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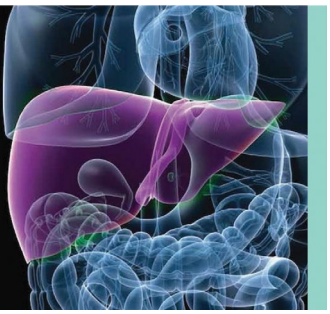

Checkpoint Inhibitors for the Treatment of Advanced Hepatocellular Carcinoma

Laura A. Huppert, M.D., John D. Gordan, M.D., Ph.D.,* and Robin Kate Kelley, M.D.†*

Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer and the second leading cause of cancer-related deaths worldwide.[1] In the United States, HCC is the fastest rising cause of cancer death, owing in part to the obesity epidemic.[2] The high rate of mortality has been attributed to an aggressive tumor biology, comorbid underlying liver disease in a majority of patients, late stage of disease at diagnosis in many cases, and a lack of effective systemic therapy options. For more than a decade, the multikinase inhibitor (MKI) sorafenib has been the only systemic therapy to improve survival in advanced HCC, although median survival prolongation from sorafenib is less than 3 months and fewer than 5% of patients achieve objective response rate (ORR) in the pivotal sorafenib trials.[3,4] Since 2017, multiple new drugs, including lenvatinib, regorafenib, and cabozantinib, have demonstrated noninferiority to sorafenib in the treatment of advanced HCC, leading to regulatory approvals and dramatically expanding the treatment landscape for advanced HCC. Despite these advances, the median overall survival (OS) remains only about 1 year after the start of systemic therapy, the duration of treatment response is limited, and new treatment strategies are still urgently needed.

Cancer immunotherapy with checkpoint inhibitors (CPIs) is an exciting and rapidly evolving area of oncology that has dramatically increased survival in patients with many types of cancer.[5] HCC arises in the setting of proinflammatory conditions, such as hepatitis B/C infections and liver cirrhosis, and demonstrates an immunosuppressive

Abbreviations: APC, antigen-presenting cell; ASCO, American Society of Clinical Oncology; BSC, best supportive care; CPI, checkpoint inhibitor; CTLA-4, cytotoxic T lymphocyte–associated protein 4; FDA, US Food and Drug Administration; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IRAE, immune-related adverse event; MHC, major histocompatibility complex; MKI, multikinase inhibitor; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TACE, transarterial chemoembolization; VEGFR, vascular endothelial growth factor receptor.

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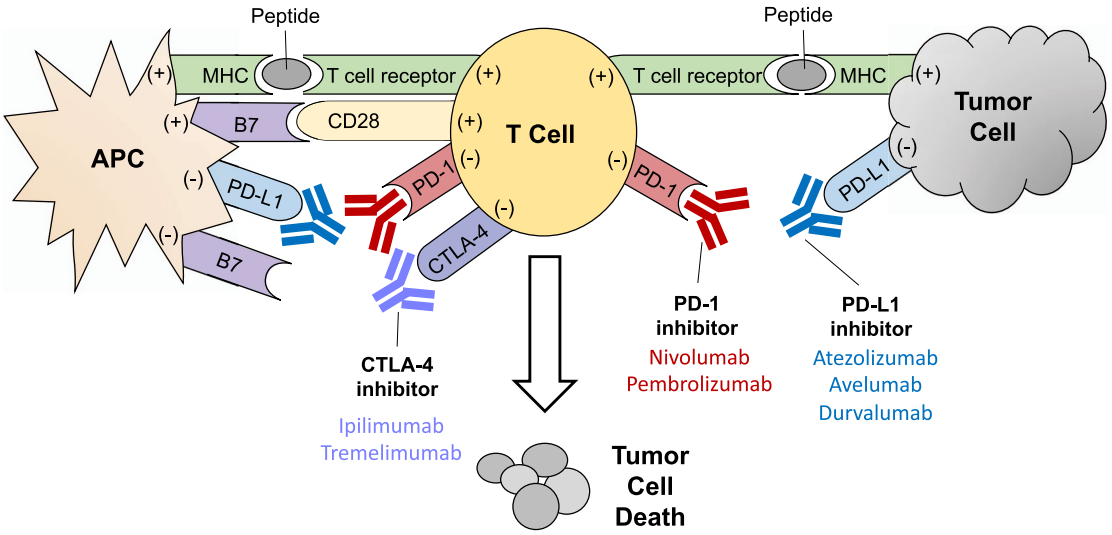

FIG 1 Mechanisms of T cell activation and inhibition. T cell activation is mediated by the interaction of the T cell receptor with the MHC and the CD28 receptor with the B7 costimulatory molecule on the APC. Activating interactions are noted with a plus sign (+). T cell inhibition is mediated by the interaction of PD-L1 and PD-1, as well as CTLA-4 and B7. Inhibitory interactions are noted with a minus sign (–). Inhibitors of PD-1, PD-L1, and CTLA-4 prevent the inactivation of T cells, thus allowing the T cells to destroy the tumor cell more effectively. The FDA-approved CPIs are listed.

microenvironment. These features are associated with response to immunotherapy in other cancer types, suggesting that CPI may have potential benefit in HCC as well. In this review, we will first discuss the basic principles of cancer immunology and mechanisms of immunotherapy. Then, we will highlight key clinical trials that demonstrate the therapeutic potential of immunotherapy in the treatment of advanced HCC. Finally, we will comment on challenges and future directions in this field.

CANCER IMMUNOTHERAPY BACKGROUND

To understand the mechanism of immunotherapy agents, it is first important to review the basic principles of cancer immunology. The immune system is a critical regulator of tumor biology with the capacity to support or inhibit tumor development, growth, invasion, and metastasis. T cells selectively recognize foreign or malignant cells and target them for destruction. The immune system has multiple negative regulators of T cells, or "checkpoints," to ensure that the immune inflammatory response is not constantly activated, thus acting as "brakes" for continuous T cell activation. However, in cancer, malignant cells are able to evade tumor immunosurveillance by manipulating their own characteristics or those of their local microenvironment to evade these negative regulators and proliferate unchecked. CPIs block negative regulators of T cells, thus enhancing potential for T cell activation to effect antitumor activity[6] (Fig. 1). To date, there are seven CPIs that have been approved by the US Food and Drug Administration (FDA) for various oncology indications: ipilimumab and tremelimumab are cytotoxic T lymphocyte–associated protein 4 (CTLA-4) inhibitors; nivolumab and pembrolizumab are anti–programmed cell death protein 1 (anti-PD-1) agents; and atezolizumab, avelumab, and durvalumab are anti–programmed death-ligand 1 (PD-L1) agents. CPIs have become a mainstay in the treatment of many cancers including metastatic melanoma, non-small-cell lung cancer, urothelial carcinoma, and renal cell carcinoma, and numerous clinical trials are underway to study the safety and efficacy of these agents in other solid and hematological malignancies, including for patients with HCC.

CPI MONOTHERAPY FOR THE TREATMENT OF ADVANCED HCC

Multiple clinical trials have studied the use of CPI monotherapy in HCC, demonstrating durable and sustained treatment responses in some patients (Table 1). In the CheckMate 040 trial (NCT01658878), El-Khoueiry and colleagues studied the safety and efficacy of the anti–PD-1 monoclonal antibody nivolumab in 262 patients

TABLE 1. IMMUNE CHECKPOINT MONOTHERAPY FOR THE TREATMENT OF HCC

ClinicalTrials.gov Identifier	Treatment	Target	Design	Endpoints	Comments/Accrual Status
NCT01658878 (CheckMate 040)	Nivolumab	PD-1	Phase I/II	Safety, tolerability	Tumor shrinkage in up to 20% of patients with median duration of response of 17 months; led to FDA approval of nivolumab after sorafenib failure
NCT02702414 (KEYNOTE-224)	Pembrolizumab	PD-1	Phase II	ORR	Response rate of 17% of patients, with most responders showing a durable response for at least 9 months; led to FDA approval of pembrolizumab after sorafenib failure
NCT02989922	Camrelizumab (SHR-1210)	PD-1	Phase II	ORR/OS	Response rate 14%, median OS 14.4 months in predominately HBV^+ patients
NCT02576509 (CheckMate 459)	Nivolumab versus sorafenib as first-line therapy	PD-1	Phase III	TTP/OS	Press release indicated no statistical significance for OS primary endpoint; final analysis pending
NCT03412773	Tislelizumab (BGB-A317) versus sorafenib as first-line therapy	PD-1	Phase III	OS/Safety	Active accrual
NCT02702401 (KEYNOTE-240)	Pembrolizumab versus BSC as second-line therapy	PD-1	Phase III	PFS/OS	Accrual complete: reported negative results at ASCO 2019, but final analysis pending
NCT03062358 (KEYNOTE-394)	Pembrolizumab versus BSC as second-line therapy	PD-1	Phase III	OS	Active accrual in Asia (China, Hong Kong, Korea, Malaysia, and Taiwan)

with advanced HCC.[7,8] They demonstrated a manageable safety profile with low rates of immune-related toxicity and showed that nivolumab achieved robust and durable tumor shrinkage in up to 20% of patients, with the median duration of response exceeding 17 months. The median OS was 15 months in 154 patients with prior sorafenib therapy, whereas the median OS was more than 28 months in 81 patients treated with nivolumab in the first-line setting without prior systemic therapy, a result comparable with the outcomes from transarterial chemoembolization (TACE) in the intermediate stage setting.[9,10] The relatively high response rate coupled with prolonged survival in the CheckMate 040 trial cohort led to conditional regulatory approval of nivolumab by the FDA as a treatment option after sorafenib failure in advanced HCC.

Subsequently, other CPIs have been tested in patients with advanced HCC. In the KEYNOTE-224 trial (NCT02702414), Zhu et al. studied the PD-1 inhibitor pembrolizumab as a monotherapy in 104 patients with advanced HCC, demonstrating a response rate of 17%, with most responders showing a durable response for at least 9 months, comparable with the outcomes from nivolumab.[11] In both CheckMate 040 and KEYNOTE-224, clinical response was observed across etiologies of liver disease and HCC, including in patients with hepatitis B virus (HBV), hepatitis C virus (HCV), and nonviral liver disease. Similarly, another phase II clinical trial in China (NCT02989922) including 217 predominantly HBV-positive patients with advanced HCC reported a response rate of approximately 14% and median OS of 14.4 months for the PD-1 inhibitor camrelizumab (SHR-1210), an important finding given that systemic therapy studies have historically demonstrated worse outcomes in Asian HBV-positive populations.[12]

These uncontrolled studies of CPIs as monotherapy collectively establish the potential for robust and durable antitumor responses in subsets of patients with advanced HCC across disease etiologies, although their efficacy has not been confirmed in randomized phase III trials to date. Multiple ongoing phase III clinical trials are evaluating CPI monotherapy in advanced HCC (Table 2). In the first-line setting, several pivotal randomized phase III trials are expected to report results in the near future, including CheckMate 459 (NCT02576509) comparing the efficacy of nivolumab with sorafenib and NCT03412773 comparing the efficacy of the PD-1 inhibitor tislelizumab (BGB-A317) with sorafenib. Preliminary results of CheckMate 459 indicate that pembrolizumab did not significantly prolong either of the dual primary endpoints of progression-free survival (PFS) or OS compared with placebo, although there was a trend toward improvement in both primary endpoints, and further analysis of secondary endpoints is needed. In the second-line setting after prior sorafenib treatment, the double-blind phase III trial KEYNOTE-240 (NCT02702401) compared pembrolizumab with placebo.[13] Preliminary results presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2019 indicate that this study did not meet the statistical criteria for either of the dual endpoints of OS and PFS, although there were trends toward prolongation in both endpoints in the pembrolizumab arm, along with substantially higher duration of median response with pembrolizumab therapy

TABLE 2. CPI COMBINATION THERAPY FOR THE TREATMENT OF HCC

ClinicalTrials.gov Identifier	Treatment	Target	Design	Endpoints	Comments/Accrual Status
NCT03298451 (HIMALAYA)	Durvalumab ± tremelimumab versus sorafenib	PD-L1 CTLA-4	Phase III	OS	Accrual complete
NCT03434379 (IMbrave 150)	Atezolizumab + bevacizumab versus sorafenib	PD-L1 VEGFR	Phase II	OS	Accrual complete
NCT03713593 (LEAP-002)	Pembrolizumab + lenvatinib versus lenvatinib	PD-1 MKI	Phase III	PFS, OS	Active accrual
NCT03755791 (COSMIC-312)	Atezolizumab + cabozantinib versus sorafenib	PD-L1 MKI	Phase III	PFS, OS	Active accrual
NCT03383458 (CheckMate 9DX)	Adjuvant nivolumab versus placebo after curative hepatic resection or ablation	PD-1	Phase III	OS, time to recurrence	Active accrual
NCT03847428 (EMERALD-2)	Adjuvant durvalumab ± bevacizumab after curative treatment	PD-L1 VEGRF	Phase III	Recurrence-free survival	Active accrual
NCT03778957 (EMERALD-1)	TACE ± durvalumab + bevacizumab	PD-L1 VEGRF	Phase III	PFS	Active accrual

(18.3 months with pembrolizumab versus 4.4 months with placebo, $P = 0.00007$). Another second-line therapy trial KEYNOTE-394 (NCT03062358) is also comparing pembrolizumab therapy with placebo in Asian patients with previously treated advanced HCC, with results not yet reported.

CPI COMBINATION THERAPY FOR ADVANCED HCC

Multiple clinical trials are now underway across tumor types including HCC to study CPI combinations as a strategy to overcome primary and acquired resistance, and thereby improve the proportion of patients with response. In HCC, randomized phase III trials are ongoing with various combination strategies, including PD-L1 plus CTLA-4 inhibition (HIMALAYA, NCT03298451), CPI plus antiangiogenic agents such as bevacizumab (IMbrave 150, NCT03434379), and checkpoint inhibition plus MKIs such as lenvatinib (LEAP-002, NCT03713593) or cabozantinib (COSMIC-312, NCT03755791). CPIs are also being studied in earlier stages of HCC, including as adjuvant therapy after resection or ablation (CheckMate 9DX, NCT03383458; EMERALD-2, NCT03847428), or in combination with TACE (EMERALD-1, NCT03778957).

IMMUNE-RELATED ADVERSE EFFECTS AND TREATMENT

Despite the promise of immunotherapy in HCC, there are important challenges that must be addressed. First, although most patients tolerate immunotherapy well, modulating the immune response confers a risk for immune-related adverse events (IRAEs), or toxicity arising from immune activation in normal, noncancerous tissues. IRAEs can range from mild endocrinopathies such as hypothyroidism to life-threatening complications such as myocarditis, pneumonitis, or encephalitis.[14] In HCC, there is particular concern for treatment-related adverse events involving hepatic function given that most patients with HCC have underlying liver disease and risk for decompensation with additional insults. In the studies of CPIs in HCC to date, immune-mediated hepatitis (defined as requirement of steroids and no-alternative etiology) has occurred rarely, with grade ≥3 side effects affecting only 4% of patients treated with nivolumab in the dose-escalation arm of CheckMate 040[7] and 3% of patients treated with pembrolizumab in both KEYNOTE-224[11] and KEYNOTE-240.[13] Increase in liver enzymes (elevated AST, ALT, and bilirubin) without clinical impairment in hepatic function was more common, with grade 3 to 4 laboratory treatment-related adverse events noted in 16% of patients in the dose-escalation arm of CheckMate 040,[7] 12% of the patients in KEYNOTE-224,[11] and 11% more patients in the treatment arm than in the placebo arm in KEYNOTE-240.[13] Treatment of serious IRAEs includes stopping the CPI and inducing temporary immunosuppression with steroids or other steroid-sparing agents. No prospective trials have defined the best treatment approach, but manufacturer prescribing recommendations provide some guidance. For pembrolizumab, manufacturer prescribing information recommends that providers monitor for changes in liver function and administer corticosteroids (initial dose of 0.5-1 mg/kg/day for grade 2 hepatitis and 1-2 mg/kg/day for grade 3 or greater hepatitis prednisone or equivalent, followed by a taper, and based on the severity of the liver enzyme elevations, withhold or discontinue pembrolizumab administration).[15] Similarly, for nivolumab, the manufacturer prescribing information recommends that providers administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for grade 2 transaminase elevations and a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a taper for grade 3 or higher transaminase elevations with or without concomitant bilirubin elevations.[16]

For patients with HCC, prescribing recommendations specifically indicate that nivolumab should be held for patients with grade 2 immune-mediated hepatitis and permanently discontinued for grade 3 or 4 immune-mediated hepatitis. If not promptly recognized, IRAEs can be life-threatening, so it is important to have an experienced provider and multidisciplinary team to monitor for and treat these rare but serious side effects.

Second, although immunotherapy has demonstrated impressive outcomes for some patients with HCC, it is critical to better understand which patients are most likely to benefit from immunotherapy versus alternative treatment approaches including multikinase inhibition, now that multiple MKIs are available. Translational research studying biospecimens from prospective clinical trials will be essential to identify biomarkers that may be able to predict treatment response.

Third, immunotherapy currently cannot be used in the peritransplant setting because of the risk for acute rejection and graft loss in unselected patients without biomarkers of response or rejection.[17] Therefore, it will be important to determine when to pursue transplant or immunotherapy for patients with HCC, and ultimately study whether there are ways to reduce the risk for rejection to provide the option to use these therapies concurrently in the future.

Finally, CPI monotherapy can cause durable responses in many patients, but many patients eventually relapse. Acquired resistance develops because of changes in antigen presentation and interferon γ signaling pathways, but these mechanisms are poorly understood. Combination therapies may overcome resistance by targeting multiple pathways, but additional studies are needed.

CONCLUSION

Immune CPIs have established the potential for durable, robust, and meaningful responses across agents and subgroups of patients with advanced HCC. Ongoing clinical trial biomarker analyses aim to define features associated with response to CPI monotherapy. In addition, combination approaches are underway to determine whether the addition of tyrosine kinase inhibition, the anti–vascular endothelial growth factor antibody bevacizumab, or additional immune CPIs can augment the proportion of patients with response to PD-1 or PD-L1 inhibition. The unprecedented activity of CPI in patients with advanced stage HCC has prompted a new generation of clinical trials in early and intermediate stages of disease in hopes of improving the proportion of patients who achieve disease cure.

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