

# Immunotherapy of Hepatocellular Carcinoma: Facts and Hopes

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## Abstract

Treatment of patients with hepatocellular carcinoma (HCC) in the advanced stage remains a great challenge, with very few drugs approved. After decades of failure of immune therapies, immune checkpoint inhibitors have emerged as potentially effective treatments for patients with HCC in the advanced stage. Immune checkpoints, including human cancer, cytotoxic T-lymphocyte protein 4 (CTLA-4), and programmed cell death protein 1 (PD-1), are surface proteins expressed in a variety of immune cells and mostly provide immunosuppressive signals. Monoclonal antibodies able to block these molecules have shown anti-tumor activity against a wide spectrum of human cancers. Clinical experience with checkpoint inhibitors in HCC includes early trials with the anti-CTLA-4 agent tremelimumab and a large phase II trial with the anti-PD-1 agent nivolumab. The

latter has shown strong activity particularly as second-line therapy, both in terms of tumor response and patient survival. At least three topics should be the focus of future research: (i) the search for activity in patients at less-advanced stages, including the adjuvant treatment of patients with resectable or ablatable tumors; (ii) the enhanced efficacy of combination therapies, including particularly the combination with those targeted and locoregional therapies that may have a synergistic effect or act upon mechanisms of primary or acquired resistance to checkpoint inhibitors; and (iii) the identification of clinical features and serum or tissue biomarkers that would allow a better patient selection for individual treatments. Hopefully, ongoing trials will help to design better treatments in the future. *Clin Cancer Res*; 24(7); 1518–24. ©2017 AACR.

## Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is now the second most common cause of cancer-related death worldwide (1). Most HCCs arise on a cirrhotic liver, with chronic infection by hepatitis B and hepatitis C viruses as the main cause, followed by other etiologies of cirrhosis, including alcohol consumption and fatty liver disease associated with the metabolic syndrome (2). Immune therapies had been repeatedly but unsuccessfully tested in HCC for decades (3). The objective clinical activity of immune checkpoint inhibitors has changed this vision, and the near future will very likely take immunotherapy into the frontline of systemic treatment of HCC. This review covers the available information about the use of immune therapies to treat HCC and reflects on the opportunities prompted by current evidence.

## The Facts

Tumor progression depends on the escape from immunologic surveillance. The mechanisms of escape are complex and incompletely understood, yet they have provided the main rationales for the development of immunotherapy in HCC (4). These mechanisms include defective antigen presentation,

effector T-cell dysfunctions, alterations in immune checkpoint molecules, regulatory T cells (Treg), immunosuppressive myeloid cells, and disarray of cytokine profiles.

Immune checkpoints are best defined as surface glycoproteins that deliver inhibitory signals for T- or natural killer cell activation and are crucial for the induction and maintenance of tumor immune tolerance. Immune checkpoints and their ligands are expressed on different cell types involved in the immune response, including B and T cells, natural killer cells, dendritic cells, tumor-associated macrophages, monocytes, and myeloid-derived suppressor cells. Under physiologic conditions, most of these molecules play immunosuppressive activities that prevent T-cell overactivation during immune responses against infection and thereby limit collateral tissue damage. The two most well-studied immune checkpoints in human cancer are cytotoxic T-lymphocyte protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), but there are many more with functional evidence for very relevant roles in the immune response against cancer.

CTLA-4 is expressed on activated T cells and counteracts T-cell costimulation via CD28 in immune synapses upon antigen presentation. CTLA-4 is also constitutively expressed on Tregs, where it is required for effector T-cell inhibition through various mechanisms (5). Yet, the role of CTLA-4 is not restricted to the T-cell priming phase because CTLA-4 also promotes immunosuppression in the tumor microenvironment by enhancing Treg activity and differentiation as well as interfering with the function of dendritic cells (6).

PD-1 is considered a key regulatory factor in the effector phase of T-cell-mediated immune responses. It is expressed by activated T cells, B cells, natural killer cells, Tregs, myeloid-derived suppressor cells, monocytes, and dendritic cells. PD-L1 and PD-L2 are the ligands of PD-1, and they are expressed on

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hematopoietic cells (PD-L1 and PD-L2) and on different types of parenchymal cells (PD-L1). Upon binding to its ligands, PD-1 inhibits CD8<sup>+</sup> T-cell activation by blocking the T-cell receptor (TCR) and CD28 signaling (7). Reportedly, it also inhibits CD4<sup>+</sup> activation and proliferation through increased secretion of IL10 and directly favors Treg functions. Cancer cells may also express PD-L1 and PD-L2 on their surface and use this mechanism as a key mechanism to escape from immune surveillance. In the tumor microenvironment, there is chronic antigen exposure, and IFN- $\gamma$  produced by tumor-associated antigen-specific T cells induces PD-1 expression on reactive T lymphocytes and upregulates PD-L1 in antigen-presenting cells and tumor cells via an IFN- $\gamma$ -dependent loop (8). PD-1/PD-L1 engagement then blocks TCR and CD28 signaling to inhibit T-cell proliferation and secretion of cytotoxic mediators, reaching a status often referred to as T-cell exhaustion (9). Blocking PD-1 and CTLA-4 immune checkpoints has several consequences in the malignant tissue that include the amplification of the T-cell response, avoidance of T-cell exhaustion, and in some experiments, the reduction of Treg numbers and function.

The discovery of agents in the form of monoclonal antibodies able to block immune checkpoint molecules has transformed the treatment of cancer. Over the last 5 years, immune-based therapies of this sort have shown that they can prolong patient survival in a wide variety of tumors. CTLA-4 or/and PD-1/PD-L1 blockade has become the standard of care for patients suffering from metastatic melanoma, and PD-1 blockade has been approved for patients with refractory Hodgkin disease, metastatic non-small cell lung cancer, renal cell carcinoma, head and neck cancer, microsatellite instable carcinomas, Merckel cell carcinoma, urothelial carcinoma, and very recently, HCC.

### Clinical Experience with the Use of Checkpoint Inhibitors in HCC

The available information about the use of immune checkpoint inhibitors in the treatment of HCC is summarized in Table 1. Tremelimumab (a fully human IgG2 monoclonal antibody that blocks CTLA-4 binding to CD80/86) was first evaluated in a small phase II trial that targeted patients with HCC and chronic hepatitis C virus infection (10). Twenty-one patients with advanced disease were enrolled, including a significant proportion (42.9%) of patients in Child-Pugh B class. Despite receiving what is now considered a suboptimal dose regimen of tremelimumab, a notable disease control rate of 76.4% was observed among 17 evaluable patients, including three partial responses and four prolonged (>6 months) disease stabilizations. Median time to

progression was 6.48 months [95% confidence interval (CI), 3.95–9.14 months], and median overall survival (OS) was 8.2 months (95% CI, 4.64–21.34 months). This OS is similar to that observed in the placebo arms of different second-line trials (11–15) in which only Child-Pugh A class patients were eligible. An increase in circulating Treg percentages following tremelimumab was reported, but the lack of paired pre- and on-treatment tumor biopsies precludes any interpretation on the mechanism behind the antitumor activity. Tremelimumab was well tolerated, with few patients experiencing grade 3 disabling adverse events (AE), even in the presence of liver dysfunction. In a second small pilot trial, incomplete tumor ablation using percutaneous radiofrequency or transarterial chemoembolization (TACE) was combined in an attempt to enhance the effects of tremelimumab by inducing immunogenic tumor cell death and local inflammation (16). In this study, liver function was preserved in most patients, all etiologies were included, and the dose of tremelimumab was the current standard. Nineteen patients were evaluable for response because they had measurable target lesions that were not ablated by radiofrequency or TACE. A disease control rate of 89% was reported, including five partial responses (26%) and five prolonged disease stabilizations. A median OS of 12.3 months compares well with placebo-treated patients in clinical trials addressing the second-line setting. The better survival in this second trial could be explained on the basis of a better liver function, but a true systemic activity of prior ablation may not be ruled out.

The encouraging results from the first tremelimumab trial were an invitation to similarly test anti-PD-1 agents. As a matter of fact, a high number of tumor-infiltrating cytotoxic T cells expressing PD-1 may predict an earlier and more likely disease progression among patients with HCC who have their tumors surgically resected (17). Nivolumab (a fully human IgG4 monoclonal antibody that blocks PD-1 interaction with PD-L1 and PD-L2) was the first to be tested. Patients with HCC with different etiologies, preserved liver function (Child-Pugh A class), and intermediate or advanced tumors who were candidates for systemic therapy (most of them previously treated with sorafenib) were included in a phase Ib/II, open-label, dose-escalation trial (18). Every 2 weeks, patients received doses that ranged from 0.3 to 10 mg/kg (dose-escalation cohort,  $n = 48$  patients) or a fixed dose of 3 mg/kg (expansion cohort,  $n = 214$  patients). Treatment was very well tolerated in spite of frequent, concurrent inflammatory liver conditions. The MTD was not reached, and the most frequent AEs such as hypertransaminasemia (20%), rash (23%), pruritus (21%), and diarrhea (13%) were observed at similar rates through dose levels and etiology cohorts. Immune-related

**Table 1.** A summary of efficacy data from clinical trials of immune checkpoint inhibitors in advanced HCC

Agent/dose	n	Sorafenib exposure	ORR/DCR	Median survival	Reference
Tremelimumab 15 mg/kg q 3 months	21	Naive, intolerant, or progressed to sorafenib	3/17 (17.6%) PR 13/17 (76.4%) DCR	8.2 months	(10)
Tremelimumab 3.5–10 mg/kg q 28 days + ablation	32	Progressed to sorafenib	5/19 (26.3%) PR	12.3 months	(16)
Nivolumab 3 mg/kg q 15 days <sup>a</sup>	80	Naive to sorafenib	1/80 (1.2%) CR 17/80 (21.2%) PR 50/80 (62.5%) DCR	28.6 months	(19)
Nivolumab 3 mg/kg q 15 days <sup>a</sup>	182	Intolerant or progressed to sorafenib	7/182 (3.8%) CR 27/182 (14.8%) PR 114/182 (62.6%) DCR	15–15.6 months	(19)

Abbreviations: CR, complete response; DCR, disease control rate; ORR, overall response rate; PR, partial response; q, every.

<sup>a</sup>Dose from 0.3 mg/kg to 10 mg/kg in the dose-escalation cohort.

hepatitis requiring steroid therapy occurred very rarely, only 3% of patients discontinued nivolumab due to treatment-related AEs, and no treatment-related deaths were reported.

Very persuasive signs of efficacy were found. RECIST 1.1 objective tumor responses were reported in 15% of patients in the dose-escalation cohort and 20% of patients in the expansion cohort. Importantly, they were clinically meaningful, durable responses that occurred mostly during the first 3 months on treatment and lasted for a median of 17 months in the more mature dose-escalation cohort. Responses occurred at a similar rate across different etiologies, and both in sorafenib-naïve and sorafenib-experienced patients. An additional 45% of patients had stable disease that was frequently durable too, lasting more than 6 months in most cases. These signs of efficacy were consistent with the more recently reported median OS of 28.6 months [95% CI, 16.6–non-estimable (NE)] in the population naïve to sorafenib and 15.6 months (95% CI, 13.2–18.9) in the much larger population exposed to sorafenib (90% sorafenib progressors; ref. 19). This OS in second-line systemic treatment advantageously compares with any other phase II or III clinical trial of targeted agents, including regorafenib, the first agent shown to prolong survival following sorafenib in a selected group of sorafenib-tolerant patients with preserved liver function (15). On the basis of these data, the FDA recently granted accelerated approval to nivolumab for the treatment of HCC in patients who have been previously treated with sorafenib. A randomized, nivolumab-versus-sorafenib, phase III clinical trial (NCT02576509) is fully recruited, and its results are expected in 2018.

## The Hopes

### Hope for a broad spectrum of activity

The story of drug development for HCC has been disappointing in the years following the approval of sorafenib for the treatment of patients in the advanced stage. In the second-line setting, several drugs failed to show signs of activity in phase II trials or to prove superior to placebo in phase III trials, whereas in first-line, phase III trials, no agent or combination of agents did better than sorafenib. Very recently, an increase in survival was shown in patients with HCC who had tolerated sorafenib but eventually had radiologic progression and were next treated with regorafenib

(15). In this dire scenario, sorafenib failed to show antitumor activity when given in combination with locoregional therapies such as TACE (20) or as adjuvant therapy after resection or percutaneous ablation (21).

Following the aforementioned strong objective activity of nivolumab in the second-line scenario, phase III trials are testing the activity of pembrolizumab (another PD-1-blocking agent) against best supportive care for the treatment of sorafenib-exposed patients (NCT02702401) and the effect of nivolumab against sorafenib for patients naïve to systemic therapy (NCT02576509). Although we wait to see if the results of these trials change the current paradigm in the treatment of advanced HCC, the facts support the investigation of PD-1 blockade in earlier scenarios where there are still big unmet clinical needs, for instance, in combination with locoregional treatments for patients in the intermediate stage. TACE is the mainstay of treatment for these patients (22), and the combination of TACE and nivolumab has to be tested. Radioembolization using yttrium-90-loaded microspheres, also called selective internal radiotherapy (SIRT), is used in many tertiary care centers to treat those patients who are not good candidates for TACE, have failed TACE, or may benefit from the superior downstaging ability of SIRT (23). Radiation is considered an inducer of immunogenic cell death (24), and immune-mediated abscopal effects of radiation have already been reported in patients with HCC treated with external beam radiation (25, 26) and SIRT (27). Not surprisingly, the combination of SIRT and anti-PD-1 agents is already being explored in phase II trials summarized in Table 2. Beyond this point, it is worth testing the role of nivolumab in the adjuvant treatment of patients in the early stage with tumors that have been resected or ablated but remain at a high chance of recurrence, including those with microvascular invasion or tumors larger than 3 cm (21). The demonstrated benefit of ipilimumab for the adjuvant treatment of stage III melanoma [5-year recurrence-free survival (RFS): 40.8 vs. 30.3%, HR, 0.76,  $P < 0.001$ ; 5-year OS: 65.4 vs. 54.4%, HR, 0.72,  $P = 0.001$ ] supports this strategy (28).

Finally, there is a unique and challenging subset of patients that deserves special attention, that is, those in whom HCC recurs after liver transplantation. Organ transplantation has been an exclusion criterion in every clinical trial testing checkpoint inhibitors, and there are two main concerns in

**Table 2.** Phase II trials testing the combination of PD-1/PD-L1 blockade with other agents specifically for the treatment of HCC

Anti-PD-1/PD-L1 agent	Combining agent	Mechanism of action	Patients	ClinicalTrials.gov identifier
<i>Combinations with other immunotherapies</i>				
Nivolumab	Ipilimumab	Anti-CTLA-4	620 <sup>a</sup>	NCT01658878
Durvalumab	Tremelimumab	Anti-CTLA-4	144	NCT02519348
Nivolumab	Pexa-Vec (JX-594 or pexastimogene devacirepvec; Jennerex Biotherapeutics)	GM-CSF-armed oncolytic virus	30	NCT03071094
<i>Combinations with targeted agents</i>				
PDR001	FGF401	FGFR4 inhibitor	238	NCT02325739
PDR001	INC280	c-met inhibitor	108	NCT02795429
Nivolumab	Galunisertib	TGF- $\beta$ inhibitor	75	NCT02423343
Nivolumab	CC-122	Pleiotropic pathway modifier	50	NCT02859324
PDR001	Sorafenib	Multi-TKI	50	NCT02988440
Pembrolizumab	Lenvatinib	Multi-TKI	30	NCT03006926
<i>Combinations with locoregional therapies</i>				
Nivolumab	TACE	Ischemia	14	NCT03143270
Nivolumab	Y90	Beta radiation	40	NCT03033446
Nivolumab	Y90	Beta radiation	35	NCT02837029
Pembrolizumab	Y90	Beta radiation	30	NCT03099564

Abbreviation: TKI, tyrosine kinase inhibitor.

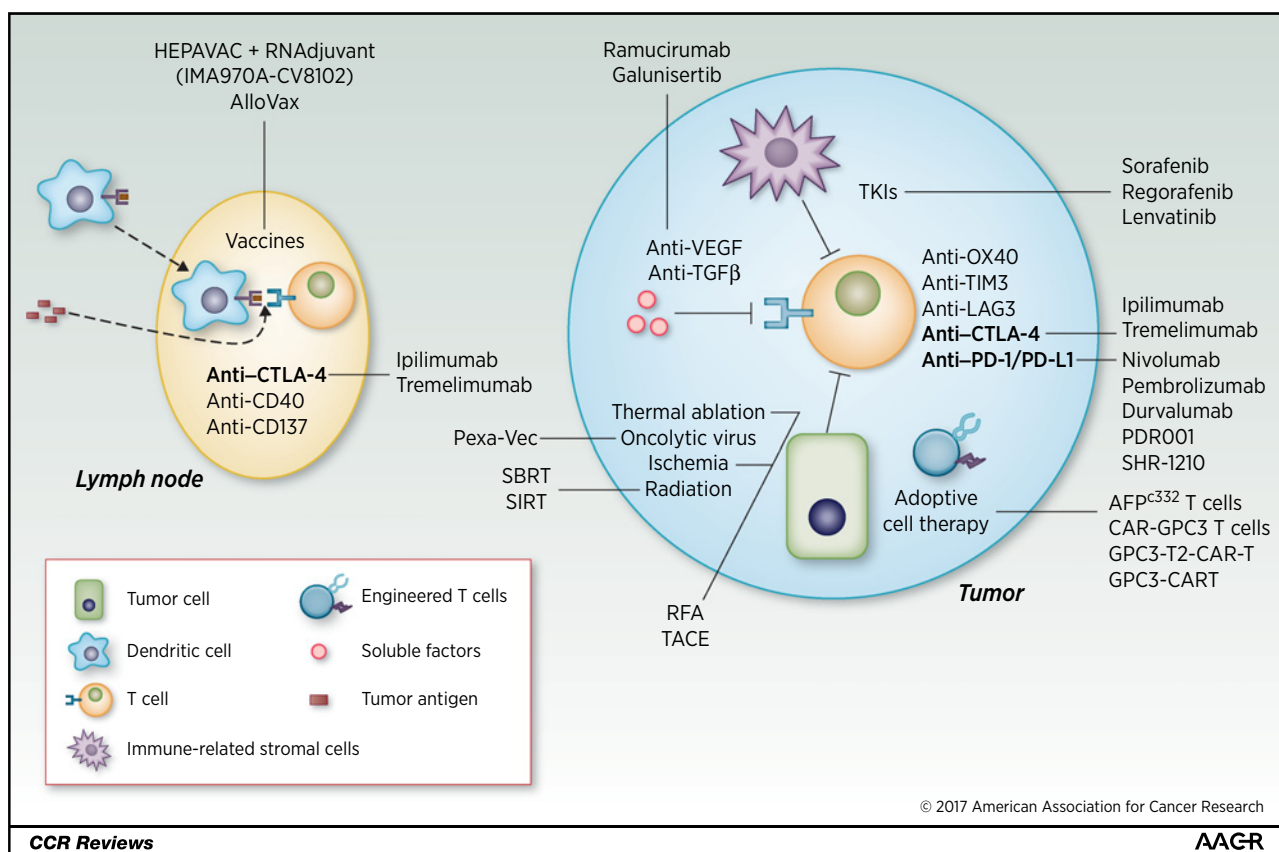
<sup>a</sup>Includes nivolumab monotherapy.

this population. First, checkpoint inhibitors could precipitate allograft rejection by activating T cells specific for non-self-antigens expressed by the allograft. There is little doubt that the PD-1/PD-L1 pathway is involved in liver allograft rejection. In animal models, PD-L1 upregulation on liver allograft cells plays an important role in the apoptosis of immune-infiltrating cells, thus contributing to spontaneous tolerance (29). In humans, several cell types, including hepatocytes and cholangiocytes, express PD-L1, whereas allograft-infiltrating T cells abundantly express PD-1. Furthermore, PD-L1 blockade enhances allogeneic proliferative responses of these graft-infiltrating T cells *in vitro* (30). Off-label use of nivolumab in two young patients with posttransplant recurrent, refractory fibrolamellar HCC was followed by a rapid and irreversible acute liver rejection that resulted in a fatal outcome (31). The role of CTLA-4 in liver allograft rejection is not so well understood, but treatment with a CTLA-4/Ig fusion protein prevents early rejection in an animal model of liver transplantation (32). Off-label use of ipilimumab in two patients who developed melanoma after liver transplantation was not followed by organ rejection or immune-related AEs (33, 34). A

second concern is the potential for reduced efficacy due to immunosuppression because checkpoint inhibitors require competent T-cell populations to exert their antitumor effects. One of the two patients with melanoma treated with ipilimumab showed an intense and durable tumor response, providing a proof of concept that low-dose immunosuppression might not interfere with the antitumor activity of anti-CTLA-4 agents. Hence, until we get experience from prospective studies, the use of any checkpoint inhibitor but particularly PD1/PD-L1–blocking agents should be avoided in the posttransplant setting.

#### Hope for increased efficacy

At least 30% of patients have unequivocal primary progression to checkpoint inhibitors. Understanding resistance to anti-PD-1/PD-L1 therapies is important to improve their outcome by means of combination therapies (Fig. 1). Mechanisms of resistance should affect tumor immunogenicity, antigen presentation, and generation of effector T cells; contact of antigen and PD-L1 by tumor-specific T cells; effective tumor cell killing; or the induction of immunologic memory (35). Hence, sensitivity to anti-PD-1



**Figure 1.**

Potential combination therapies based on synergies with and mechanisms of resistance to immune checkpoint inhibitors. Immune-related stromal cells include dendritic cells, Tregs, tumor-associated macrophages, or myeloid-derived suppressor cells. Soluble factors include TGF- $\beta$ , VEGF, indoleamine 2,3-dioxygenase (IDO), and others. AlloVax (anticancer vaccine consisting of Chaperone Rich Cell Lysate as the source of tumor antigen and activated allogeneic Th1 memory T cells containing cytolytic granules; Immunovatives Therapies); HEPAVAC (IMA970A or multipeptide-based HCC vaccine; Immatics Biotechnologies); Pexa-Vec (JX-594 or pexastimogene devacirepvec; Jennerex Biotherapeutics); RNAadjuvant (CV8102 or RNA-based adjuvant; CureVac). RFA, radiofrequency ablation; TKI, tyrosine kinase inhibitor; SBRT, stereotactic body radiation therapy.

therapy could be enhanced by (i) priming adaptive responses through therapies that release tumor antigens (radiotherapy or chemotherapy) or cancer vaccination strategies (36); (ii) enhancing antigen presentation and T-cell stimulation by intratumoral delivery of oncolytic virus or RNA adjuvants (37); (iii) enhancing dendritic cell function with agents that inhibit VEGF and TGF- $\beta$  (38); (iv) removing immunosuppressive cells such as Tregs from the tumor microenvironment using anti-CTLA-4 or anti-OX40 agents (39, 40); or (v) providing further T-cell empowering through agonistic antibodies that target immunostimulatory molecules such as CD40 or CD137 (41). It is possible that to make the most of immunotherapy, we will have to eventually move into the use of triplets, as suggested by a combination of PD-L1 blockade and CD137 plus OX40 agonists against spontaneous liver cancer in transgenic mice (42).

The interest in the combination of checkpoint inhibitors with sorafenib and other tyrosine kinase inhibitors is powered not only by the consistent efficacy of sorafenib in advanced HCC but also by potential mechanisms of antitumor synergy. Sorafenib also alters macrophage polarization *in vitro* and partially inhibits macrophage activation in patients (43). Finally, 4 weeks of sorafenib therapy reduces circulating Foxp3<sup>+</sup> Tregs and increases CD4<sup>+</sup> PD-1<sup>+</sup> T cells in patients with HCC, and both effects are associated with improved survival (44). In animal models, the combination of PD-1 blockade with sorafenib has no additive effect, but the combination with lenvatinib synergistically upregulates IFN signaling-related genes and increases memory T cells in association with an increased antitumor effect (45).

When it comes to the strategies under current development, very different combinations of checkpoint inhibitors with other therapies are being tested (Table 2). They are frequently based on the potential additive effect of a therapy with treatment benefit that is already proven (sorafenib) or is being investigated (ramucirumab, cabozantinib). Yet, some combinations try to exploit synergistic effects (tumor vaccines, oncolytic virotherapy) or to avoid primary resistance (anti-CTLA-4 plus anti-PD1/PD-L1, tumor vaccines). In preclinical models, combination with Toll-like receptor (TLR) agonists enhances the antitumor effect of sorafenib through changes in the tumor microenvironment that include activation of local natural killer cells, macrophages, and dendritic cells; decreased expression of PD-1 in tumor-infiltrating CD8<sup>+</sup> cells; and reduction in tumor infiltration by myeloid-derived suppressor cells (46). Concomitant CTLA-4 and PD-1/PD-L1 blockade with ipilimumab and nivolumab has shown an impressive overall response rate in patients with metastatic melanoma. It is too early to say if there is meaningful clinical benefit in the combination over nivolumab because over 40% of patients have to discontinue this combination immunotherapy due to immune-related serious AEs. Having said so, this combination is of great interest in HCC because both types of agents may have clinical activity. As a consequence, clinical trials testing the combinations of nivolumab plus ipilimumab and durvalumab plus tremelimumab are in progress (Table 2).

Other immunotherapies such as adoptive chimeric antigen receptor T (CART) cells redirected to glypican, engineered-TCR cells directed against alpha-fetoprotein, and cytokine-induced killer cells are under clinical development. It is too early to say whether adoptive T-cell therapy will find a niche in HCC, but it is worth mentioning that in patients with lymphoma, combination of anti-CD19 CART cells and PD-1 blockade

attains synergistic effects, as described in relapsed patients and mouse models (47, 48).

### Hope for improved patient selection

With four drugs showing activity in advanced HCC (sorafenib, regorafenib, lenvatinib, and nivolumab), we need tools that may help us in selecting the best individualized option. For first-line treatment, we should wait for the subgroup analysis of the nivolumab, phase III trial to see if patient characteristics may help in this regard. For second line, contraindication or poor tolerability to sorafenib defines a subpopulation perhaps better served by nivolumab. Nevertheless, it would be great to have clinical indicators and serum or tissue biomarkers with a strong predictive value either pretreatment or early on treatment.

Regarding clinical factors, subgroup analysis of the ongoing first-line, controlled trial will provide precious information. For tremelimumab, patients with objective remissions in non-ablated lesions had higher post-tremelimumab CD3<sup>+</sup> and CD8<sup>+</sup> T-cell infiltration compared with nonresponders (16), although a cutoff value was not identified. For nivolumab, we only have data for PD-L1 expression on tumor cells. Even with a low cutoff value for positivity of 1% of cells stained for PD-L1 expression, there was only a nonstatistical trend toward a higher response rate among patients with PD-L1 expression. Tumor samples in this analysis could be fresh or archival, but it seems unlikely that PD-L1 expression could serve as a component of clinically putatively predictive biomarker algorithms. Whether other serum or tissue biomarkers could be useful is still an open question. This includes particularly PD-L1 expression in stromal cells, infiltrating-cell subsets, and the nonsynonymous mutational load. Tumors with a low mutation rate (associated with fewer neoantigens) such as pancreas and prostate are poorly immunogenic and most often resistant to anti-PD-1 agents (49). The combination of PD-L1 expression and high mutational burden may have increased sensitivity for the prediction of response (50). We are starting to improve our understanding of the intricate patterns of T-cell populations inside HCC tumors. Around one fourth of resected HCC nodules show high expression levels of PD-1 and PD-L1 and an enrichment of signatures identifying immune cell subsets (T cells, CD8<sup>+</sup> T cells), immune-related genes (TCR components, chemokines), IFN-signaling genes, and other inflammation-related genes such as TGF- $\beta$  (51). Interestingly, there were no differences in the mutational load between this so-called immune class and other tumor nodules. Furthermore, it seems that the preferential accumulation of Tregs and exhausted CD8<sup>+</sup> T cells in HCC is a result of local expansion of these cells mainly recruited from the periphery (52). We will have to wait until clinical trials show if these molecular characteristics define a subgroup of patients highly responsive to checkpoint inhibition or other immunotherapeutic strategies.

### Disclosure of Potential Conflicts of Interest

I. Melero reports receiving commercial research grants from Alligator, Bristol-Myers Squibb, and Roche and is a consultant/advisory board member for AstraZeneca, Bayer, Bristol-Myers Squibb, Lilly, Merck Serono, Roche, Servier, and Tusk. B. Sangro reports receiving speakers bureau honoraria from Bayer and Bristol-Myers Squibb and is a consultant/advisory board member for Adapimmune, AstraZeneca, Bayer, Bristol-Myers Squibb, and Onxeo. No potential conflicts of interest were disclosed by the other author.

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