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The Current Landscape of Immune Checkpoint Blockade in Hepatocellular Carcinoma A Review

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Abstract

IMPORTANCE—For more than a decade, sorafenib has been the only systemic treatment option for patients with advanced hepatocellular carcinoma (HCC). However, rapid progress over the past few years led to approval of other angiogenesis inhibitors and several immune checkpoint blockers (ICBs) that have been added to the treatment armamentarium for advanced HCC. Moreover, the recent success of a combination of bevacizumab with atezolizumab signals an important change in the front-line treatment of HCC.

OBSERVATIONS—This review summarizes rapidly emerging clinical data on the promise and challenges of implementing ICBs in HCC and discusses the unmet need of biomarkers to predict response or resistance to therapy. Two strategies to target immunosuppression in tumors are also discussed: one proven (vascular endothelial growth factor pathway inhibition) and one currently under investigation (transforming growth factor-β pathway inhibition). The rationale and preliminary evidence on how their inhibition may reprogram the immunosuppressive milieu and enhance the efficacy of ICBs in HCC are reviewed.

CONCLUSION AND RELEVANCE—The recent successes and failures of angiogenesis inhibitors and ICBs, alone and in combination, have provided important insights into how to implement this novel systemic therapy in HCC and led to new avenues to enhance immunotherapy efficacy in this disease.

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a leading cause of cancer-related mortality. Early HCC can be treated curatively with surgery or

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ablation, but at advanced stages, available HCC treatments (eg, transarterial chemoembolization, systemic therapies) are merely palliative.[1] The development of the multityrosine kinase inhibitor (mTKI) sorafenib represented the first systemic therapy for advanced HCC.[2] While sorafenib was the only systemic therapy option for more than a decade, the field has evolved rapidly over the past 4 years.[1] Four more agents succeeded in phase 3 trials and were eventually approved: lenvatinib mesylate (mTKI) in front-line treatment and regorafenib, cabozantinib S-malate (both mTKIs), and ramucirumab (anti-vascular endothelial growth factor [anti-VEGF] receptor(R)2) in second-line treatment.[1] In addition, immune checkpoint blockers (ICBs) against the programmed cell death protein (PD)-1 and cytotoxic T lymphocyte antigen 4 have been approved for HCC in second-line treatment.[3–5] Fueled by this progress, a large number of studies are currently testing ICBs worldwide, alone or in combination with other systemic or locoregional therapies.

There is a rationale supporting the use of immunotherapy in liver cancer.[6] While HCC could be immunogenic, the tumor cells and the infiltrating stromal and immune cells promote an immunosuppressive tumor microenvironment (TME), including by upregulation of immune checkpoint molecules on their surface. Moreover, the tolerogenic liver environment, as well as chronic inflammation caused by the underlying liver disease present in most patients with HCC, further enhance immunosuppression, which enables the cancer cells to evade immune surveillance and potentially resist ICB treatment.[6]

In this review, we summarize recent clinical data on the use of ICBs in HCC and discuss the need for biomarkers to estimate the probable response or resistance to immunotherapy. We also elaborate on the roles of 2 of the pathways known to contribute to tumor immunosuppression: the VEGF and transforming growth factor (TGF)-β pathways. We summarize the rationale and preliminary evidence on how inhibition of these pathways may reprogram the immunosuppressive TME and enhance the efficacy of ICBs in HCC.

ICBs in Advanced HCC

Several ICBs have been tested in clinical phase 1, 2, and 3 trials in advanced HCC, either alone or in combination with targeted therapies or other ICBs. Response rates to ICB monotherapy ranged from 15% to 23% and increased to approximately 30% after combination treatment (Table 1[3–5,7–16] and Table 2).[17–19] Based on durable antitumor responses from phase 2 trials of nivolumab and pembrolizumab (both anti–programmed cell death protein 1 [PD-1] antibodies) and nivolumab with ipilimumab (anti–cytotoxic T lymphocyte antigen-4 antibody) combination in HCC, the US Food and Drug Administration granted conditional approval for these ICBs.[3–5,7,8] The CheckMate 040 study tested nivolumab alone or with ipilimumab and reported an overall response rate (ORR) of 22.5% for sorafenib-naive and 18.7% for sorafenib-experienced patients for nivolumab and 33% for the nivolumab-ipilimumab combination; median overall survival (OS) rates were 29 months (sorafenib naive), 15 months (sorafenib experienced), and 23 months (nivolumab-ipilimumab combination).[3,5,7,8] The KEYNOTE-224 study investigated pembrolizumab in sorafenib-experienced patients and demonstrated an ORR of 17% and a median OS of 13 months.[4]

Despite the positive signals from phase 1/2 studies, 2 subsequent randomized phase 3 trials testing nivolumab and pembrolizumab in advanced HCC failed to meet their primary end points.[17,19] The CheckMate 459 study compared nivolumab vs sorafenib in the first-line setting in advanced HCC (Table 2).[17] The predefined threshold of significance for the primary end point OS was not reached (hazard ratio [HR], 0.85; $P = .09$). However, the median OS was substantially longer with nivolumab (16.4 vs 14.7 months) and was the longest ever seen for any drug monotherapy in advanced HCC. While relatively low, the ORR was double with nivolumab vs sorafenib (15% vs 7%), and 4% of the patients achieved a complete response. Nivolumab also showed an improved safety profile and quality of life compared with sorafenib.[17] Another randomized phase 3 trial (KEYNOTE-240) tested pembrolizumab vs placebo in sorafenib-experienced patients with HCC and also missed the predefined significance levels for its coprimary end points of OS and progression-free survival (PFS) (Table 2).[19] Median OS for pembrolizumab vs placebo was 13.9 vs 10.6 months (HR, 0.78; $P = .02$), and median PFS was 3.0 vs 2.8 months (HR, 0.78; $P = .02$). Pembrolizumab was well tolerated and improved ORR vs placebo (18.3 vs 4.4%); median duration of response was 13.8 months.[19] The failure of both phase 3 trials despite clear activity of the ICBs could be explained by the unexpectedly long median OS in the control arms, which was likely impacted by poststudy treatment (including ICBs).[19] Another phase 3 trial testing pembrolizumab vs placebo after previous sorafenib therapy in Asian patients is ongoing (KEYNOTE-394).[20]

The setbacks for ICB monotherapy indicated that combinations with additional agents might be necessary to enhance ICBs' efficacy. In a randomized phase 3 trial,[18] first-line atezolizumab (anti-PD-ligand [L]1 antibody) plus bevacizumab (anti-VEGF antibody) significantly improved the coprimary end points median OS vs sorafenib (not estimable vs 13.2 months; HR, 0.58; $P < .001$) and PFS (6.8 vs 4.3 months; HR, 0.59; $P < .001$) (Table 2). The safety profile was also more favorable, with fewer treatment-related grade 3 to 4 adverse events in the combination arm. These data are especially important given the limited impact of bevacizumab in HCC reported previously.[21]

Thus, despite recent successes, much remains to be understood for optimal integration of ICBs in HCC. Safety and efficacy of ICBs have been researched in combination ICB studies. Large studies have confirmed the durability of responses seen in smaller studies, but both phase 3 trials testing anti-PD-1 monotherapy failed. Clearly, patient selection using predictive biomarkers would be highly desirable. Moreover, the impressive outcome data seen with the combination of nivolumab with ipilimumab and atezolizumab with bevacizumab demonstrate that combinatorial approaches represent valid strategies to increase the efficacy of immunotherapy in HCC.

Potential Predictors of Response

Even though combination with targeted therapy nearly doubled the ORR of ICB, still more than half of the patients did not respond.[18] Moreover, ICBs can cause severe immune-related adverse events as well as hyper progression (accelerated tumor growth) as a new pattern of progression during PD-1/PD-L1-targeted therapy (8% in HCC).[22,23] Patient selection based

on biomarkers could help to maximize the efficacy and reduce the number of patients who may not benefit or even be harmed from ICBs.

To our knowledge, no predictive biomarkers for ICB response currently exist. Several potential biomarkers have been proposed based on exploratory end points in HCC trials. These biomarkers mainly include PD-L1 expression, tumor mutational burden, and specific genomic alterations.

Expression of PD-L1 on immunohistochemistry is routinely being used for patient stratification in non–small cell lung cancer or gastric cancer; however, some patients with PD-L1–negative tumors respond to ICBs, and PD-L1 expression did not correlate with response in other tumor types.[24] In HCC, tumoral PD-L1 expression (cutoff ≥1%) was not predictive for response to nivolumab or pembrolizumab.[3,4,17] The combined positive score (PD-L1 on tumor and immune cells), assessed in only a subset of patients (n = 52), was associated with response to pembrolizumab and PFS.[4]

High tumor mutational burden (ie, number of nonsynonymous single nucleotide variants) may increase the likelihood of ICB response, as seen in some patients with ICB-treated cancer.[24] Moreover, tumors with high microsatellite instability have a high tumor mutational burden, making them more likely to be sensitive to ICBs. Pembrolizumab was granted approval for any microsatellite instability–high or mismatch repair deficient tumors by the US Food and Drug Administration in 2017 and became the first drug to be approved with a tumor-agnostic indication.[24,25] In HCC, tumor mutational burden is generally low, and its utility as a biomarker to predict response to ICB is not supported by available data.[26] Similarly, the prevalence of microsatellite instability–high status is rare in HCC.[27]

Activated Wnt/β-catenin signaling has been associated with immune exclusion (cold, non–T-cell inflamed tumors) in HCC and proposed as potential biomarker of resistance to immunotherapy.[28,29] However, this observation needs prospective confirmation.

On the basis of these findings, biomarker-associated patient selection for ICB may increase the likelihood of durable responses, but, to our knowledge, no such biomarkers have been confirmed for HCC. Based on the current clinical evidence, a predictive model that incorporates several factors (genetic and microenvironmental) may be more likely to estimate the probability of response to immunotherapy than a single biomarker.[24]

Targeting the Immune TME

Several immune and stromal cells of the TME directly or indirectly orchestrate antitumor immunity. Tumor-infiltrating $CD4^+$ and $CD8^+$ effector T lymphocytes are thought to mediate responses to ICBs. These cells are primed in the draining lymph nodes through tumor antigen presentation by dendritic cells. In addition, natural killer cells have the ability to directly recognize tumor cells and also contribute to antitumor immunity. Tumor-associated endothelial cells and the aberrant tumor vasculature hinder trafficking of immune effector cells while promoting the recruitment of immunosuppressive cell types. These cell types include regulatory T cells and myeloid-derived suppressor cells, which suppress effector T-cell proliferation, function, and cytotoxicity. Tumor-associated macrophages

display different phenotypes; M1-like TAMs are considered to have antitumor activity, while M2-like tumor-associated macrophages exert immunosuppressive and tumor-promoting effects. Cancer-associated fibroblasts contribute to immunosuppression by inhibiting T-cell function and secretion of extracellular matrix, which represents a physical barrier to T-cell infiltration.[30–32]

Each of these components represents a potential target to reprogram the immunosuppressive TME. Herein, we focus on VEGF and TGF-β signaling—2 immunosuppressive pathways that are characteristic of HCC and modulate several cell types of the TME—as targets for reprogramming the HCC TME and enhance ICB efficacy.

Targeting VEGF Signaling

Hepatocellular carcinoma is a highly vascularized tumor that exploits the active formation of new blood vessels (angiogenesis) to grow and disseminate.[33] The VEGF pathway is a key regulator of tumor angiogenesis and upregulated in most cancer types.[34] All 5 targeted therapies with proven efficacy against HCC inhibit VEGF signaling,[1] which supports the notion that this pathway mediates HCC progression.

In addition to its widely studied role in promoting angiogenesis, VEGF can directly affect immune cells of both myeloid and lymphoid lineage and promote immune evasion in different tumor types (Figure 1).[30] For example, VEGF can impair maturation and function of dendritic cells, which are key antigen-presenting cells,[35,36] and promote accumulation of regulatory T cells and myeloid-derived suppressor cells.[37,38] In addition, VEGF can directly and indirectly inhibit infiltration and function of cytotoxic T lymphocytes,[39,40] and increase PD-1 expression on intratumoral $CD8^+$ T cells.[41] Vascular endothelial growth factor indirectly affects immunity by increasing vessel permeability (leakiness), a main feature of the aberrant tumor vasculature.[42,43] Leakiness impairs tumor blood flow and increases interstitial fluid pressure, consequently leading to hypoxia and acidosis,[43] which promote immunosuppression by impairing the function of antigen-presenting cells and cytotoxic T lymphocytes, and by increasing accumulation of immunosuppressive cells and immune checkpoint expression.[31,43,44]

Inhibition of VEGF has also been shown to impact not just the vasculature, but also the immune TME of HCC, but the results have been inconsistent. Some preclinical studies showed that treatment with sorafenib, 30 mg/kg/d, decreased the intratumoral accumulation of regulatory T cells and myeloid-derived suppressor cells in subcutaneous and orthotopic murine HCC models.[45,46] Another study showed that sorafenib, 10–90 mg/kg/d, triggered a natural killer cell response against HCC by inducing proinflammatory activity mediated in part by treatment-induced pyroptosis—a potentially immunogenic type of cell death—in tumor-associated macrophages.[47] On the other hand, excessive vessel pruning caused by anti-VEGF therapy can increase tumor hypoxia and counteract these effects by promoting immunosuppression.[43] In addition, antivascular effects can impair drug delivery to tumors and may thus reduce the efficacy of the anti-VEGF agent itself or concomitant ICBs.[42] In experimental models of HCC, sorafenib, 40–50 mg/kg, treatment intensified tumor hypoxia and increased the accumulation of immunosuppressive cell types (eg, myeloid-derived

suppressor cells, regulatory T cells, and M2-like macrophages) as well as PD-L1 expression in tumors.[48,49] While anti-PD-1 therapy had no additional efficacy when combined with sorafenib, a triple combination with a CXCR4 inhibitor, that prevented polarization toward an immunosuppressive milieu, delayed tumor growth and reduced dissemination.[49]

Judicious dosing of anti-VEGF drugs to normalize the dysfunctional tumor vasculature instead of causing excessive vessel pruning may improve tumor perfusion, alleviate tumor hypoxia, and increase delivery of concomitant systemic therapy (eg, immunotherapy) (Figure 1).[42] This hypothesis was supported by emerging clinical data: bevacizumab (anti-VEGF antibody) improved tumor vessel function in patients with rectal cancer,[50] and increased tumor blood perfusion upon treatment with a VEGF receptor (R)-targeted TKI was associated with prolonged survival in patients with glioblastoma.[51]

Immune checkpoint blocker itself may normalize vascular structure and function when eliciting immune responses via $CD4^+$ and $CD8^+$ lymphocytes (Figure 1).[52,53] Moreover, combination of lower, vascular-normalizing doses of anti-VEGF treatment with active immunotherapy showed efficacy in preclinical[54] as well as clinical studies.[55] In murine breast cancer models, lower doses of anti-VEGFR2 therapy induced vascular normalization and thereby alleviated tumor hypoxia, reprogrammed the immunosuppressive TME, and enhanced the efficacy of immunotherapy.[54] A recent phase 1b trial reported encouraging efficacy data for the combination of regorafenib, 80 mg/d (half the standard dose), plus nivolumab (>35% ORR) in advanced gastric or colorectal cancer.[55] A similar trial, using regorafenib, 80 mg/kg/d, and anti-PD1 antibodies is ongoing in HCC.[56]

Preclinical studies provided several insights into the effect of this treatment interaction in murine HCC models. One study showed that dual inhibition of VEGFR2 and PD-1 resulted in normalized vessel formation mediated by CD4+ T cells and was accompanied by augmented antitumor immune response and improved efficacy, including in ICB-resistant HCC models.[57] Another study showed that lenvatinib—but not sorafenib—decreased the tumor infiltration by monocytes and macrophages, increased the numbers of $CD8^+$ T cells, and augmented the antitumor effect of anti-PD-1 treatment in a subcutaneous murine model of HCC.[58]

In HCC, several trials are currently investigating anti-VEGF–based therapies in combination with ICBs (Table 3).[59–86] Based on preliminary data, the combinations of lenvatinib plus pembrolizumab and bevacizumab plus atezolizumab have both been granted breakthrough therapy designation for advanced HCC by the US Food and Drug Administration (Table 1).[12,14] The latter combination improved both coprimary end points (OS and PFS) over sorafenib alone in the first-line setting of advanced HCC in the recently reported IMbrave150 phase 3 study[18] and is currently being investigated in another phase 3 study as an adjuvant therapy after resection or local ablation (IMbrave050).[64] Lenvatinib plus pembrolizumab is currently being tested in a phase 3 front-line trial, and data are forthcoming.[63]

Taken together, the role of targeting the immune TME of HCC has been confirmed clinically using anti-VEGF/VEGFR therapy. The effects may be dose and agent dependent when using

mTKIs. The use of lower, vascular-normalizing doses of anti-VEGF therapies is supported by emerging clinical data,[55] but needs further confirmation in larger studies in HCC. This mechanistic complexity notwithstanding, given that combining anti-VEGF and ICB treatment is the new standard of care in HCC, future therapeutic approaches will have to improve on this new backbone treatment.

Targeting TGF-β Signaling

The TGF-β pathway has complex functions in the liver tissue, where it regulates homeostasis. Dysregulated TGF-β signaling is involved in the pathogenesis of several liver diseases, including HCC development. Moreover, TGF-β has a dual role in carcinogenesis as it can act as a tumor suppressor, particularly in early tumor stages, but can also promote tumor progression and dissemination in more advanced cancers. Several components of the TME, including fibroblasts, immune cells, and extracellular matrix components, mediate these context-dependent functions.[87,88]

Regulation of tumor immune evasion is also seen with TGF-β, especially in advanced tumor stages.[88] The immunosuppressive effects are mediated by dampening T-cell responses, but TGF-β may also affect other immune cells.[88] For example, TGF-β inhibits natural killer cell function and increases the number of regulatory T cells.[89,90] Another action of TGF-β is promotion of antigen-specific T-cell exhaustion by upregulating PD-1.[91] In addition, this cytokine affects tumor-associated macrophages by inducing an M2-like (tumor-promoting) phenotype.[92] The expression of VEGF in different cell types of the TME is induced by TGF-β, including immune, tumor, and stromal cells.[93,94] This crosstalk between TGF-β and VEGF signaling may further promote TGF-β–mediated immunosuppression.

Moreover, the profibrotic effects of TGF-β can indirectly contribute to immunosuppression. TGF-β activates myofibroblasts and upregulates the deposition of extracellular matrix proteins in the tumor,[95] which may act as a physical barrier and lead to exclusion of effector T cells (Figure 2).[96]

Activated TGF-β signaling was linked to an exhausted immune subclass in HCC (approximately 10% of cases) characterized by exhausted T cells, impaired cytotoxicity, M2-like tumor-associated macrophages, and an upregulation of immunosuppressive cytokines.[28] In addition, 4 distinct clusters with different levels of TGF-β disruption were described recently with use of The Cancer Genome Atlas transcriptome sequencing database,[97] and the highly activated TGF-β cluster overlapped with the exhausted immune subclass.[28,97] Patients with the least disrupted TGF-β signaling had a better outcome than those with activated or inactivated TGF-β signaling. These data implicate TGF-β in immunotherapy resistance. A phase 2 study reported that high pretreatment plasma TGF-β levels correlated with HCC resistance to pembrolizumab.[98]

These data also suggest that TGF-β inhibition may reprogram the TME to enhance ICB efficacy, especially in HCCs with activated TGF-β signaling. In preclinical (non-HCC) tumor models, blockade of TGF-β reduced infiltration of regulatory effector T cells and myeloid-derived suppressor cells, facilitated T-cell infiltration, and enhanced the efficacy of

anti-PD-L1 and anti–cytotoxic T lymphocyte antigen-4 treatment.[96,99] Phase 2 studies testing the TGF-β receptor 1 kinase inhibitor galunisertib alone[100] or combined with sorafenib[101] showed acceptable safety and prolonged survival in advanced HCC, especially in patients who experienced a decrease in circulating TGF-β. The combination of galunisertib plus nivolumab is currently being investigated as second-line treatment in a phase 2 study.[102] In addition, a phase 1 study is testing the combination of NIS793 (anti-TGF-β antibody) and spartalizumab (anti-PD-1 antibody) in patients with advanced cancers, including HCC.[103]

In addition to directly targeting TGF-β, TGF-β activity can be downregulated using inhibitors of the angiotensin II (AngII)/AngII type I receptor (AT1R) axis of the renin-angiotensin system.[104,105] Apart from reducing TGF-β expression, blocking AngII/AT1R signaling can also prevent other immunosuppressive effects of the renin-angiotensin system (Figure 2).[31] Inhibition of AT1R normalized the desmoplastic stroma in several preclinical tumor models and consequently decreased solid stress and thereby improved vascular perfusion and reduced hypoxia.[104–106] Inhibition of AT1R also reduced infiltration of tumor-associated neutrophils and regulatory T cells and increased $CD8^+$ T-cell infiltration in pancreatic tumors of obese mice.[107] In patients with pancreatic cancer, gene expression profiles indicated reduced activation of Wnt signaling in lisinopril users.[108] These data suggest that inhibition of the renin-angiotensin system could have the potential to enhance ICB efficacy and may help to overcome primary resistance to immunotherapy, which may be associated with activated Wnt/β-catenin signaling in HCC.[28,29] In preclinical breast and pancreatic cancer models, AngII/AT1R blockade reprogrammed the immunosuppressive TME and improved the efficacy of ICBs directed against PD-1 and cytotoxic T lymphocyte antigen-4.[106] A phase 2 study is currently investigating the AT1R blocker losartan plus nivolumab in combination with chemoradiotherapy in patients with pancreatic cancer.[109] In HCC, the use of renin-angiotensin system inhibitors decreased tumor growth preclinically[110] and was associated with improved outcome in patients with advanced HCC treated with sorafenib.[111]

In summary, TGF-β signaling is often upregulated in HCC and contributes to an immunosuppressive TME, mainly by inhibiting effector T-cell function. The profibrotic effects of TGF-β also contribute to immunosuppression by inhibiting immune cell infiltration. The combination of TGF-β (or renin-angiotensin system) inhibition and ICBs is currently being tested in early phase clinical trials. Whether these approaches will be effective in reprogramming the immunosuppressive TME of HCC will need prospective confirmation.

Conclusions and Future Perspectives

Immune checkpoint blocker monotherapy with nivolumab and pembrolizumab did not show significant benefit in randomized phase 3 trials in HCC.[17,19] The hypothesis that efficacy of immunotherapy in HCC can be safely achieved by using combination therapies was confirmed by the recent success of dual VEGF/PD-L1 blockade in front-line (IMbrave150 study) treatment.[18] This breakthrough signals an important change in the standard treatment for advanced HCC. Moreover, the success of this therapy will directly affect the future use

of currently approved targeted therapies in first- and second-line treatment. These drugs have been tested against sorafenib or in sorafenib-experienced patients, respectively, but not in patients who have previously received anti-VEGF/PD-L1 treatment. The patterns of tumor recurrence are expected to differ. Thus, establishing the optimal treatment sequence of anti-VEGF(R) antibodies, mTKIs, and ICBs will become an important challenge in the management of HCC. This new first-line treatment will also impact ongoing clinical studies as well as the design of future trials in advanced HCC, and perhaps the implementation of immunotherapy with other treatment modalities (eg, surgery, radiotherapy, and transarterial chemoembolization) at earlier stages of the disease.

Another challenge will be addressing treatment resistance. Even though dual VEGF/PD-L1 blockade doubled the response rates, more than two-thirds of the patients still do not respond. Whether targeting other pathways, such as TGF-β or AT1R, will be effective with ICBs in these patients needs to be demonstrated.[112]

Estimating the probability of response or resistance to immunotherapy remains a challenge. Identification of biomarkers will help to improve patient outcomes and reduce adverse effects and economic burden of these treatments. Currently, there is no clinically available biomarker to estimate response to ICBs. Tumor tissue should routinely be gathered within clinical HCC trials to better characterize the TME and identify potential biomarkers.

The underlying cause of HCC may also have implications for ICB response. Chronic inflammation, as seen in patients with viral hepatitis, induces the expression of immune checkpoint molecules and promoteseffectorT-cellexhaustion.[113] Results from phase 3 trials demonstrated higher efficacy of ICBs in patients with underlying viral disease vs other etiologic factors, including nonalcoholic fatty liver disease.[17,18] Nonalcoholic fatty liver disease can cause $CD4^+$ T-cell loss and induce protumor effects in natural killer T cells, $CD8^+$ T-cells, and helper T17 cells.[114] In preclinical models, nonalcoholic fatty liver disease impaired the efficacy of immunotherapy.[115] Given the expected surge in nonalcoholic fatty liver disease–associated HCC and reduction in viral-related disease, these observations warrant further investigation of the immune cell landscape of HCC with respect to the cause of the disease.

These challenges not with standing, the systemic therapy of HCC has rapidly changed with the development of multiple antiangiogenic agents and immunotherapies over the past 3 to 4 years, raising expectations for unprecedented durable responses and increased survival in this aggressive cancer.

Conflict of Interest Disclosures:

Dr Pinter is an investigator for Bayer, Bristol Myers Squibb, Lilly, and Roche; he received speaker honoraria from Bayer, Bristol Myers Squibb, Eisai, Lilly, and MSD; he is a paid consultant for Bayer, Bristol Myers Squibb, Eisai, Ipsen, Lilly, MSD, and Roche; he received travel support from Bayer and Bristol Myers Squibb. Dr Jain received honorarium from Amgen and consultant fees from Chugai, Ophthotech, Merck, SPARC, SynDevRx, and XTuit. Dr Jain owns equity in XTuit, Enlight, SPARC, SynDevRx, and Accurius Therapeutics and serves as a paid member of the boards of trustees of Tekla Healthcare Investors, Tekla Life Sciences Investors, Tekla Healthcare Opportunities Fund, and Tekla World Healthcare Fund. He is a member of the scientific advisory board of Accurius Therapeutics. He is listed as an inventor on US Patents: 2011329638 (issued April 13, 2017) and application 16/063,353 (pending). The research of Dr Jain is supported by National Institutes of Health grants P01-CA080124, R35-CA197743, R01-CA208205, and U01-CA224173, and by the National Foundation for Cancer Research, Harvard

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REFERENCES

1. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol. 2019;16(10):589–604. doi:10.1038/s41575-019-0186-y [PubMed: 31439937]
2. Llovet JM, Ricci S, Mazzaferro V, et al.; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359 (4):378–390. doi:10.1056/NEJMoa0708857 [PubMed: 18650514]
3. 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):2492–2502. doi:10.1016/S0140-6736(17)31046-2 [PubMed: 28434648]
4. Zhu AX, Finn RS, Edeline J, et al.; KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018;19(7):940–952. doi:10.1016/S1470-2045(18)30351-6 [PubMed: 29875066]
5. Yau T, Kang YK, Kim TY, et al. Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): results from CheckMate 040 [abstract 4012]. J Clin Oncol. 2019;37(15)(suppl):4012. doi:10.1200/JCO.2019.37.15_suppl.4012
6. Hato T, Goyal L, Greten TF, Duda DG, Zhu AX. Immune checkpoint blockade in hepatocellular carcinoma: current progress and future directions. Hepatology. 2014;60(5):1776–1782. doi:10.1002/hep.27246 [PubMed: 24912948]
7. Crocenzi TS, El-Khoueiry AB, Yau TC, et al. Nivolumab (nivo) in sorafenib (sor)-naive and -experienced pts with advanced hepatocellular carcinoma (HCC): CheckMate 040 study [abstract 4013]. J Clin Oncol. 2017;35(suppl):4013. doi:10.1200/JCO.2017.35.15_suppl.4013
8. Sangro B, Melero I, Wadhawan S, et al. Association of inflammatory biomarkers with clinical outcomes in nivolumab-treated patients with advanced hepatocellular carcinoma. J Hepatol. 2020;S0168–8278(20)30479–7. Published online July 2, 2020. doi:10.1016/j.jhep.2020.07.026
9. Wainberg ZA, Segal NH, Jaeger D, et al. Safety and clinical activity of durvalumab monotherapy in patients with hepatocellular carcinoma (HCC) [abstract 4071]. J Clin Oncol. 2017;35(suppl):4071. doi:10.1200/JCO.2017.35.15_suppl.4071
10. Qin S, Ren Z, Meng Z, et al. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial. Lancet Oncol. 2020;21(4):571–580. doi:10.1016/S1470-2045(20)30011-5 [PubMed: 32112738]
11. 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 [abstract 4073]. J Clin Oncol. 2017;35 (suppl):4073. doi:10.1200/JCO.2017.35.15_suppl.4073
12. Lee MS, Ryoo BY, Hsu CH, et al. Atezolizumab + bevacizumab in previously untreated patients with unresectable or advanced hepatocellular carcinoma: analysis of a phase Ib study [abstract O-034]. Liver Cancer. 2019;8(suppl 1):107.
13. Lee M, Ryoo B, Hsu C, et al. Randomised efficacy and safety results for atezolizumab (Atezo) + bevacizumab (Bev) in patients (pts) with previously untreated, unresectable hepatocellular carcinoma [abstract LBA39]. Ann Oncol. 2019;30 (suppl 5):ix183–ix202. doi:10.1093/annonc/mdz394.030
14. Llovet JM, Finn RS, Ikeda M, et al. A phase 1b trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) in unresectable hepatocellular carcinoma (uHCC): updated results [abstract 747P]. Ann Oncol. 2019;30(suppl 5):v253–v324. doi:10.1093/annonc/mdz247.073
15. 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 [abstract 478]. J Clin Oncol. 2020;38(suppl 4):478. doi:10.1200/JCO.2020.38.4_suppl.478

16. Schwartz LH, Seymour L, Litière S, et al. RECIST 1.1—standardisation and disease-specific adaptations: perspectives from the RECIST Working Group. Eur J Cancer. 2016;62:138–145. doi:10.1016/j.ejca.2016.03.082 [PubMed: 27237360]
17. Yau T, Park JW, Finn RS, et al. CheckMate 459: a randomized, multi-center phase 3 study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma [abstract LBA38_PR]. Ann Oncol. 2019;30(suppl 5):v851–v934. doi:10.1093/annonc/mdz394.029
18. Finn RS, Qin S, Ikeda M, et al.; IMbrave150 Investigators. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745 [PubMed: 32402160]
19. Finn RS, Ryoo BY, Merle P, et al.; KEYNOTE-240 investigators. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. J Clin Oncol. 2020;38 (3):193–202. doi:10.1200/JCO.19.01307 [PubMed: 31790344]
20. Study of pembrolizumab (MK-3475) or placebo given with best supportive care in Asian participants with previously treated advanced hepatocellular carcinoma (MK-3475–394/KEYNOTE-394). ClinicalTrials.gov identifier: NCT03062358. Updated January 27, 2020. Accessed December 15, 2019. https://www.clinicaltrials.gov/ct2/show/NCT03062358
21. Pinter M, Ulbrich G, Sieghart W, et al. Hepatocellular carcinoma: a phase II randomized controlled double-blind trial of transarterial chemoembolization in combination with biweekly intravenous administration of bevacizumab or a placebo. Radiology. 2015;277(3):903–912. doi:10.1148/radiol.2015142140 [PubMed: 26131911]
22. Champiat S, Ferrara R, Massard C, et al. Hyperprogressive disease: recognizing a novel pattern to improve patient management. Nat Rev Clin Oncol. 2018;15(12):748–762. doi:10.1038/s41571-018-0111-2 [PubMed: 30361681]
23. Scheiner B, Kirstein MM, Hucke F, et al. Programmed cell death protein-1 (PD-1)–targeted immunotherapy in advanced hepatocellular carcinoma: efficacy and safety data from an international multicentre real-world cohort. Aliment Pharmacol Ther. 2019;49(10):1323–1333. doi:10.1111/apt.15245 [PubMed: 30980420]
24. Havel JJ, Chowell D, Chan TA. The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. Nat Rev Cancer. 2019;19(3):133–150. doi:10.1038/s41568-019-0116-x [PubMed: 30755690]
25. US Food and Drug Administration. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. Published May 30, 2017. Accessed December 15, 2019. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pembrolizumab-first-tissuesite-agnostic-indication
26. Ang C, Klempner SJ, Ali SM, et al. Prevalence of established and emerging biomarkers of immune checkpoint inhibitor response in advanced hepatocellular carcinoma. Oncotarget. 2019;10 (40):4018–4025. doi:10.18632/oncotarget.26998 [PubMed: 31258846]
27. Bonneville R, Krook MA, Kautto EA, et al. Landscape of microsatellite instability across 39 cancer types. JCO Precis Oncol. 2017;2017. Published online October 3, 2017. doi:10.1200/PO.17.00073
28. Sia D, Jiao Y, Martinez-Quetglas I, et al. Identification of an immune-specific class of hepatocellular carcinoma, based on molecular features. Gastroenterology. 2017;153(3):812–826. doi:10.1053/j.gastro.2017.06.007 [PubMed: 28624577]
29. Ruiz de Galarreta M, Bresnahan E, Molina-Sánchez P, et al. β-catenin activation promotes immune escape and resistance to anti-PD-1 therapy in hepatocellular carcinoma. Cancer Discov. 2019;9(8):1124–1141. doi:10.1158/2159-8290.CD-19-0074 [PubMed: 31186238]
30. Datta M, Coussens LM, Nishikawa H, Hodi FS, Jain RK. Reprogramming the tumor microenvironment to improve immunotherapy: emerging strategies and combination therapies. Am Soc Clin Oncol Educ Book. 2019;39:165–174. doi:10.1200/EDBK_237987 [PubMed: 31099649]

31. Pinter M, Jain RK. Targeting the renin-angiotensin system to improve cancer treatment: Implications for immunotherapy. Sci Transl Med. 2017;9(410):eaan5616. doi:10.1126/scitranslmed.aan5616 [PubMed: 28978752]
32. Sahai E, Astsaturov I, Cukierman E, et al. A framework for advancing our understanding of cancer-associated fibroblasts. Nat Rev Cancer. 2020;20(3):174–186. doi:10.1038/s41568-019-0238-1 [PubMed: 31980749]
33. Zhu AX, Duda DG, Sahani DV, Jain RK. HCC and angiogenesis: possible targets and future directions. Nat Rev Clin Oncol. 2011;8(5):292–301. doi:10.1038/nrclinonc.2011.30 [PubMed: 21386818]
34. Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. Nature. 2011;473(7347):298–307. doi:10.1038/nature10144 [PubMed: 21593862]
35. Alfaro C, Suarez N, Gonzalez A, et al. Influence of bevacizumab, sunitinib and sorafenib as single agents or in combination on the inhibitory effects of VEGF on human dendritic cell differentiation from monocytes. Br J Cancer. 2009;100(7):1111–1119. doi:10.1038/sj.bjc.6604965 [PubMed: 19277038]
36. Mimura K, Kono K, Takahashi A, Kawaguchi Y, Fujii H. Vascular endothelial growth factor inhibits the function of human mature dendritic cells mediated by VEGF receptor-2. Cancer Immunol Immunother. 2007;56(6):761–770. doi:10.1007/s00262-006-0234-7 [PubMed: 17086423]
37. Gabrilovich D, Ishida T, Oyama T, et al. Vascular endothelial growth factor inhibits the development of dendritic cells and dramatically affects the differentiation of multiple hematopoietic lineages in vivo. Blood. 1998;92(11):4150–4166. doi:10.1182/blood.V92.11.4150 [PubMed: 9834220]
38. Terme M, Pernot S, Marcheteau E, et al. VEGFA-VEGFR pathway blockade inhibits tumor-induced regulatory T-cell proliferation in colorectal cancer. Cancer Res. 2013;73(2):539–549. doi:10.1158/0008-5472.CAN-12-2325 [PubMed: 23108136]
39. 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):607–615. doi:10.1038/nm.3541 [PubMed: 24793239]
40. Noman MZ, Buart S, Van Pelt J, et al. The cooperative induction of hypoxia-inducible factor-1 alpha and STAT3 during hypoxia induced an impairment of tumor susceptibility to CTL-mediated cell lysis. J Immunol. 2009;182(6): 3510–3521. doi:10.4049/jimmunol.0800854 [PubMed: 19265129]
41. 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): 139–148. doi:10.1084/jem.20140559 [PubMed: 25601652]
42. Jain RK. Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers. J Clin Oncol. 2013;31(17):2205–2218. doi:10.1200/JCO.2012.46.3653 [PubMed: 23669226]
43. Jain RK. Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia. Cancer Cell. 2014;26(5):605–622. doi:10.1016/j.ccell.2014.10.006 [PubMed: 25517747]
44. Huang Y, Goel S, Duda DG, Fukumura D, Jain RK. Vascular normalization as an emerging strategy to enhance cancer immunotherapy. Cancer Res. 2013;73(10):2943–2948. doi:10.1158/0008-5472.CAN-12-4354 [PubMed: 23440426]
45. Cao M, Xu Y, Youn JI, et al. Kinase inhibitor sorafenib modulates immunosuppressive cell populations in a murine liver cancer model. Lab Invest. 2011;91(4):598–608. doi:10.1038/labinvest.2010.205 [PubMed: 21321535]
46. Chen ML, Yan BS, Lu WC, et al. Sorafenib relieves cell-intrinsic and cell-extrinsic inhibitions of effector T cells in tumor microenvironment to augment antitumor immunity. Int J Cancer. 2014; 134(2):319–331. doi:10.1002/ijc.28362 [PubMed: 23818246]
47. Hage C, Hoves S, Strauss L, et al. Sorafenib induces pyroptosis in macrophages and triggers natural killer cell–mediated cytotoxicity against hepatocellular carcinoma. Hepatology. 2019;70(4): 1280–1297. doi:10.1002/hep.30666 [PubMed: 31002440]
48. Chen Y, Huang Y, Reiberger T, et al. Differential effects of sorafenib on liver versus tumor fibrosis mediated by stromal-derived factor 1 alpha/C-X-C receptor type 4 axis and myeloid differentiation

antigen-positive myeloid cell infiltration in mice. Hepatology. 2014;59(4):1435–1447. doi:10.1002/hep.26790 [PubMed: 24242874]

49. Chen Y, Ramjiawan RR, Reiberger T, et al. CXCR4 inhibition in tumor microenvironment facilitates anti-programmed death receptor-1 immunotherapy in sorafenib-treated hepatocellular carcinoma in mice. Hepatology. 2015;61(5):1591–1602. doi:10.1002/hep.27665 [PubMed: 25529917]
50. Willett CG, Duda DG, di Tomaso E, et al. Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radiation therapy, and fluorouracil in rectal cancer: a multidisciplinary phase II study. J Clin Oncol. 2009;27(18):3020–3026. doi:10.1200/JCO.2008.21.1771 [PubMed: 19470921]
51. Sorensen AG, Emblem KE, Polaskova P, et al. Increased survival of glioblastoma patients who respond to antiangiogenic therapy with elevated blood perfusion. Cancer Res. 2012;72(2):402–407. doi:10.1158/0008-5472.CAN-11-2464 [PubMed: 22127927]
52. Tian L, Goldstein A, Wang H, et al. Mutual regulation of tumour vessel normalization and immunostimulatory reprogramming. Nature. 2017; 544(7649):250–254. doi:10.1038/nature21724 [PubMed: 28371798]
53. Zheng X, Fang Z, Liu X, et al. Increased vessel perfusion predicts the efficacy of immune checkpoint blockade. J Clin Invest. 2018;128(5): 2104–2115. doi:10.1172/JCI96582 [PubMed: 29664018]
54. Huang Y, Yuan J, Righi E, et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. Proc Natl Acad Sci U S A. 2012;109(43):17561–17566. doi:10.1073/pnas.1215397109 [PubMed: 23045683]
55. Fukuoka S, Hara H, Takahashi N, et al. Regorafenib plus nivolumab in patients with advanced gastric or colorectal cancer: an open-label, dose-escalation, and dose-expansion phase Ib trial (REGONIVO, EPOC1603). J Clin Oncol. 2020;38(18):2053–2061. doi:10.1200/JCO.19.03296 [PubMed: 32343640]
56. Regorafenib plus tislelizumab as first-line systemic therapy for patients with advanced hepatocellular carcinoma. ClinicalTrials.gov identifier NCT04183088. Updated January 2, 2020. Accessed December 15, 2019. https://www.clinicaltrials.gov/ct2/show/NCT04183088
57. Shigeta K, Datta M, Hato T, et al. Dual programmed death receptor-1 and vascular endothelial growth factor receptor-2 blockade promotes vascular normalization and enhances antitumor immune responses in hepatocellular carcinoma. Hepatology. 2020;71(4):1247–1261. doi:10.1002/hep.30889 [PubMed: 31378984]
58. Kimura T, Kato Y, Ozawa Y, et al. Immunomodulatory activity of lenvatinib contributes to antitumor activity in the Hepa1-6 hepatocellular carcinoma model. Cancer Sci. 2018; 109(12):3993–4002. doi:10.1111/cas.13806 [PubMed: 30447042]
59. Study of cabozantinib in combination with atezolizumab versus sorafenib in subjects with advanced HCC who have not received previous systemic anticancer therapy (COSMIC-312). ClinicalTrials.gov identifier NCT03755791. Updated July 16, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03755791
60. Global study to evaluate transarterial chemoembolization (TACE) in combination with durvalumab and bevacizumab therapy in patients with locoregional hepatocellular carcinoma (EMERALD-1). ClinicalTrials.gov identifier NCT03778957. Updated September 10, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03778957
61. A study to evaluate SHR-1210 in combination with apatinib as first-line therapy in patients with advanced HCC. ClinicalTrials.gov identifier NCT03764293. Updated December 3, 2019. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03764293
62. Assess efficacy and safety of durvalumab alone or combined with bevacizumab in high risk of recurrence HCC patients after curative treatment (EMERALD-2). ClinicalTrials.gov identifier NCT03847428. Updated August 12, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03847428
63. Safety and efficacy of lenvatinib (E7080/MK-7902) in combination with pembrolizumab (MK-3475) versus lenvatinib as first-line therapy in participants with advanced hepatocellular carcinoma (MK-7902–002/E7080-G000–311/LEAP-002). ClinicalTrials.gov identifier

NCT03713593. Updated April 10, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03713593

64. A study of atezolizumab plus bevacizumab versus active surveillance as adjuvant therapy in patients with hepatocellular carcinoma at high risk of recurrence after surgical resection or ablation (IMbrave050). ClinicalTrials.gov identifier NCT04102098. Updated September 10, 2020. Accessed December 15, 2019. https://www.clinicaltrials.gov/ct2/show/NCT04102098
65. A study of nivolumab in combination with ipilimumab in participants with advanced hepatocellular carcinoma (CheckMate 9DW). ClinicalTrials.gov identifier NCT04039607. Updated September 11, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT04039607
66. Lenvatinib plus nivolumab versus lenvatinib for advanced hepatocellular carcinoma with hepatitis B virus infection. ClinicalTrials.gov identifier NCT04044651. Updated January 9, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT04044651
67. A study to evaluate the efficacy and safety of sintilimab in combination with IBI305 (anti-VEGF monoclonal antibody) compared to sorafenib as the first-line treatment for advanced hepatocellular carcinoma. ClinicalTrials.gov identifier NCT03794440. Updated July 15, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03794440
68. A study of SHR-1210 in combination with apatinib or chemotherapy in subjects with advanced PLC or BTC. ClinicalTrials.gov identifier NCT03092895. Updated July 26, 2018. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03092895
69. Anlotinib hydrochloride combined with sintilimab injection in the treatment of advanced hepatocellular carcinoma (HCC). ClinicalTrials.gov identifier NCT04052152. Updated August 9, 2019. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT04052152
70. Sorafenib and nivolumab in treating participants with unresectable, locally advanced or metastatic liver cancer. ClinicalTrials.gov identifier NCT03439891. Updated March 31, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03439891
71. Systemic chemotherapy plus lenvatinib and toripalimab for HCC with extrahepatic metastasis. ClinicalTrials.gov identifier NCT04170179. Updated November 20, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT04170179
72. Immunotherapy with nivolumab in combination with lenvatinib for advanced stage hepatocellular carcinoma. ClinicalTrials.gov identifier NCT03841201. Updated June 14, 2019. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03841201
73. Atezolizumab plus bevacizumab with HCC and HBV infection. ClinicalTrials.gov identifier NCT04180072. Updated November 27, 2019. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT04180072
74. A trial of hepatic arterial infusion combined with apatinib and camrelizumab for C-staged hepatocellular carcinoma in BCLC classification (TRIPLET). ClinicalTrials.gov identifier NCT04191889. Updated April 16, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT04191889
75. Sintilimab combined with lenvatinib in local advanced hepatocellular carcinoma. ClinicalTrials.gov identifier NCT04042805. Updated August 2, 2019. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT04042805
76. Combined treatment of durvalumab, bevacizumab, and transarterial chemoembolization (TACE) in subjects with hepatocellular carcinoma. ClinicalTrials.gov identifier NCT03937830. Updated September 14, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03937830
77. Exploratory clinical study of apatinib and SHR-1210 in treating advanced hepatocellular carcinoma or gastric cancer. ClinicalTrials.gov identifier NCT02942329. Updated February 26, 2018. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT02942329
78. Sorafenib tosylate and pembrolizumab in treating patients with advanced or metastatic liver cancer. ClinicalTrials.gov identifier NCT03211416. Updated September 3, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03211416
79. Sorafenib plus toripalimab for unresectable HCC with portal vein tumor thrombus (STUHCCPVTT). ClinicalTrials.gov identifier NCT04069949. Updated October 25, 2019. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT04069949

80. A study of tivozanib in combination with durvalumab in subjects with untreated advanced hepatocellular carcinoma (DEDUCTIVE). ClinicalTrials.gov identifier NCT03970616. Updated September 14, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03970616
81. Regorafenib followed by nivolumab in patients with hepatocellular carcinoma (GOING) (GOING). ClinicalTrials.gov identifier NCT04170556. Updated March 25, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT04170556
82. A trial of lenvatinib plus pembrolizumab in subjects with hepatocellular carcinoma. ClinicalTrials.gov identifier NCT03006926. Updated February 6, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03006926
83. Study of safety and tolerability of PDR001 in combination with sorafenib and to identify the maximum tolerated dose and/or phase 2 dose for this combination in advanced hepatocellular patients. ClinicalTrials.gov identifier NCT02988440. Updated August 13, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT02988440
84. A study of lenvatinib plus nivolumab in participants with hepatocellular carcinoma. ClinicalTrials.gov identifier NCT03418922. Updated April 15, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03418922
85. Regorafenib plus pembrolizumab in first line systemic treatment of HCC. ClinicalTrials.gov identifier NCT03347292. Updated September 14, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03347292
86. Feasibility and efficacy of neoadjuvant cabozantinib plus nivolumab (CaboNivo) followed by definitive resection for patients with locally advanced hepatocellular carcinoma (HCC). ClinicalTrials.gov identifier NCT03299946. Updated March 4, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03299946
87. Dituri F, Mancarella S, Cigliano A, Chieti A, Giannelli G. TGF-β as multifaceted orchestrator in HCC progression: signaling, EMT, immune microenvironment, and novel therapeutic perspectives. Semin Liver Dis. 2019;39(1):53–69. doi:10.1055/s-0038-1676121 [PubMed: 30586675]
88. Principe DR, Doll JA, Bauer J, et al. TGF-β: duality of function between tumor prevention and carcinogenesis. J Natl Cancer Inst. 2014;106(2): djt369. doi:10.1093/jnci/djt369 [PubMed: 24511106]
89. Patel SA, Meyer JR, Greco SJ, Corcoran KE, Bryan M, Rameshwar P. Mesenchymal stem cells protect breast cancer cells through regulatory T cells: role of mesenchymal stem cell-derived TGF-beta. J Immunol. 2010;184(10):5885–5894. doi:10.4049/jimmunol.0903143 [PubMed: 20382885]
90. Zhao ZG, Cao Z, Xu W, et al. Immune protection function of multipotent mesenchymal stromal cells: role of transforming growth factor-β1. Cancer Invest. 2012;30(9):646–656. doi:10.3109/07357907.2012.721038 [PubMed: 23020627]
91. Park BV, Freeman ZT, Ghasemzadeh A, et al. TGFβ1-mediated SMAD3 enhances PD-1 expression on antigen-specific T cells in cancer. Cancer Discov. 2016;6(12):1366–1381. doi:10.1158/2159-8290.CD-15-1347 [PubMed: 27683557]
92. Neuzillet C, Tijeras-Raballand A, Cohen R, et al. Targeting the TGFβ pathway for cancer therapy. Pharmacol Ther. 2015;147:22–31. doi:10.1016/j.pharmthera.2014.11.001 [PubMed: 25444759]
93. Sánchez-Elsner T, Botella LM, Velasco B, Corbí A, Attisano L, Bernabéu C. Synergistic cooperation between hypoxia and transforming growth factor-beta pathways on human vascular endothelial growth factor gene expression. J Biol Chem. 2001;276(42):38527–38535. doi:10.1074/jbc.M104536200 [PubMed: 11486006]
94. Teraoka H, Sawada T, Nishihara T, et al. Enhanced VEGF production and decreased immunogenicity induced by TGF-beta 1 promote liver metastasis of pancreatic cancer. Br J Cancer. 2001;85(4):612–617. doi:10.1054/bjoc.2001.1941 [PubMed: 11506504]
95. Papageorgis P, Stylianopoulos T. Role of TGFβ in regulation of the tumor microenvironment and drug delivery. Int J Oncol. 2015;46(3):933–943. doi:10.3892/ijo.2015.2816 [PubMed: 25573346]
96. Mariathasan S, Turley SJ, Nickles D, et al. TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. Nature. 2018; 554(7693):544–548. doi:10.1038/nature25501 [PubMed: 29443960]

97. Chen J, Zaidi S, Rao S, et al. Analysis of genomes and transcriptomes of hepatocellular carcinomas identifies mutations and gene expression changes in the transforming growth factor-β pathway. Gastroenterology. 2018;154(1): 195–210. doi:10.1053/j.gastro.2017.09.007 [PubMed: 28918914]

98. Feun LG, Li YY, Wu C, et al. Phase 2 study of pembrolizumab and circulating biomarkers to predict anticancer response in advanced, unresectable hepatocellular carcinoma. Cancer. 2019;125(20):3603–3614. doi:10.1002/cncr.32339 [PubMed: 31251403]

99. Courau T, Nehar-Belaid D, Florez L, et al. TGF-β and VEGF cooperatively control the immunotolerant tumor environment and the efficacy of cancer immunotherapies. JCI Insight. 2016;1(9):e85974. doi:10.1172/jci.insight.85974 [PubMed: 27699271]

100. Faivre S, Santoro A, Kelley RK, et al. Novel transforming growth factor beta receptor I kinase inhibitor galunisertib (LY2157299) in advanced hepatocellular carcinoma. Liver Int. 2019;39(8): 1468–1477. doi:10.1111/liv.14113 [PubMed: 30963691]

101. Kelley RK, Gane E, Assenat E, et al. A phase 2 study of galunisertib (TGF-β1 receptor type I inhibitor) and sorafenib in patients with advanced hepatocellular carcinoma. Clin Transl Gastroenterol. 2019;10(7):e00056. doi:10.14309/ctg.0000000000000056 [PubMed: 31295152]

102. A study of galunisertib (LY2157299) in combination with nivolumab in advanced refractory solid tumors and in recurrent or refractory NSCLC, or hepatocellular carcinoma. ClinicalTrials.gov identifier NCT02423343. Updated August 5, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT02423343

103. Phase I/Ib study of NIS793 in combination With PDR001 in patients with advanced malignancies. ClinicalTrials.gov identifier NCT02947165. Updated August 5, 2020. Accessed December 15, 2019. https://www.clinicaltrials.gov/ct2/show/NCT02947165

104. Chauhan VP, Martin JD, Liu H, et al. Angiotensin inhibition enhances drug delivery and potentiates chemotherapy by decompressing tumour blood vessels. Nat Commun. 2013;4:2516. doi:10.1038/ncomms3516 [PubMed: 24084631]

105. Diop-Frimpong B, Chauhan VP, Krane S, Boucher Y, Jain RK. Losartan inhibits collagen I synthesis and improves the distribution and efficacy of nanotherapeutics in tumors. Proc Natl Acad Sci U S A. 2011;108(7):2909–2914. doi:10.1073/pnas.1018892108 [PubMed: 21282607]

106. Chauhan VP, Chen IX, Tong R, et al. Reprogramming the microenvironment with tumor-selective angiotensin blockers enhances cancer immunotherapy. Proc Natl Acad Sci U S A. 2019;116(22):10674–10680. doi:10.1073/pnas.1819889116 [PubMed: 31040208]

107. Incio J, Liu H, Suboj P, et al. Obesity-induced inflammation and desmoplasia promote pancreatic cancer progression and resistance to chemotherapy. Cancer Discov. 2016;6(8):852–869. doi:10.1158/2159-8290.CD-15-1177 [PubMed: 27246539]

108. Liu H, Naxerova K, Pinter M, et al. Use of angiotensin system inhibitors is associated with immune activation and longer survival in nonmetastatic pancreatic ductal adenocarcinoma. Clin Cancer Res. 2017;23(19):5959–5969. doi:10.1158/1078-0432.CCR-17-0256 [PubMed: 28600474]

109. Losartan and nivolumab in combination with FOLFIRINOX and SBRT in localized pancreatic cancer. ClinicalTrials.gov identifier NCT03563248. Updated September 9, 2020. Accessed December 15, 2019. https://clinicaltrials.gov/ct2/show/NCT03563248

110. Yoshiji H, Kuriyama S, Kawata M, et al. The angiotensin-I–converting enzyme inhibitor perindopril suppresses tumor growth and angiogenesis: possible role of the vascular endothelial growth factor. Clin Cancer Res. 2001;7(4):1073–1078. [PubMed: 11309359]

111. Pinter M, Weinmann A, Wörns MA, et al. Use of inhibitors of the renin-angiotensin system is associated with longer survival in patients with hepatocellular carcinoma. United European Gastroenterol J. 2017;5(7):987–996. doi:10.1177/2050640617695698

112. Mpekris F, Voutouri C, Baish JW, et al. Combining microenvironment normalization strategies to improve cancer immunotherapy. Proc Natl Acad Sci U S A. 2020;117(7):3728–3737. doi:10.1073/pnas.1919764117 [PubMed: 32015113]

113. Harding JJ, El Dika I, Abou-Alfa GK. Immunotherapy in hepatocellular carcinoma: primed to make a difference? Cancer. 2016;122(3): 367–377. doi:10.1002/cncr.29769 [PubMed: 26540029]

114. Ma C, Zhang Q, Greten TF. Nonalcoholic fatty liver disease promotes hepatocellular carcinoma through direct and indirect effects on hepatocytes. FEBS J. 2018;285(4):752–762. doi:10.1111/febs.14209 [PubMed: 28857485]

115. Heinrich B, Brown ZJ, Mathias V, et al. Nonalcoholic steatohepatitis (NASH) impairs treatment of intrahepatic metastases with CD4+ T cell dependent RNA vaccine [abstract 1728]. Cancer Res. 2018;78(13)(suppl):1728.

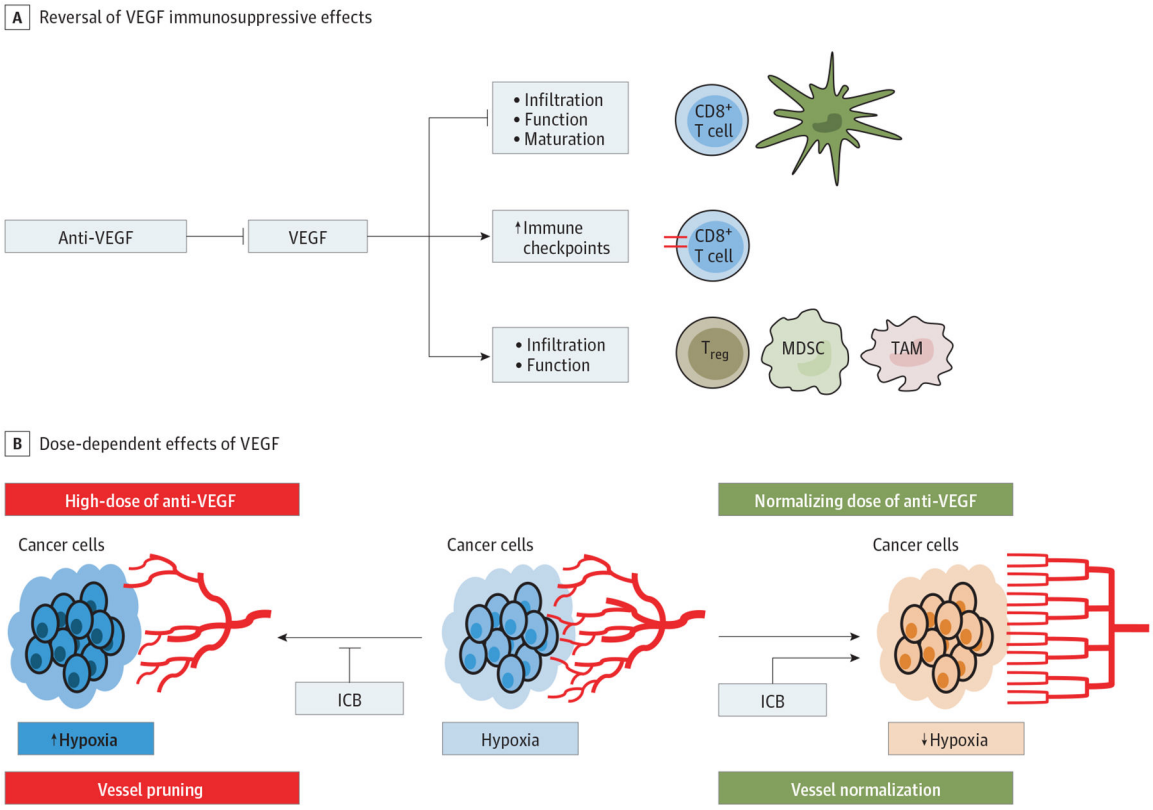

Figure 1.

Effects of Anti-Vascular Endothelial Growth Factor (Anti-VEGF) Treatment on the Tumor Immune Microenvironment A, VEGF-targeted therapy can revert the immunosuppressive effects of VEGF. These effects include the inhibition of dendritic cell (DC) function and maturation, impairment of $CD8^+$ T-cell function and infiltration, upregulation of immune checkpoint molecules, as well as the accumulation of immunosuppressive cell types, including tumor-associated macrophages (TAM), myeloid-derived suppressor cells (MDSC), and regulatory T cells (Treg). B, The effects of anti-VEGF treatment are dose-dependent. Higher doses lead to blood vessel pruning and thereby aggravate tumor hypoxia and acidosis, which supports tumor immune evasion. In contrast, low-dose anti-VEGF treatment may normalize the aberrant and dysfunctional tumor vasculature and thereby improve tumor perfusion, alleviate tumor hypoxia, reprogram the immunosuppressive milieu, and increase drug delivery of concomitant therapies, including immune checkpoint blockers (ICBs). Since anti-PD(L)-1 and anti–cytotoxic T lymphocyte antigen-4 antibodies may also normalize blood vessels and make them refractory to pruning by anti-VEGF(R) antibodies, even higher doses of anti-VEGF(R) may normalize tumor vessels when co-administered with immune checkpoint blockers (ICBs).

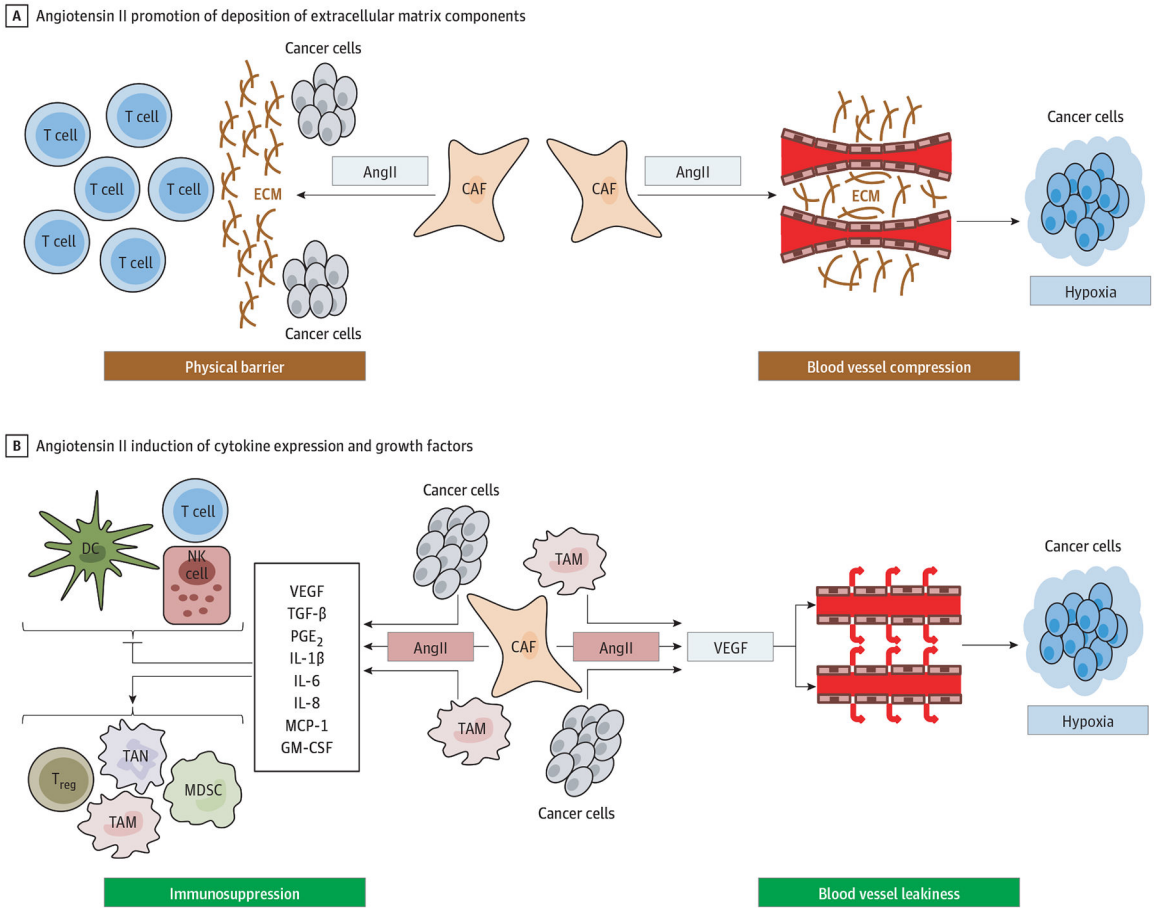

Figure 2.

The Angiotensin II (AngII)/AngII Type I Receptor Axis Promotes Tumor Immune Evasion by Affecting Cancer Cells as Well as Various Stromal Cells A, AngII activates profibrotic pathways and promotes the deposition of extracellular matrix (ECM) components from fibroblasts. ECM acts as a physical barrier to T-cell infiltration, which hampers an antitumor immune response. ECM also leads to blood vessel compression, which impairs tumor perfusion and aggravates tumor hypoxia and acidosis. The hypoxic and acidic milieu further promotes immunosuppressive mechanisms. B, AngII also induced the secretion of different cytokines and growth factors from cancer and stromal cells. These cytokines inhibit function and accumulation of dendritic cells (DC), natural killer (NK) cells, and T-cells, and promote the accumulation of immunosuppressive cell types, including regulatory T cells (Treg), tumor-associated macrophages (TAM), and neutrophils (TAN), and myeloid derived suppressor cells (MDSC). Finally, tumor hypoxia is further aggravated by AngII-mediated upregulation of vascular endothelial growth factor (VEGF), which increases vascular leakiness and impairs tumor blood perfusion. CAF indicates cancer-associated fibroblast; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; MCP, monocyte chemoattractant protein-1; PGE_2, prostaglandin E_2; and TGF-β, transforming growth factor-β.

Table 1.

Selected Phase 1/2 Trials of Immune Checkpoint Blockers in Advanced Hepatocellular Carcinoma[a]

Source	Treatment (No. of patients)	Prior sorafenib (%)	ORR (%)	TTP/PFS, mo	OS, mo
Monotherapy trials					
El-Khoueiry et al,[3] Crocenzi et al,[7] Sangro et al,[8] 2017	Nivolumab (80)	0	22.5[b]	NR/NR	28.6
El-Khoueiry et al,[3] Crocenzi et al,[7] Sangro et al,[8] 2017	Nivolumab (182)	100	18.7[b]	NR/NR	Approximately 15
Wainberg et al,[9] 2017	Durvalumab (40)	92.5	10[b]	NR/2.7	13.2
Zhu et al,[4] 2018	Pembrolizumab (104)	100	17[b]	4.9/4.9	12.9
Qin et al,[10]2020	Camrelizumab (217)	72.8	14.7[b]	NR/2.1	13.8
Combination therapy trials					
Kelley et al,[11] 2017	Durvalumab + tremelimumab (40)	75.0	25[b]	NR/NR	NR
Yau et al,[5] 2019	Nivolumab + ipilimumab (148)[c]	99	31–32[b]	NR/NR	12.5–22.8
Lee et al,[12] 2019	Atezolizumab + bevacizumab (104)	0	36[b]	NR/7.3	17.1
Lee et al,[13] 2019	Atezolizumab + bevacizumab (60) vs atezolizumab (59)	0	20 vs 17[b]	NR/5.6 vs 3.4; HR 0.55 (80% CI, 0.40–0.74); $P = .01$	NR
Llovet et al,[14] 2019	Pembrolizumab + lenvatinib (67)	6	52.2[d]	11.8/9.7	20.4
Yau et al,[15] 2020	Nivolumab + cabozantinib S-malate (36) vs nivolumab + ipilimumab + cabozantinib S-malate (35)	53 vs 66	14 vs 31[b]	NR/5.4 vs NR/6.8	21.5 vs NR

Abbreviations: NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

[a]Only trials with a sample size of at least 35 patients included.

[b]According to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[16]

[c]Three arms with 3 different dosing regimens.

[d]According to modified RECIST.

Table 2.

Randomized Phase 3 Trials of Immune Checkpoint Blockers in Advanced Hepatocellular Carcinoma

Source	Treatment (No. of patients)	Main efficacy and safety results							
		OS			PFS			ORR	Grade 3–4 TRAEs
		Median	HR (95% CI)	*P* value	Median	HR (95% CI)	*P* value		
First-line									
Yau et al,[17] 2019 (CheckMate 459)	Nivolumab (371) vs sorafenib (372)	16.4 vs 14.7 mo	0.85 (0.72–1.02)	.08[a]	3.7 vs 3.8 mo	0.93 (0.79–1.10)		15% vs 7% (RECIST v1.1)	22% vs 49%
Finn etal,[18] 2020 (IMbravel50)	Atezolizumab + bevacizumab (336) vs sorafenib (165)	NE vs 13.2 mo	0.58 (0.42–0.79)	<.001[b]	6.8 vs 4.3 mo	0.59 (0.47–0.76)	<.001[b]	27% vs 12% (RECIST v1.1); 33% vs 13% (mRECIST)	36% vs 46%
Second-line									
Finn et al,[19] 2020 (KEYNOTE-240)	Pembrolizumab (278) vs placebo (135)	13.9 vs 10.6 mo	0.781 (0.611–0.998)	.02[a]	3.0 vs 2.8 mo	0.775 (0.609–0.987)	.02[a]	18.3% vs 4.4% (RECIST v1.1)	18.6% vs 7.5%

Abbreviations: HR, hazard ratio; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NE, not estimable; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TRAEs, treatment-related adverse events; TTP, time to progression.

[a]Primary end points not met.

[b]Primary end points met.

Table 3.

Selected Ongoing Studies Testing Immune Checkpoint Blockers in Combination With Anti-VEGF(R)-Targeted Therapies in Hepatocellular Carcinoma

Drug (mechanism)	Phase, setting	Primary end point	Primary completion	ClinicalTrials.gov identifier
Atezolizumab (PD-L1 mAb) + cabozantinib S-malate (TKI) vs sorafenib (TKI)	Phase 3, advanced	PFS/OS	Q3 2020	NCT03755791[59]
TACE + durvalumab (PD-L1 mAb) +/− bevacizumab (VEGF mAb) vs TACE + placebos	Phase 3, intermediate	PFS	Q1 2021	NCT03778957[60]
Camrelizumab (PD-1 mAb) + apatinib (TKI) vs sorafenib (TKI)	Phase 3, advanced	OS, PFS	Q4 2021	NCT03764293[61]
Durvalumab (PD-L1 mAb) +/− bevacizumab (VEGF mAb) vs placebo	Phase 3, early adjuvant	RFS	Q2 2022	NCT03847428[62]
Prembrolizumab (PD-1 mAb) + lenvatinib (TKI) vs lenvatinib (TKI)	Phase 3, advanced	PFS/OS	Q3 2022	NCT03713593[63]
Atezolizumab (PD-L1 mAb) + bevacizumab (VEGF mAb) vs active surveillance	Phase 3, early adjuvant	RFS	Q1 2023	NCT04102098[64]
Nivolumab + ipilimumab vs sorafenib/lenvatinib	Phase 3, advanced	OS	Q3 2023	NCT04039607[65]
Nivolumab (PD-1 mAb) + lenvatinib (TKI) vs lenvatinib (TKI)	Phase 2/3, advanced	OS	Q1 2021	NCT04044651[66]
Sintilimab (PD-1 mAb) + IBI305 (VEGF mAb) vs sorafenib (TKI)	Phase 2/3, advanced	OS, ORR	Q4 2022	NCT03794440[67]
Camrelizumab + apatinib or FOLFOX4 or GEMOX	Phase 2	Safety	Q4 2018	NCT03092895[68]
Sintilimab (PD-1 mAb) + anlotinib hydrochloride (TKI)	Phase 2, advanced	ORR, safety	Q4 2019	NCT04052152[69]
Nivolumab (PD-1 mAb) + sorafenib (TKI)	Phase 2, advanced	MTD, ORR	Q2 2020	NCT03439891[70]
Toripalimab (PD-1 mAb) + lenvatinib (TKI) + systemic chemotherapy	Phase 2, advanced	6-mos PFS	Q4 2020	NCT04170179[71]
Nivolumab (PD-1 mAb) + lenvatinib (TKI)	Phase 2, advanced	ORR, safety	Q3 2021	NCT03841201[72]
Atezolizumab (PD-L1 mAb) + bevacizumab (VEGF mAb)	Phase 2, advanced	ORR	Q4 2021	NCT04180072[73]
HAIC + camrelizumab (PD-1 mAb) + apatinib (TKI)	Phase 2, advanced	ORR	Q4 2021	NCT04191889[74]
Sintilimab (PD-1 mAb) + lenvatinib (TKI)	Phase 2, advanced	ORR	Q3 2022	NCT04042805[75]
TACE + durvalumab (PD-L1 mAb) + bevacizumab (VEGF mAb)	Phase 2, intermediate and advanced	6-mo PFS	Q4 2022	NCT03937830[76]
Camrelizumab (PD-1 mAb) + apatinib (TKI)	Phase 1/2, advanced	OS	Q4 2018	NCT02942329[77]
Pembrolizumab (PD-1 mAb) + sorafenib (TKI)	Phase 1/2, advanced	ORR	Q3 2020	NCT03211416[78]
Toripalimab (PD-1 mAb) + sorafenib (TKI)	Phase 1/2, advanced	6-mos PFS, safety	Q4 2020	NCT04069949[79]
Durvalumab (PD-L1 mAb) + tivozanib (TKI)	Phase 1/2, advanced	Safety	Q3 2021	NCT03970616[80]
Nivolumab (PD-1 mAb) + regorafenib (TKI)	Phase 1/2, advanced	Safety	Q4 2022	NCT04170556[81]
Pembrolizumab (PD-1 mAb) + lenvatinib (TKI)	Phase 1, advanced	Safety, ORR, DOR	Q3 2019	NCT03006926[82]

Drug (mechanism)	Phase, setting	Primary end point	Primary completion	ClinicalTrials.gov identifier
Spartalizumab (PD-1 mAb) + sorafenib (TKI)	Phase 1, advanced	Safety	Q1 2020	NCT02988440[83]
Nivolumab (PD-1 mAb) + lenvatinib (TKI)	Phase 1, advanced	Safety	Q2 2020	NCT03418922[84]
Pembrolizumab (PD-1 mAb) + regorafenib (TKI)	Phase 1, advanced	Safety	Q3 2020	NCT03347292[85]
Nivolumab (PD-1 mAb) + cabozantinib (TKI)	Phase 1, early neoadjuvant	Safety, completion	Q1 2022	NCT03299946[86]

Abbreviations: DOR, duration of response; FOLFOX4, fluorouracil, leucovorin, and oxaliplatin; GEMOX, gemcitabine and oxaliplatin; HAIC, hepatic arterial infusion chemotherapy; mAb, monoclonal antibody; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death 1 ligand 1; PFS, progression-free survival; Q, quarter; RFS, recurrence-free survival; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; VEGF(R), vascular endothelial growth factor (receptor).