of tumor-specific T cells.[41,42] The combination of immune checkpoint blockade with these therapies activates CD4 and CD8 T cells and enhances antitumor activity.[43] Emerging clinical trials evaluating the combination of local therapy and immune checkpoint treatment are under way.

IMMUNOTHERAPY USE IN TRANSPLANT CANDIDATES

Adjuvant immunotherapy after resection or ablation is being explored in the Emerald-2 (NCT03847428), CheckMate 9Dx (NCT03383458), and KEYNOTE 937 (NCT03867084) trials, and results are pending.

One issue arising from the unique transplant-eligible population of patients with HCC is the role of immunotherapy before or after liver transplantation and potential complications that may arise. The HCC liver transplant population has been excluded

Table 2
Cases of immunotherapy use after liver transplant

Case	Reason for Liver Transplant	Immuno-Suppression	Immunotherapy	Reason for Immunotherapy	Response of Malignancy to Immunotherapy	Toxicity to Transplant
Morales et al,[45] 2015	Fulminant liver failure, HCV, HCC	Tacrolimus and mycophenolate mofetil	Ipilimumab	Cutaneous melanoma	Partial response	Mild liver enzyme elevation, no evidence of graft rejection
Ranganath et al,[48] 2015	Cirrhosis from alpha-1 antitrypsin deficiency	Tacrolimus	Ipilimumab	Cutaneous melanoma	No response	No AEs or graft rejection
Schvartsman et al,[49] 2017	Biliary atresia	Tacrolimus	Pembrolizumab	Cutaneous melanoma	Complete response	Hepatitis 10 d after second dose requiring steroids and mycophenolate
De Toni et al,[50] 2017	HCC	Tacrolimus	Nivolumab	Recurrent HCC	Partial response	No AEs or graft rejection
Friend et al,[51] 2017	HCC	Sirolimus	Nivolumab	Recurrent HCC	NA	Elevated liver enzymes, acute and chronic graft rejection leading to death
	HCC	Tacrolimus	Nivolumab	Recurrent HCC	NA	Elevated liver enzymes, acute graft rejection leading to death
Rai et al,[52] 2017	NA	NA	Pembrolizumab	Melanoma	NA	Acute graft rejection leading to death
Varkaris et al,[53] 2017	HCC	Tacrolimus	Pembrolizumab	Recurrent HCC	Disease Progression	No AEs or graft rejection
Kuo et al,[54–63] 2018	HCC	Sirolimus and mycophenolate mofetil	Ipilimumab followed by pembrolizumab at time of progression	Malignant peripheral nerve sheath tumor-like melanoma	Partial response to both agents	No AEs or graft rejection

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Table 2
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Case	Reason for Liver Transplant	Immuno-Suppression	Immunotherapy	Reason for Immunotherapy	Response of Malignancy to Immunotherapy	Toxicity to Transplant
DeLeon et al,[47] 2018	HCC	Tacrolimus	Nivolumab	HCC	Disease progression	No AEs or graft regression
	HCC	Everolimus and mycophenolate mofetil	Pembrolizumab	Melanoma	Complete response	No AEs or graft regression
	HCC	Mycophenolate mofetil and sirolimus	Nivolumab	HCC	Disease Progression	No AEs or graft regression
	HCC	Tacrolimus	Nivolumab	HCC	Disease progression	No AEs or graft regression
	HCC	Tacrolimus	Nivolumab	HCC	NA	No AEs or graft regression
	HCC	Sirolimus	Nivolumab	HCC	NA	Acute graft rejection
	Cholangiocarcinoma	Mycophenolate Mofetil and prednisone	Pembrolizumab	Melanoma	NA	Acute graft rejection

from clinical trials testing the safety and efficacy of immunotherapy because of their need for chronic immunosuppression and concern surrounding the induction of acute organ rejection and ultimately organ failure. Although no large trial has been or is being conducted in this specific population, there have been conflicting published case reports. On the one hand, successful treatment with immunotherapy after organ transplant has been reported, with a trend toward reduced toxicity if the transplant was received several years before immunotherapy and the patient was able to tolerate a reduction in immunosuppressant (antirejection) medication,[44–46]; but on the other hand, rapid acute transplant rejection in the setting of single agent or combination immunotherapy has been seen within 5 days of treatment initiation.[44] One retrospective pilot evaluation of immunotherapy use after liver transplantation involved 7 patients, 2 of whom rejected their organ within approximately 24 days of initiation of immunotherapy.[47] **Table 2** highlights cases of immunotherapy use after liver transplantation and their specific outcomes.

POTENTIAL BIOMARKERS

Currently, there are no confirmed roles for molecular biomarkers in HCC to guide specific targeted therapies or identify specific subgroups likely to respond, or not respond to immunotherapy. Biomarkers of interest include tumor mutational burden and PD-L1. Tumors with the highest rates of mutations per megabase include melanoma, non-small cell lung cancer, and bladder cancer,[64,65] and all tend to respond to immunotherapy. However, the value of tumor mutational burden as a predictive biomarker for immunotherapy response in HCC has not yet been explored, and in one retrospective study of 1170 HCC samples, it was found that a higher tumor mutational burden was associated with significantly worse progression-free survival and overall survival ($P<.0072$ and $P<.0001$, respectively).[66] Further study is needed. In the CheckMate 459 trial, higher response rates were seen with nivolumab in tumors that expressed PD-L1.[21] Tumors with less than 1% PD-L1 expression had a 12% response versus a 28% response in those with greater than 1% PD-L1 expression.[21] The role of PD-L1 in predicting HCC response to checkpoint inhibitors needs to be further explored.

SUMMARY

HCC holds a high patient mortality rate despite multiple local and systemic treatments. Immunotherapy is currently changing the landscape of treatment for patients with advanced disease, but in patients who have undergone transplantation or are transplant candidates, the use of immune therapy remains controversial. In some cases, there is a reported absence of adverse reactions, whereas in other cases, life-threatening acute graft rejections are observed. Further research is needed in all HCC scenarios to help guide the sequencing of treatments and improve strategies for patient selection and prognosis.

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DISCLOSURE

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70(1). https://doi.org/10.3322/caac.21590.
2. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2018;144(8):1941–53.
3. Fattovich G, Stroffolini T, Zagni I, et al. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004;127:S35–50.
4. Portolani N, Coniglio A, Ghidoni S, et al. Early and late recurrence after liver resection for hepatocellular carcinoma: prognostic and therapeutic implications. Ann Surg 2006;243:229–35.
5. Vivarelli M, Cucchetti A, La Barba G, et al. Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors: reassessment of risk factors for tumor recurrence. Ann Surg 2008;248:857–62.
6. Llovet JM, Ricci S, Mazzaferro V, et al, SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–90.
7. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10(1):25–34.
8. Parks AL, McWhirter RM, Evason K, et al. Cases of spontaneous tumor regression in hepatobiliary cancers: implications for immunotherapy? J Gastrointest Cancer 2015;46:161–5.
9. Iwanaga T. Studies on cases of spontaneous regression of cancer in Japan in 2011, and of hepatic carcinoma, lung cancer and pulmonary metastases in the world between 2006 and 2011. Gan To Kagaku Ryoho 2013;40:1475–87.
10. Kumar A, Le DT. Hepatocellular carcinoma regression after cessation of immunosuppressive therapy. J Clin Oncol 2016;34(10):e90–2.
11. Unitt E, Marshall A, Gelson W, et al. Tumour lymphocytic infiltrate and recurrence of hepatocellular carcinoma following liver transplantation. J Hepatol 2006;45: 246–53.
12. Gao Q, Qiu SJ, Fan J, Zhou J, Wang XY, Xiao YS, Xu Y, Li YW, Tang ZY. Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection. J Clin Oncol 2007;25(18):2586–93.
13. Flecken T, Schmidt N, Hild S, et al. Immunodominance and functional alterations of tumor-associated antigen-specific CD8+ T-cell responses in hepatocellular carcinoma. Hepatology 2014;59(4):1415–26.
14. Liang J, Ding T, Guo ZW, et al. Expression pattern of tumour-associated antigens in hepatocellular carcinoma: association with immune infiltration and disease progression. Br J Cancer 2013;109:1031–9.
15. Jung HI, Jeong D, Ji S, et al. Overexpression of PD-L1 and PD-L2 is associated with poor prognosis in patients with hepatocellular carcinoma. Cancer Res Treat 2017;49(1):246–54.
16. Liao H, Chen W, Dai Y, et al. Expression of programmed cell death-ligands in hepatocellular carcinoma: correlation with immune microenvironment and survival outcomes. Front Oncol 2019;9:883.
17. Melero I, Sangro B, Riezu-Boj JI, et al. Abstract 4387: antiviral and antitumoral effects of the anti-CTLA4 agent tremelimumab in patients with hepatocellular carcinoma (HCC) and chronic hepatitis C virus (HCV) infection: results from a phase II clinical trial. Immunology 2012. https://doi.org/10.1158/1538-7445.am2012-4387.

18. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389(10088): 2492–502.
19. Kudo M, Matilla A, Santoro A, et al. Checkmate-040: nivolumab (NIVO) in patients (Pts) with advanced hepatocellular carcinoma (AHCC) and child-Pugh B (CPB) status. J Clin Oncol 2019;37(4_suppl):327.
20. Kambhampati S, Bauer KE, Bracci PM, et al. "Nivolumab in patients with advanced hepatocellular carcinoma and child-Pugh Class B cirrhosis: safety and clinical outcomes in a retrospective case series. Cancer 2019;125(18):3234–41.
21. Yau T, Park JW, Finn RS, et al. CheckMate 459: a randomized, multi-center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (Pts) with advanced hepatocellular carcinoma (AHCC). Ann Oncol 2019;30: v874–5.
22. Finn RS, Ryoo B-Y, Merle P, et al. Results of KEYNOTE-240: phase 3 study of pembrolizumab (Pembro) vs best supportive care (BSC) for second line therapy in advanced hepatocellular carcinoma (HCC). J Clin Oncol 2019;37(15_suppl): 4004.
23. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined Nivolumab and Ipilimumab in advanced melanoma. N Engl J Med 2017;377(14): 1345–56.
24. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378(14):1277–90.
25. Overman MJ, Lonardi S, Wong KYM, et al. Nivolumab (NIVO) + low-dose ipilimumab (IPI) in previously treated patients (pts) with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): long-term follow-up. J Clin Oncol 2019;37(4_suppl):635.
26. Kelley RK, Abou-Alfa GK, Bendell JC, et al. Phase I/II study of durvalumab and tremelimumab in patients with unresectable hepatocellular carcinoma (HCC): phase I safety and efficacy analyses. J Clin Oncol 2017;35(15_suppl):4073.
27. Yau T, Kang Y-K, Kim T-Y, et al. Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (AHCC): results from CheckMate 040. J Clin Oncol 2019;37(15_suppl):4012.
28. Boige V, Malka D, Bourredjem A, et al. Efficacy, safety, and biomarkers of single-agent bevacizumab therapy in patients with advanced hepatocellular carcinoma. Oncologist 2012;17(8):1063–72.
29. Frenette C, Gish R. Targeted systemic therapies for hepatocellular carcinoma: clinical perspectives, challenges and implications. World J Gastroenterol 2012; 18(6):498–506.
30. Motz GT, Santoro SP, Wang LP, et al. Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors. Nat Med 2014;20(6): 607–15.
31. Oelkrug C, Ramage JM. Enhancement of T Cell recruitment and infiltration into tumours. Clin Exp Immunol 2014;178(1):1–8.
32. Wallin JJ, Bendell JC, Funke R, et al. Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. Nat Commun 2016;7:12624.
33. Manning EA, Ullman JG, Leatherman JM, et al. A vascular endothelial growth factor receptor-2 inhibitor enhances antitumor immunity through an immune-based mechanism. Clin Cancer Res 2007;13(13):3951–9.

34. Roland CL, Lynn KD, Toombs JE, et al. Cytokine levels correlate with immune cell infiltration after anti-VEGF therapy in preclinical mouse models of breast cancer. PLoS One 2009;4(11):e7669.
35. Voron T, Colussi O, Marcheteau E, et al. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. J Exp Med 2015;212(2):139–48.
36. Lee M, Ryoo B-Y, Hsu C-H, et al. Randomised efficacy and safety results for atezolizumab (Atezo) + bevacizumab (Bev) in patients (pts) with previously untreated, unresectable hepatocellular carcinoma (HCC). Presented at 2019 ESMO Congress. Barcelona, Spain, September 27 to October 1, 2019. Abstract LBA39.
37. Cheng AL, Qin S, Ikeda M, et al. LBA3 - IMbrave150: efficacy and safety results from a ph III study evaluating atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). ESMO Asia 2019. Singapore, November 22-24, 2019.
38. Ikeda M, Sung MW, Kudo M, et al. A phase 1b trial of lenvatinib (LEN) plus pembrolizumab (PEM) in patients (pts) with unresectable hepatocellular carcinoma (UHCC). J Clin Oncol 2018;36(15_suppl):4076.
39. Yau T, Zagonel V, Santoro A, et al. Nivolumab (NIVO) + ipilimumab (IPI) + cabozantinib (CABO) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): results from CheckMate 040. J Clin Oncol 2020;38(suppl 4). abstr 478.
40. Zhu AX, Knox JJ, Kudo M, et al. KEYNOTE-224: phase II study of pembrolizumab in patients with previously treated advanced hepatocellular carcinoma. J Clin Oncol 2017;35(4_suppl):TPS504.
41. Ali MY, Grimm CF, Ritter M, et al. Activation of dendritic cells by local ablation of hepatocellular carcinoma. J Hepatol 2005;43(5):817–22.
42. Dromi SA, Walsh MP, Herby S, et al. Radiofrequency ablation induces antigen-presenting cell infiltration and amplification of weak tumor-induced immunity. Radiology 2009;251:58–66.
43. Aerts M, Benteyn D, Van Vlierberghe H, et al. Current status and perspectives of immune-based therapies for hepatocellular carcinoma. World J Gastroenterol 2016;22(1):253–61.
44. Chae YK, Galvez C, Anker JF, et al. Cancer immunotherapy in a neglected population: the current use and future of T-cell-mediated checkpoint inhibitors in organ transplant patients. Cancer Treat Rev 2018;63:116–21. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29276997.
45. Morales RE, Shoushtari AN, Walsh MM, et al. Safety and efficacy of ipilimumab to treat advanced melanoma in the setting of liver transplantation. J Immunother Cancer 2015;3:22.
46. Lipson EJ, Bodell MA, Kraus ES, et al. Successful administration of ipilimumab to two kidney transplantation patients with metastatic melanoma. J Clin Oncol 2014;32(19):e69–71.
47. DeLeon T, Salomao M, Bashar A. Pilot evaluation of PD-1 inhibition in metastatic cancer patients with liver transplantations: the Mayo Clinic experience. J Clin Oncol 2018;(suppl 4S). abstr 328.
48. Ranganath HA, Panella TJ. Administration of ipilimumab to a liver transplant recipient with unresectable metastatic melanoma. J Immunother 2015;38(5):211.
49. Schvartsman G, Perez K, Sood G, et al. Immune checkpoint inhibitor therapy in a liver transplant recipient with melanoma. Ann Intern Med 2017;167(5):361–2.
50. De Toni EN, Gerbes AL. Tapering of immunosuppression and sustained treatment with nivolumab in a liver transplant recipient. Gastroenterology 2017;152(6):1631–3.

51. Friend BD, Venick RS, McDiarmid SV, et al. Fatal orthotopic liver transplant organ rejection induced by a checkpoint inhibitor in two patients with refractory, metastatic hepatocellular carcinoma. Pediatr Blood Cancer 2017;64(12). https://doi.org/10.1002/pbc.26682. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28643391.
52. Rai R, Ezeoke OM, McQuade JL, et al. Immunotherapy in patients with concurrent solid organ transplant, HIV, and hepatitis B and C. Ann Oncol 2017;28:403–27.
53. Varkaris A, Lewis DW, Nugent FW. Preserved liver transplant after PD-1 pathway inhibitor for hepatocellular carcinoma. Am J Gastroenterol 2017;112(12):1895–6.
54. Kuo JC, Lilly LB, Hogg D. Immune checkpoint inhibitor therapy in a liver transplant recipient with a rare subtype of melanoma: a case report and literature review. Melanoma Res 2018;28(1):61–4.
55. Ungerechts G, Engeland CE, Buchholz CJ, et al. Virotherapy research in Germany: from engineering to translation. Hum Gene Ther 2017;28(10):800–19.
56. Li N, Zhou J, Weng D, et al. Adjuvant adenovirus-mediated delivery of herpes simplex virus thymidine kinase administration improves outcome of liver transplantation in patients with advanced hepatocellular carcinoma. Clin Cancer Res 2007;13(19):5847–54.
57. Abudoureyimu M, Lai Y, Tian C, et al. Oncolytic adenovirus-A Nova for gene-targeted oncolytic viral therapy in HCC. Front Oncol 2019;9:1182. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31781493.
58. Sangro B, Mazzolini G, Ruiz M, et al. A phase I clinical trial of thymidine kinase-based gene therapy in advanced hepatocellular carcinoma. Cancer Gene Ther 2010;17(12):837–43.
59. Martinez M, Moon EK. CAR T cells for solid tumors: new strategies for finding, infiltrating, and surviving in the tumor microenvironment. Front Immunol 2019;10:128.
60. Liu C, Liu H, Wang Y, et al. ET140202 t-cells: a novel therapy targeting AFP/MHC complex, that is both safe and effective in treating metastatic hepatocellular carcinoma. J Clin Oncol 2019;37(15_suppl). https://doi.org/10.1200/jco.2019.37.15_suppl.e15614.
61. Zhai B, Shi D, Gao H, et al. A phase I study of anti-GPC3 chimeric antigen receptor modified T cells (GPC3 CAR-T) in Chinese patients with refractory or relapsed GPC3+ hepatocellular carcinoma (r/r GPC3+ HCC). J Clin Oncol 2017;35(15_suppl):3049.
62. Wang Y, Chen M, Wu Z, et al. CD133-directed CAR T cells for advanced metastasis malignancies: a phase I trial. Oncoimmunology 2018;7:e1440169.
63. Yao W, He JC, Yang Y, et al. The prognostic value of tumor-infiltrating lymphocytes in hepatocellular carcinoma: a systematic review and meta-analysis. Sci Rep 2017;7(1). https://doi.org/10.1038/s41598-017-08128-1.
64. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature 2013;500(7463):415–21.
65. Lawrence MS, Stojanov P, Polak P, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature 2013;499(7457):214–8.
66. Shrestha R, Prithviraj P, Anaka M, et al. Monitoring immune checkpoint regulators as predictive biomarkers in hepatocellular carcinoma. Front Oncol 2018;8:269.