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HEPATIC CANCER (A SINGAL AND A MUFTI, SECTION EDITORS)

Current State of Immunotherapy for HCC—Supporting Data and Toxicity Management

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Abstract

Purpose of Review After having tyrosine kinase inhibitor as only available one drug class to treat advanced hepatocellular carcinoma (HCC) for more than a decade, immunotherapy agents are now approved for second-line therapy and are currently being compared head-to-head with sorafenib for first-line treatment. It is becoming increasingly important for hepatologists to become aware of agents in development, potential adverse events, and suggested treatment monitoring.

Recent Findings Nivolumab and pembrolizumab have both shown promising phase II data in the second-line setting for HCC and phase III data in both the first-line and second-line settings are anticipated soon. Durable responses of 15–20% is seen as a potential breakthrough and may translate into improved survival for patients with advanced HCC. While immunotherapies are well tolerated overall, rare but serious immune-mediated adverse events are possible and warrant monitoring to facilitate early treatment when needed. There is ongoing research of combinations with immunotherapy agents and other systemic agents and/or locoregional therapies to further enhance response rates.

Summary Ongoing studies will define the role of immunotherapy for treatment of HCC, both as single agents as well as in combination with other therapies.

Keywords Hepatocellular carcinoma · HCC · Immunotherapy · Checkpoint blockade · PD-1 · PD-L1 · Nivolumab · Pembrolizumab · Atezolizumab · Durvalumab · CTLA-4

Introduction

The observation by Dr. William Coley that some malignancies undergo spontaneous remissions lent support to the idea that the immune system could be harnessed to treat cancer. The concept that at least some cancers evolve by avoiding immune detection dates back to the 1950s when Thomas and Burnett proposed the idea of immune surveillance [1]. Two of the diseases that are quoted as having a higher incidence of this observation are renal cell carcinoma and melanoma [2]. In 1992, high-dose interleukin-2 (IL-2) was approved by the US FDA for the treatment of advanced renal cell carcinoma and in 1998 for melanoma [3]. Although limited by low response rates, IL-2 generated durable responses lasting several years for those who did respond. A stark limitation of high-dose IL-2 is its toxicity, generating cytokine release and requiring ICU level of supportive care to safely administer the medication. However, its clinical success expanded our knowledge of immunotherapy in cancer treatment, including focusing our study of CD28 as an important co-stimulator for T cell activation, and a negative regulator of this activation, namely CTLA-4 [4•].

CD28, a cell surface marker on T cells, serves as a costimulatory molecule with its counterpart, B7, on the surface of antigen-presenting cells (APCs) in the priming phase of immune activation of cytotoxic T cells. Knockout mice studies demonstrated this principle with CD28 knockouts having severely impaired T cell responses, and similar effects duplicated in B7-1/B7-2 knockout mice [5]. CTLA-4, another molecule on the surface of T cells, binds B7-1 or B7-2 similar to CD28, but with much higher affinity. CTLA-4's expression on the surface was inducible and occurred after initial activation of T cells. CTLA-4-

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deficient mice developed profound lymphoproliferative disorders with almost all T cells being activated, thus demonstrating its importance as a down-regulator of activated T cells. CTLA-4 blockade in mouse models resulted in rejection of several types of solid tumors transplanted into the mice [6]. Although this response is limited by the inherent immunogenicity of the tumors, as CTLA-4 is not involved in lymphocyte trafficking. Therapeutic blocking CTLA-4 with the monoclonal antibody ipilumimab resulted in its initial approval for the treatment of metastatic melanoma, a previously established immunogenic tumor, in 2011 [7] (Table 1).

While CTLA-4 blockade results in generalized activated T cell responses, tumors may escape extended immune activation. One such mechanism is through tumor expression of programmed death ligand 1 (PD-L1) on its cell surface, binding to PD-1 on the surface of tumor-infiltrating lymphocytes (TILs). Tumor PD-L1 expression is predominantly induced by lymphocytes themselves but also through other signaling pathways not yet well characterized [8]. Signaling through PD-1/PD-L1 interaction results in reduced cytotoxic function of the T cells and reduced interaction between the TILs and tumor cells. PD-1 expression is also inducible on other

Table 1 Current immunotherapy approvals in oncology

Drugs/treatment	Malignancy type	Treatment setting
Ipilimumab	Stage III melanoma	Adjuvant treatment
Ipilimumab	Metastatic melanoma	Any line
Avelumab	Metastatic Merkel cell carcinoma	Any line
Atezolumab	Metastatic NSCLC	Disease progression during or following platinum-containing chemotherapy, and have progressed on an appropriate FDA-approved targeted therapy if their tumor has EGFR or ALK gene abnormalities
Durvalumab	Stage III NSCLC	Unresectable and not progressed after chemotherapy and radiation (chemoradiation)
Pembrolizumab	Metastastic NSCLC	First line with PD-L1 ≥ 50 or after disease progression on or after platinum-containing chemotherapy with PD-L1 ≥ 1
Pembrolizumab	Classical Hodgkin lymphoma	Relapsed after three or more prior lines of therapy
Pembrolizumab	Unresectable or metastatic solid tumors MSI-H or dMMR	Progressed on prior treatments
Pembrolizumab	Recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma with PD-L1 ≥ 1	Disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy
Pembrolizumab or atezolizumab	Locally advanced or metastatic urothelial carcinoma	Ineligible for cisplatin-containing chemotherapy
Pembrolizumab and Carbo/Pem	Metastatic non-squamous NSCLC	First line
Nivolumab	Metastatic RCC	Prior anti-angiogenic therapy
Nivolumab	Metastatic NSCLC	Progression on or after platinum-based chemotherapy
Nivolumab	Classical Hodgkin lymphoma	Relapsed or progressed after autologous hematopoietic stem cell transplantation (auto-HSCT) and post-transplantation brentuximab vedotin
Nivolumab	MSI-H or dMMR metastatic colorectal cancer	Progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan
Nivolumab	HCC	Second line after sorafenib failure
Nivolumab	Melanoma	Adjuvant treatment with involvement of lymph nodes or metastatic disease who have undergone complete resection
Nivolumab or pembrolizumab	Recurrent or metastatic squamous cell carcinoma of the head and neck	Disease progression on or after platinum-based therapy
Nivolumab or pembrolizumab or durvalumab or atezolizumab or avelumab	Locally advanced or metastatic urothelial carcinoma	Disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
Nivolumab or pembrolizumab	Melanoma	BRAF V600 wild-type and BRAF V600 mutation-positive unresectable or metastatic melanoma
Nivolumab with ipilimumab	Melanoma	BRAF V600 wild-type and BRAF V600 mutation-positive unresectable or metastatic melanoma
Nivolumab with ipilimumab	Intermediate-poor risk metastatic RCC	First line

immune effector cells in the tumor microenvironment, such as regulatory T cells, B cells, and NK cells, with signaling impairing the function of the B/NK cells and enhanced down-regulation of immune response with the regulatory T cells [9]. Given its prevalence and importance in immune evasion, PD-L1 has been very attractive as a therapeutic target and has a number of approvals to date (Table 1). Figure 1 demonstrates the interactions of PD-1 and PD-L1 in regulating the immune system.

Biologic Rationale for Immunotherapy in Hepatocellular Carcinoma

It is well established that hepatocellular carcinoma (HCC) occurs in the background of chronic liver disease in more than 90% of patients [10•]. Globally, the leading cause of HCC is viral hepatitis (both hepatitis C and B) but other well-known causes include heavy alcohol use, non-alcoholic steatohepatitis (NASH), and metabolic disorders (i.e., hemochromatosis, Wilson's disease, etc.). Liver injury results in chronic inflammation and recruitment of an inflammatory milieu that includes pro-angiogenic factors, activated fibroblasts and macrophages, and T cells. Over time, this process promotes tumorigenesis by inducing genetic instability and the activation of cell survival and growth-promoting pathways. These altered pathways have been actively targeted in the treatment of liver cancer [11–13].

Historically, the only drug that has been shown to improve survival in advanced HCC was sorafenib. Sorafenib is an oral small molecule multikinase inhibitor of the vascular endothelial growth factor (VEGF) receptor as well as the platelet-derived growth factor receptor (PDGFR) and *raf* kinase (SHARP) [14] However, after a decade of negative phase 3 studies, we now have four new drugs proven to improve survival in advanced HCC. In the front-line setting, this includes the multikinase inhibitor lenvatinib, which like sorafenib not only targets VEGF receptor and PDGFR, but also potently inhibits the fibroblast growth factor receptor (FGFR) family [15]. In the second-line setting, regorafenib, a multikinase inhibitor targeting VEGF receptor, TIE-2, PDGFR, RET, KIT, and FGFR1 and has global approval in this indication [16, 17]. Cabozantinib, a multitargeted kinase inhibitor of VEGF receptor, c-MET, and AXL, has been shown to improve overall survival in the second and third lines as well [18]. Recently, data with the VEGF receptor monoclonal antibody ramucirumab in the second-line setting has shown an improvement in survival in patients with an elevated alfa-fetoprotein greater than or equal to 400 ng/mL [19]. While a

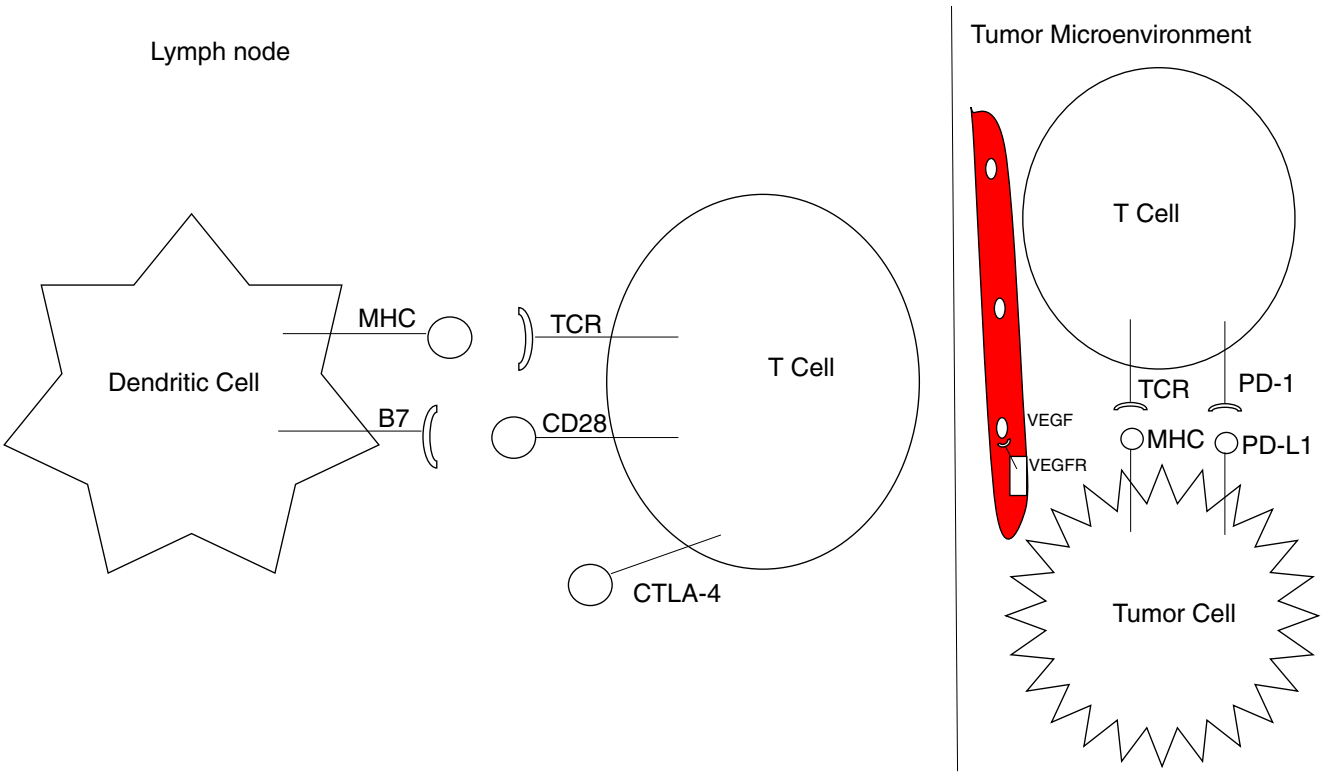

Fig. 1 A depiction of an immune checkpoint at the priming phase. In a lymph node, the antigen-presenting cell (here, a dendritic cell) presents antigen via MHC/TCR interaction and the T cell is activated after co-stimulation with B7/CD 28. The activated T cell enters the tumor microenvironment, an environment established via several growth factors including VEGF. The T cell activity is downregulated by PD-L1 expression on tumor cells interacting with PD-1 on the T cell. This results in an exhausted T cell phenotype

monoclonal antibody only interacts with one target, the exact mechanism of the multitargeted kinase inhibitor is unclear. Even after a decade of use, the exact mechanism of sorafenib's anticancer activity in patients is largely unknown. Radiographic responses with all of the agents that have yielded survival benefits in phase 3 HCC studies are generally uncommon, or, when they do occur, are not of a long duration. This has raised the question in HCC clinical research of the utility of response in predicting survival in HCC [20].

Antibodies that modulate some aspects of the immune system have been proven in numerous phase 3 studies in multiple tumors [4•] . Only more recently, with the experience in other tumor types, investigators have focused this approach to overcome the anergy that often develops in HCC. The liver itself maintains an immunotolerant phenotype, as it is constantly exposed to antigens and must avoid overstimulation of the immune system. Regulatory T cells are a key mediator of this tolerance, as they are abundant in the liver at baseline, further amplified by Kupffer cell signaling, recruited from the peripheral blood through CCR6 [11]. A preponderance of Tregs over CD8+ TILs is associated with worse prognosis in HCC [11]. Although cytotoxic CD8+ T cells paradoxically secrete oncogenic lymphotoxins, large numbers of CD8+ TILs have been correlated with an improved survival in HCC after curative resection as they are the main tumor effectors. This observation has been made in other tumor types as well. Similarly, CD8+ cells specific to tumor antigens in the peripheral blood demonstrate antineoplastic activity with IFNγ. However, when these cells enter the tumor microenvironment and lose their cytotoxic abilities, they demonstrate what is termed T cell "exhaustion" [21]. The immune regulators CTLA-4 and PD-1 play a role in the reduced tumor lymphocyte effectiveness and "exhaustion" phenotype. CTLA-4 signaling helps maintain the preponderance of Tregs in both normal liver and HCC by inducing activity and differentiation of T cells into Tregs. CTLA-4 also increases IL-10 in dendritic cells which further activates Tregs and promotes a Th2 response associated with vascular invasion and metastases [21, 22].

This mechanism is also seen with PD-L1, as PD-1 and PD-L1 interaction with tumor microenvironment macrophages also leads to IL-10 expression. PD-L1 expression on tumor cells and other tumor microenvironment cells in HCC is induced quite readily under hypoxic conditions. Hypoxia-inducible factor-1 alpha levels mediate increased PD-L1 expression, and sorafenib treatment leads to reduced Tregs and increased PD-1 expression on Th1 cells [23].

Current Immunotherapy Data and Approvals in HCC

The use of immunotherapy agents in HCC, as with most systemic agents in HCC, is somewhat of a late development. This delay has generally been driven by theoretical concerns about safety in a population of patients with underlying liver disease. As a class, checkpoint inhibitors can have very broad and dramatic autoimmune effects. Essentially no organ system can be spared, though some are more common such as autoimmune colitis, pneumonitis, thyroid disorders, hypophysitis, and especially concerning here, immune-mediated hepatitis. So far, single-agent studies have not shown any unique toxicities in HCC patients but these have generally been done in clinical trial populations, carefully selected with typical clinical characteristics such as good performance status, Child-Pugh A liver disease, and otherwise adequate hematologic and other organ function. Experience with Child-Pugh B liver disease is limited, and initial retrospective case series with nivolumab suggest higher rates of all cause grade ≥ 3 adverse events [24].

Tremelimumab

Tremelimumab is a fully human IgG2 monoclonal antibody that binds to CTLA-4 expressed on activated T-lymphocytes, which was initially studied in a small study including 20 patients with HCV-related HCC [25]. Only 24% of patients had prior sorafenib. Of note, 43% had Child-Pugh Class B cirrhosis. Tremelimumab was given at a dose of 15 mg/kg intravenously every 90 days until disease progression, unacceptable toxicity, or up to 4 cycles RECIST criteria was used to assess antitumor activity with assessments only every 90 days. There were no complete responses (CRs). The partial response rate was 17.6%, disease control rate 76.4%, and median time to progression (TTP) was 6.48 months (95% CI 3.95–9.14). The most common clinical toxicities were generally low-grade rash, fatigue, anorexia, edema, ascites, and diarrhea. Laboratory abnormalities were common including low-grade hypoalbumineia, hyponatremia, and increased bilirubin. Notably, 43% of patients experienced a grade 3 transaminitis after the first infusion. This appeared transient, and none required intervention nor resulted in subsequent liver function decline. There were no treatment-related deaths. Interestingly, tremelimumab induced a decrease in HCV viral loads in a number of patients. After this study, there was no further single-agent development of tremelimumab in HCC and it is currently not approved for any cancer indication; however, tremelimumab is now being developed in combinations for HCC therapy as discussed below.

Nivolumab

Nivolumab is a fully human immunoglobulin G4 monoclonal antibody targeting PD-1 that blocks its interaction with its ligand, PDL-1. The CheckMate-040 study is a phase 1/2 open-label, non-comparative, dose escalation and expansion trial that evaluated single-agent nivolumab in patients with advanced HCC [26••] . Given concerns about the safety of PD-1 blockade in patients with underlying hepatitis and

cirrhosis, nivolumab was first evaluated in a dose-escalation phase in 3 cohorts including those with no viral hepatitis, those with HBV-related HCC, and those with HCV-related HCC. In the dose escalation phase ($n = 48$), there were no new toxicities seen, and a dose of 3 mg/kg every 2 weeks, the same as in other malignancies, was established in all 3 cohorts. In the dose expansion phase ($n = 214$), nivolumab was given in four cohorts: sorafenib untreated or intolerant without viral hepatitis, sorafenib progressors without viral hepatitis, HCV-infected, and HBV-infected. The objective response rate by blinded independent central review with RECIST 1.1 was 14.3% (95% CI 9.2, 20.8), with 3 complete responses (CRs) and 19 partial responses (PRs). These responses occurred within the first 3 months of treatment (median time to response of 2.8 months) and unlike other systemic treatments studied to date, the duration of response was durable with a median of 17 months (95% CI 6–24). Underlying etiology nor expression of PD-L1 correlated with efficacy.

Based on the CheckMate 040 study, nivolumab received accelerated approval for patients with HCC who have been previously treated with sorafenib and was based on the tumor response rate and durability of response [27]. This accelerated approval is conditional on the confirmation of this activity and safety in a phase 3 study. The phase 3 CheckMate 459 study is comparing overall survival with nivolumab vs sorafenib in the front-line setting (NCT02576509). This study has completed accrual, results are event-driven, and are eagerly awaited (Table 2).

With regard to safety, in the expansion phase, grade 3/4 treatment-related adverse events were seen in 40 (19%) patients and grade 3/4 treatment-related serious adverse events were seen in nine (4%) patients. Symptomatic treatment-related adverse events were comparable in patients with and without HCV or HBV infection. Adverse events led to discontinuation in 24 patients, and there were no treatment-related deaths. The profile was generally consistent with nivolumab in non-HCC studies though those generally excluded patients with chronic hepatitis. In the FDA label, serious adverse reactions occurred in 49% of patients; the most frequent being fever, ascites, back pain, general physical deterioration, abdominal pain, and pneumonia [28]. The most common adverse reactions were fatigue (38%), musculoskeletal pain (34%), pruritis (27%), diarrhea (27%), rash (26%), cough (23%), and decreased appetite (22%). Treatment-emergent grade 3/4 elevations in AST were 18%, ALT 11%, and bilirubin 7%. There were no cases of hepatic failure while on nivolumab.

While these events were generally manageable with supportive care, the guidance for managing changes in liver enzymes is different for patients with HCC than in other tumor types. The recommendations take into account that many patients with HCC have baseline lab abnormalities to start with; keeping in mind that patients had to have AST/ALT levels less than five times the upper limit of normal and total bilirubin levels of less than 3 mg/dL prior to inclusion in the 040 study (i.e., not having worse than grade 2 AST/ALT or bilirubin elevations at baseline). The FDA label also notes the absence of data for patients with total bilirubin greater than 3 mg/dL. Table 3 is a summary of lab abnormalities with corresponding corticosteroid recommendations and whether holding nivolumab instead of permanent discontinuation of nivolumab is warranted. Table 3 represents a combination of data from the FDA label and the ASCO 2018 management guidelines for immune-related adverse events [29•]. Of note, the ASCO guidelines do not differentiate between patients with HCC and those without. When considering patients across nivolumab studies, the FDA label states that immune-mediated hepatitis occurred in 1.8% (35/1994) of patients with a median time to onset of 3.3 months. All patients required steroids and two required the addition of mycophenolate. Complete resolution of occurred in 74% of patients treated with corticosteroids and recurred in around 29% of patients rechallenged with nivolumab. In the HCC 040 study, 5% of patients developed immune-related hepatitis requiring systemic steroids. A recently published review cites their center's own experience with adjunct immune suppression, noting more frequent need for agents like mycophenolate, azathioprine, or tacrolimus [30]. The paucity of data in this setting underscores that consultation with a hepatologist may be helpful. Also, with this high complete resolution rate and limited experience easily distinguishing autoimmune hepatitis from immune-mediated hepatitis from nivolumab, biopsy for diagnosis is unlikely necessary. A small histopathologic case series showed that absence of antinuclear antibodies, normal IgG levels, and minimal confluent necrosis with lobular hepatitis on biopsy may suggest nivolumab-mediated toxicity as compared to autoimmune hepatitis [31]. Patients should receive regular lab and clinical monitoring for liver decompensation and other potential side effects such as checking a serum electrolytes, CBC, and TSH regularly. The use of steroids are generally recommended for other grade 2 or worse autoimmune toxicities or in the setting of type 1 diabetes or thyroid disorders, medical management as indicated.

Pembrolizumab

Pembrolizumab is a humanized monoclonal IgG4 against PD-1, for HCC. The Keynote 224 study was a single-arm study evaluating pembrolizumab 200 mg intravenously every 3 weeks in patients with Child-Pugh A liver disease after treatment with sorafenib ($n = 104$) [32]. The overall response rate was 17% (1 CR and 17 PRs) by RECIST 1.1. Forty-four percent of patients had stable disease (SD), and a third of patients had progression as their best response. Median time-to-response was 2.1 months, and the median duration of response was not reached at the time of publication (range 3.1–

Table 2 Ongoing clinical trials with immunotherapy agents in HCC

Drug(s)	Study name	Phase	Line of therapy	Size	Trial identifier
Nivolumab	CheckMate 459	3	1st	726	NCT02576509
Durvalumab and tremelimumab	HIMALAYA	3	1st	1200	NCT03298451
Bevacizumab and qtezolizumab	IMbrave 150	3	1st	480	NCT03434379.
Pemrbolizumab	KEYNOTE 240	3	2nd	408	NCT02702401
Pembrolizumab	KEYNOTE 394	3	2nd	330	NCT03062358
Nivolumab	CA209-9DX	3	Adjuvant	530	NCT03383458
Pembrolizumab	AURORA	2	(Neo)adjuvant	50	NCT03337841
Avelumab		2	2nd	30	NCT03389126
Nivolumab and sorafenib		1	1st	40	NCT03439891
Nivolumab and cabozantinib		1/2	1st	620	NCT01658878
Nivolumab and ipilimumab		1/2	1st	620	NCT01658878
Nivolumab and INCAGN01949 (OX40 agonist)		1/2	1st	620	NCT01658878
Nivolumab and lenvatinib		1b	1st	26	NCT03418922
Nivolumab and regorafenib		1b	1st	40	NCT03347292
Pembrolizumab and lenvatinib		1b	1st	30	NCT03006926
Pembrolizumab and nintedanib		1b	2nd	18	NCT02856425
Nivolumab and galunisertib (TGF-beta receptor)		1b/2	2nd	75	NCT02423343
PDR001 and capmatinib (C-MET inhibitor)		1b/2	2nd	108	NCT02795429
PDR001 and sorafenib		1	1st	50	NCT02988440
Nivolumab and BMS-986183		1b/2	2nd	25	NCT02828124
Nivolumab and mogamulizumab (anti-CCR4)		1b/2	2nd	114	NCT02705105
Avelumab and axitinib		1	2nd	20	NCT03289533
Durvalumab and ramucirumab		1	2nd	114	NCT02572687
Durvalumab and guadecitabine (hypomethylating agent)		Ib	2nd	90	NCT03257761
Pembrolizumab and epacadostat (IDO1 inhibitor)		1/2	2nd	166	NCT03277352
Nivolumab and pexa-Vec (oncolytic virus)		1/2a	2nd	30	NCT03071094
Pembrolizumab and T-vec	MASTERKEY-318	1b/2	2nd	244	NCT02509507
Pembrolizumab and XL 888 (Hsp90 inhibitor)		1	2nd	50	NCT03095781
Pembrolizumab and p53 Vaccine		1	2nd	19	NCT02432963
Nivolumab, ipilimumab, and INCAGN01876 (anti-glucocorticoid-induced TNF receptor)		1/2	2nd	450	NCT03126110
MSB0011359 (a bifunctional fusion protein targeting PD-L1 and TGF-β)		1	2nd	114	NCT02699515
Nivolumab and C-122 (cereblon-dependent Cul4 E3-ligase complex modulating compound)		1/2	2nd	50	NCT02859324
Durvalumab/tremelimumab TACE, RFA, or cryoablation		1/2	Advanced	40	NCT02821754
Nivolumab and Y90		1/1b	Adjuvant Y90	35	NCT02837029
Nivolumab and Y90		2	Adjuvant Y90	40	NCT03380130
Nivolumab and Y90		2	Adjuvant Y90	40	NCT03033446
Pembrolizumab and Y90		1	Adjuvant Y90	30	NCT03099564
Pembrolizumab and TACE		1b	Adjuvant TACE	26	NCT03397654
Nivolumab and drug eluting bead (deb-)TACE		1	Adjuvant TACE	14	NCT03143270
Nivolumab or Pembrolizumab and transarterial tirapazamine embolization (TATE)		2a	Intermediate	40	NCT03259867
Pembrolizumab with SBRT		2	Intermediate	30	NCT03316872
Nivolumab/ipilimumab and SBRT		1	Intermediate	50	NCT03203304

14.6+ months), but 77% of patients had a response duration greater than or equal to 9 months. Median progression-free survival was 4.9 months (95% CI 3.4–7.2), and median overall survival (OS) was 12.9 months which compares favorably with the placebo control arms in the phase 3 second-line studies of around 8 months. Like with nivolumab, response

Table 3 Management of immune-related hepatitis in HCC

AST/ALT or total bilirubin elevation from baseline	Nivolumab dose interruption or dose discontinuation	Glucocorticoid therapy
Baseline AST/ALT normal, increase to 3–5 times upper limit of normal	Hold nivolumab dose; can consider resumption when lab abnormalities return to baseline	1–2 mg/kg of prednisone, taper around 4–6 weeks
Baseline AST/ALT 1–3 times upper limit of normal, increase to 5–10 times upper limit of normal	Hold nivolumab dose; can consider resumption when lab abnormalities return to baseline	1–2 mg/kg of prednisone, taper around 4–6 weeks
Baseline AST/ALT 3–5 times upper limit of normal, increase to 8–10 times upper limit of normal	Hold nivolumab dose; can consider resumption when lab abnormalities return to baseline	1–2 mg/kg of prednisone, taper around 4–6 weeks
AST/ALT at > 10 times upper limit of normal or total bilirubin greater than 3 times upper limit of normal	Permanently discontinue nivolumab; do not rechallenge	2 mg/kg methylprednisolone, taper around 4–6 weeks, may need adjunct therapy if no response after 3 days of therapy

did not correlate with etiology of HCC. Treatment-related adverse events occurred in 76 (73%) of 104 patients, which were serious in 16 (15%) patients. Grade 3 treatment-related events were reported in 25 (24%) of the 104 patients; the most common were increased AST ($n = 7$, 17%) patients, increased ALT ($n = 4$, 4%), and fatigue ($n = 4$, 4%). One grade 4 treatment-related event of hyperbilirubinemia occurred. More common lower grade adverse events included fatigue, puritus, and diarrhea. One death associated with ulcerative esophagitis was attributed to treatment. Immune-mediated hepatitis occurred in three (3%) patients. Other typical immune-mediated effects were seen including thyroid ($n = 9$) and adrenal disorders ($n = 1$), type 1 diabetes, colitis, and skin reactions. Exploratory biomarkers in the 224 study included not only the expression of PD-L1 in tumor cells (TPS) but also the expression of PD-L1 in the combined tumor and immune cells (CPS). Though numbers are small, there was an association of a higher overall response rate with a higher CPS ($p = 0.021$) versus TPS ($p = 0.088$). Overall response rate for CPS ≥ 1 vs < 1 was 32% vs 20% and 43% vs 22% for TPS $\geq 1\%$ vs $< 1\%$. Taken together, the activity and safety of pembrolizumab is comparable to the phase 2 data with nivolumab. Keynote 240 is a placebo-controlled, randomized phase 3 study of pembrolizumab versus placebo in the second-line setting in a Western population. This study has completed accrual and results are awaited (NCT02702401). Similarly, Keynote 394 is being conducted in an Asian population (NCT03062358) (Table 2).

Durvalumab

Durvalumab is a monoclonal antibody against PD-L1. In a single-arm study in advanced HCC, including both front line and second line, the response rate was 10.3% in 40 patients [33]. Durvalumab has also been evaluated in combination with the CTLA-4 blocking antibody tremelimumab in a small phase 2 study [34]. The adverse events with this combination did not demonstrate any increased risk with the combination and was as expected for these agents. There were no adverse events related to liver injury or liver failure. This study has reported an unconfirmed response rate of 25% (10/40 patients). This regimen is now being formally tested in a phase 3 study comparing single-agent durvalumab to the combination with a high and low dose of tremelimumab versus sorafenib (HIMALAYA study, NCT03298451).

Checkpoint Inhibitors in Combination with Locoregional Therapy

An initial study by Hansler et al. demonstrated increased cytolytic activity by tumor-specific CD8+ T cells after RFA treatment [35]. Further research showed that RFA not only increases the cells' activity but also may recruit TILs to the tumor with substantial increase in IFN gamma-producing T cells against tumor antigens such as AFP, MRP3, and hTERT [36]. Disease-free survival correlated with the presence of these TILs, leading to efforts to enhance this tumor response.

The anti-CTLA-4 antibody tremelimumab was investigated on an every 28 day schedule in the neoadjuvant setting prior to subtotal radiofrequency ablation (RFA) or transarterial embolization (TACE) (on day 36) and continued after the procedure as adjuvant treatment for 3 more cycles [37]. Tumor responses were seen in the primary tumors and other multifocal disease with prospective biopsies showing increases in TILs in response to treatment without major safety signals. Although the tumors at baseline already had TILs present and the TACE or RFA's contribution to response was unclear, it showed that the tumor immune response can be augmented without major safety concerns. There is ongoing interest in the combination of checkpoint blockade with local therapies such as TACE, RFA, and radiation therapy, with the hope that these approaches will not only induce responses at the treatment site but also at distant sites (the so-called abscopal effect). Many studies are currently underway with various modifications of the timing of checkpoint blockade relative to the locoregional therapy (Table 2).

Checkpoint Inhibitors in Combination with Other Targeted Agents

Sorafenib was FDA approved in 2007 for first-line treatment of unresectable HCC. Its efficacy was postulated on its antiangiogenic effects (e.g., VEGFR, PDGFR inhibition) and its antiproliferative effects (c-Kit, FLT-3, and targets Raf/MEK/ERK signaling through its Raf inhibition) [SHARP] [14]. Only later was it identified that sorafenib treatment also increases the ratio of PD-1+ effector T cells to PD-1+ Tregs, the degree of which was correlated with overall survival [38]. Given mechanisms of immune escape involve tumor adaptive response to hypoxia, there lies a great opportunity to enhance response to TKIs by combining with checkpoint blockade.

Phase 1 trials in renal cell carcinoma have demonstrated the safety of these PD-1/PD-L1 and TKI combinations, with pembrolizumab/avelumab and axitinib/lenvatinib being the primary agents studied to date. The results from the Study 111 RCC cohort and the JAVELIN Renal 100 led to breakthrough therapy designation for lenvatinib/pembrolizumab and axitinib/avelumab, respectively, with only the JAVELIN Renal 100 results published for review [39]. On this background, many studies for these combinations in HCC are underway (Table 2).

The combination of VEGF antibody bevacizumab and the PD-L1 antibody atezolizumab has shown promising results in a small phase 1 study with confirmed response rate of 60% by RECIST and no new safety signals [40]. This combination was recently awarded a breakthrough designation by the FDA and currently in a phase 3 study vs sorafenib (ImBRAVE 150, NCT03434379) [41]. Similarly, the combination of lenvatinib and pembrolizumab has shown unconfirmed mRECIST responses of 40% and no new safety signals as well [42]. Numerous other targets are being pursued in combination with checkpoint blockade. A partial listing is included in Table 2.

Clinical Monitoring of Patients on Checkpoint Inhibitors

As discussed above, patients should receive regular lab and clinical monitoring for liver decompensation and other potential side effects with corticosteroid therapy as needed for severe immune-related adverse events. The initial appearance of progression on scans by RECIST criteria followed by improvement on second evaluation is known as pseudoprogression, occurring anywhere from 3 to 12% of all patients treated with checkpoint blockade as captured by immune-related response criteria (irRECIST) [43]. There are only a few case reports of this occurrence in patients with HCC. As with other systemic treatments in advanced HCC, imaging every 2–3 months would be appropriate while on PD-1/PD-L1 inhibitors, and in the absence of symptomatic progression, the appearance of new lesions should be confirmed on follow-up scans.

Conclusions

After a decade of no significant advances in the systemic treatment of HCC, we are now seeing a series of practice changing studies. Immunotherapy-based approaches have changed the treatment landscape of numerous solid tumors and are now coming of age in HCC. While nivolumab has an approval in the second-line setting, this was based on an accelerated approval and confirmation in a phase 3 study is awaited. Critical to the success of these agents will be managing the side effects of this class in a population of patients with underlying liver disease. The next several months will see the results of pivotal phase 3 immunotherapy studies that have the potential to set new standards of care in the management of advanced HCC. In addition, early data with novel combinations of immunotherapy and other agents are showing unprecedented response rates. To date, response rates and progression-free survival have not been good predictors of survival in HCC, but perhaps, with this new class, and the impressive tumor control we are seeing that will change in the future. The potential for these agents to impact earlier stages of disease is being explored. Ongoing research will help define the optimal sequencing of these agents in the context of other active agents in HCC. In summary, we are in an age of impressive progress in HCC, the result of ongoing research efforts despite a decade of negative results. There is little doubt the next decade will not be the same for our patients.

Compliance with Ethical Standards

Conflict of Interest Richard S. Finn reports personal fees from Astra Zeneca, Bayer, Bristol Myers Squibb, Eisai, Eli Lilly, Pfizer, Novartis, Merck, Roche/Genentech, during the conduct of the study. Anthony Bejjani declares no potential conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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