review articles

Hepatocellular Carcinoma: Pick the Winner—Tyrosine Kinase Inhibitor Versus Immuno-oncology Agent–Based Combinations

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abstract

The treatment landscape for advanced hepatocellular carcinoma has changed dramatically over the past 4 years. We now have numerous options for patients in frontline, second-line, and beyond. The most significant impact has been the introduction of immunotherapy into our treatment paradigms. We now have regimens that induce consistent double-digit objective response rates and markedly improve overall survival (OS) with favorable side effect profiles. The combination of atezolizumab and bevacizumab has demonstrated that the combination of targeting programmed death-ligand 1 and the vascular endothelial growth factor axis can improve outcomes versus sorafenib in the IMBrave150 study. Results from the COSMIC-312 study evaluating the multikinase vascular endothelial growth factor receptor, hepatocyte growth factor receptor, and *AXL* tyrosine kinase receptor inhibitor cabozantinib in combination with atezolizumab improved progression-free survival versus sorafenib, but at this time, there is no improvement in OS and response rates were lower than expected. Additional data with similar combinations are awaited on the basis of encouraging early-phase data. In addition, the combination of cytotoxic T-lymphocyte–associated protein 4 and programmed cell death-1/programmed death-ligand 1 targeting is yielding similar promising early results, and the phase III HIMALAYA study met its primary end points of improving OS versus sorafenib for durvalumab plus tremelimumab and demonstrated noninferiority for single-agent durvalumab as well. However, this combination did not improve progression-free survival and objective response rates with this combination did not seem significantly different from that with single-agent durvalumab. Although there are still knowledge gaps in this rapidly changing landscape, we will address some of the important questions relevant to making therapeutic decisions in the management of advanced hepatocellular carcinoma in the modern era on the basis of our current knowledge of the safety and efficacy of these evolving regimens. The goal is to provide clinicians with the knowledge needed to optimize outcomes for their patients.

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KEY POINTS

- Systemic therapy has been shown to improve survival in advanced hepatocellular carcinoma (HCC) with high levels of evidence.
- Candidates for systemic therapy include those with vascular invasion, extrahepatic spread, or tumor confined to the liver but have progressed after locoregional therapies (transarterial chemoembolization, Y-90) or have diffuse and/or bilobar tumor in the liver not appropriate for these approaches.
- Immune checkpoint–based combinations are the standard of care for systemic treatment of HCC.
- The combination of atezolizumab and bevacizumab is the most active regimen reported to date on the basis of objective response rates, progression-free survival, and overall survival benefit, but the combinations of tremelimumab and durvalumab or atezolizumab and cabozantinib may be options for those who cannot receive bevacizumab when they are approved.
- Numerous systemic agents have been shown to improve survival in frontline and second-line HCC, but the optimal sequence for their use is not defined given the rapidly changing landscape.
- To date, no biomarkers or clinical parameters to identify patients most likely to benefit from a given regimen have been validated.

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Accepted on March 11, 2022 and published at ascopubs.org/journal/jco on June 1, 2022: DOI https://doi.org/10.1200/JCO.21.02605

CONTEXT

Key Objective

Systemic treatment options for advanced hepatocellular carcinoma (HCC) have changed significantly in the past several years from the use of single-agent tyrosine kinase inhibitors (TKIs) to immunotherapy combinations with monoclonal antibodies and TKIs. We present an overview of the safety, efficacy, and rationale for regimens that are currently approved and in development for advanced HCC and highlight the knowledge gaps that have evolved as newer, more effective regimens have emerged.

Knowledge Generated

Atezolizumab/bevacizumab appears to be the most active approved regimen in advanced HCC. Newer combinations including atezolizumab/cabozantinib and durvalumab/tremelimumab, which have positive phase III results, or lenvatinib/pembrolizumab or ipilimumab/nivolumab, which are in phase III studies, may be options for patients not candidates for bevacizumab. TKIs remain an option for patients who cannot receive programmed cell death-1/programmed death-ligand 1 inhibitors.

Relevance

The data and discussion presented provide context for clinical decision making as this landscape continues to evolve.

INTRODUCTION

Hepatocellular carcinoma (HCC) is now listed as the third leading cause of cancer death worldwide, and its incidence continues to rise.[1] Although there have been improvements in the management of hepatitis B and hepatitis C, there is a growing concern about the relationship between fatty liver disease and the development of cirrhosis and the subsequent development of HCC, which will drive a continuous increase in cases globally.[2] Before 2008, there were no systemic therapies that had shown a benefit in improving overall survival (OS) in patients with advanced HCC. Specifically, patients with Barcelona Clinic Liver Cancer (BCLC) stage C are characterized as being advanced on the basis of having extrahepatic spread, vascular invasion, and/or tumor-related symptoms and decreased performance status.[3] In addition, for patients with intermediate liver cancer (BCLC stage B) with multifocal disease in the liver but without vascular invasion, there were no medical options when locoregional treatments (transarterial chemoembolization) stopped working. For that reason, the results of the SHARP study, which demonstrated a significant improvement in survival with sorafenib, a vascular endothelial growth factor receptor (VEGFR), multikinase inhibitor versus placebo, supported its global approval and established a new standard of care for these patients.[4] Despite numerous studies, it took about a decade to see a new systemic therapy approved in 2017.[5] Since then, we have had an explosion of positive phase III studies and new approvals including new options in the frontline setting and the second-line setting.

As of today, US Food and Drug Administration (FDA)–approved options in the frontline setting include sorafenib,[4] lenvatinib,[6] and the combination of atezolizumab and bevacizumab.[7] In addition, there have been recent presentations of positive results from two global frontline phase III studies: the COSMIC-312[8] study evaluating the combination of atezolizumab and cabozantinib versus sorafenib and the HIMALAYA[9] study evaluating the combination of tremelimumab and durvalumab vs sorafenib. The combination of sintilimab and a bevacizumab biosimilar injection was also shown to improve survival and progression-free survival (PFS) vs sorafenib in a China-based study.[10] In the second-line setting, regorafenib,[5] cabozantinib,[11] and ramucirumab[12] all have full FDA approval after progression on sorafenib, and pembrolizumab[13] and the combination of ipilimumab and nivolumab[14] have accelerated approval for the same population. Finally, a recent presentation confirms the activity of single-agent pembrolizumab in a phase III study from Asia,[15] which together with a previous global phase III study,[16] should support the full approval of pembrolizumab in this setting.

With all these positive results, recent approvals, and ongoing studies, there is an entirely new set of questions to be asked by clinicians. Here, we review the relevant data that will provide the knowledge needed to approach them.

RATIONALE BEHIND VASCULAR ENDOTHELIAL GROWTH FACTOR TARGETING, IMMUNOTHERAPY, AND COMBINATION APPROACHES IN HCC

HCC is a hypervascular tumor that arises most often in the background of chronic liver disease.[17] The cirrhotic liver is a premalignant organ, and as dysplastic nodules progress to carcinomas, neovascularization processes are initiated, which lead to a highly dysfunctional vascular tumor microenvironment.[18,19] This dysfunctional neovascularization promotes intratumoral hypoxia, which, in turn, leads to the production of hypoxia-inducible factors that contributes to tumor growth.[20] Although there are many paracrine growth factors that mediate this dysfunctional angiogenesis, vascular

endothelial growth factor (VEGF) is crucial for this process and its consequences.[21] These concepts supported the clinical development of VEGF direct therapies in patients with HCC, and the majority of the currently approved agents in HCC management are directed in part against the VEGF axis.

Overtime, our understanding of the importance of VEGF signaling in tumor biology has evolved. VEGF directly interacts with several components of the innate and cellular immune system and indirectly affects the ability of lymphocytes to infiltrate the tumor.[22,23] Regarding the innate immune system, VEGF impairs antigen presentation by dendritic cells and promotes polarization toward immunosuppressive, M2 peristromal macrophages.[22,24] VEGF also affects the ratio of regulatory T cells (Tregs) to CD8+ tumor-infiltrating lymphocytes (TILs) and impairs the production of interferon-gamma by cytotoxic T cells.[25]

Parallel with advances in understanding of angiogenic signaling came the development of immune checkpoint inhibitors (ICIs). The programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis and the cytotoxic T-lymphocyte–associated protein 4 (CTLA-4)/B7-1 axis are now known to be important immune checkpoints in human biology including normal liver function and HCC pathophysiology. In normal liver, these checkpoints help promote an immune tolerogenic phenotype to prevent excessive activation in the face of repeated, frequent antigen exposure.[26] PD-1 and CTLA-4 expression is directly correlated with the amount of CD8+ TILs and associated with shorter disease-free survival after curative resection of HCC.[27] Both PD-1 and CTLA-4 promote activation of Tregs, leading to T_H2 responses and immunosenescence, with PD-1 activity further exacerbated by tumor hypoxia.[28,29]

The immune checkpoint pathways have a considerable overlap with angiogenesis pathways, providing a rationale for treatment combinations. Sorafenib treatment is known to decrease Treg populations and increase the proportion of PD-1+ TILs compared with Tregs.[30] Anti-VEGF therapy allows dendritic cell maturation to lead to priming and activation of T cells.[31] Although anti-VEGF therapy normalizes tumor microvasculature, regional areas of hypoxia may develop and PD-1 therapy may counter the reflexive increase of PD-1 expression mediated by hypoxia-inducible factors.[32,33] Translational work in RCC demonstrated that the combination anti-VEGF and anti–PD-L1 therapy leads to increased T_H1 chemokines recruiting TILs into tumors.[34] Finally, foundational preclinical work suggested synergy between CTLA-4 inhibition and PD-1 inhibition in melanoma cell lines.[35] This led to rapid expansion of trials testing this combination in numerous malignancies, including in HCC with the aforementioned role in modulating the immunosenescence that those checkpoints promote.[36] Figure 1 summarizes the interplay of various tyrosine kinase receptors and immune checkpoint inhibitors in the tumor microenvironment.

SINGLE-AGENT DATA

Table 1 displays the significant phase III trials that have been conducted for single-agent therapies in HCC. These studies have generally concentrated on similar patient populations: those that are well compensated with Child-Pugh A liver disease; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and BCLC stage C disease or BCLC B not amenable to locoregional treatments. Sorafenib gained approval in 2008 on the basis of the results of the randomized double-blind phase III SHARP trial. In addition, another trial in the Asia-Pacific region demonstrated significantly improved OS with very similar hazard ratios (HRs) of 0.68 and 0.69, resepctively.[4,37] After these studies, there was a decade of phase III failures.

Before regorafenib, no drug had proven to improve survival after prior sorafenib, and therefore, all phase III studies in this setting were placebo-controlled. Similar to frontline trials, these studies focused on patients with Child-Pugh A liver disease and ECOG 0 or 1, but generally included patients who had refractory disease or had intolerance to only sorafenib in the frontline setting. The RESORCE trial required documented progression on prior sorafenib and a minimum period and dose of sorafenib before coming on trial, and the CELESTIAL trial included patients with up to two lines of prior therapy. Regorafenib, an oral multikinase inhibitor targeting VEGFR, platelet-derived growth factor receptor, *RET, c-kit*, fibroblast growth factor receptor (FGFR) 1, and angiopoietin-1 receptor (tyrosine kinase with Ig and epidermal growth factor [EGF] homology domains), ushered in a wave of second-line approvals after improvements in OS, were seen in the RESORCE trial.[5] In the CELESTIAL trial,[11] cabozantinib, an inhibitor of VEGFR1-3, *MET*, and *AXL* met its primary end point of improving OS. The REACH-2[12] trial accrued patients using a biomarker for patient selection, serum alpha-fetoprotein $\geq$ 400 ng/mL, and demonstrated that ramucirumab, a monoclonal antibody against VEGFR-2, also improved OS after prior sorafenib.

In the frontline setting, the REFLECT study demonstrated noninferiority of lenvatinib, a tyrosine kinase inhibitor (TKI) toward VEGFR 1-3, FGFR1-4, platelet-derived growth factor receptor-α, *RET*, and *c-kit*, versus sorafenib for the primary end point of OS.[6] Objective response rate (ORR) favored lenvatinib, which might have driven the findings in REFLECT that OS was improved in responders (22.4 months) compared with nonresponders (11.4 months).[38] With the exception of lenvatinib, which has double-digit response rates, the survival benefit from the TKIs is driven by slow progression. In a Chinese study,[39] donafenib, a deuterated sorafenib derivative, is the only single-agent TKI that has shown superiority in terms of OS when compared with sorafenib although it is not approved in the United States. All the TKIs have similar side effect profiles although the degree and frequencies vary from molecule to molecule. Most commonly, these include fatigue, anorexia

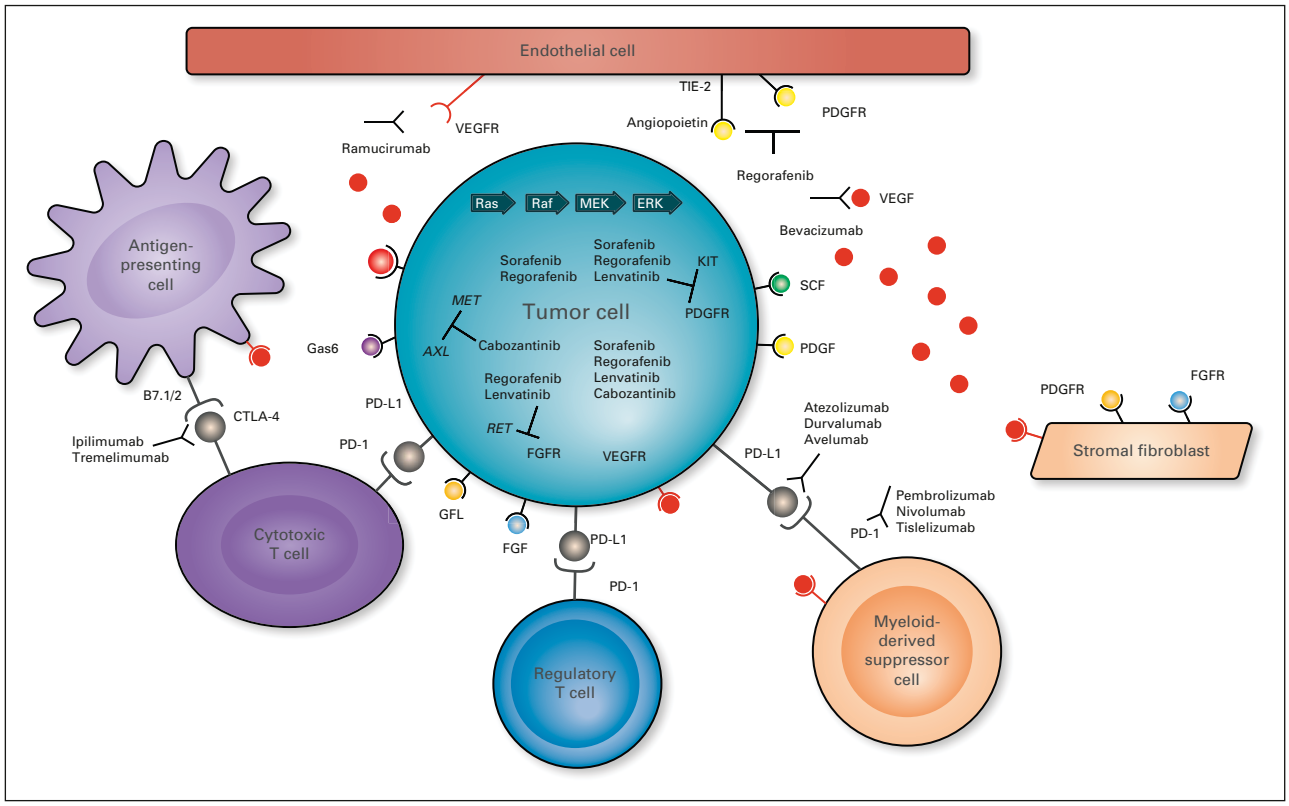

FIG 1. Interplay between various different components of the stroma, innate immune system, and cellular immune system with the cancer cell. CTLA-4, cytotoxic T-lymphocyte–associated protein 4; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; Gas6, growth arrest–specific protein 6; GFL, glial family ligand; HGF, hepatocyte growth factor; PD-1, programmed cell death-1; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PD-L1, programmed cell death-ligand 1; SCF, stem-cell factor; TIE-2, tyrosine kinase with Ig and EGF (epidermal growth factor) homology domains; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

TABLE 1. Relevant Completed Phase III Single-Agent Trials

Drug	Trial Name	Comparator Group	No.	Primary End Point Median OS	Most Frequent, Any Cause, Any Grade AEs
Sorafenib	SHARP	Placebo, first-line	602	10.7 months *v* 7.9 months (HR, 0.69; 95% CI, 0.55 to 0.87), $P < .001$	Diarrhea (39%), fatigue (22%), palmar plantar erythrodysesthesia (21%)
Lenvatinib	REFLECT	Sorafenib, first-line	954	13 months *v* 12.3 months (HR, 0.92; 95% CI, 0.79 to 1.06), noninferior	Hypertension (42%), diarrhea (39%), decreased appetite (34%)
Regorafenib	RESORCE	Placebo, second-line	573	10.6 months *v* 7.8 months (HR, 0.63; 95% CI, 0.50 to 0.79), $P < .0001$	Palmar plantar erythrodysesthesia (52%), diarrhea (33%), fatigue (29%)
Cabozantinib	CELESTIAL	Placebo, second- or third-line	707	10.2 months *v* 8 months (HR, 0.76; 95% CI, 0.63 to 0.92), $P = .005$	Diarrhea (54%), decreased appetite (48%), palmar plantar erythrodysesthesia (46%)
Ramucirumab	REACH-2	Placebo, second-line, AFP > 400 ng/mL	292	8.5 months *v* 7.3 months (HR, 0.71; 95% CI, 0.531 to 0.949), $P = .0199$	Fatigue (24%), peripheral edema (24%), decreased appetite (22%)
Nivolumab	Checkmate 459	Sorafenib, first-line	743	16.4 months *v* 14.8 months (HR, 0.58; 95% CI, 0.72 to 1.00), $P = .0522$	Fatigue (14%), pruritus (12%), rash (11%)
Pembrolizumab	KEYNOTE 240	Placebo, second-line	413	13.9 months *v* 10.6 months (HR, 0.781; 95% CI, 0.611 to 0.998), $P = .0238$ ($P = .0174$ for significance)	AST increase (22.6%), bilirubin increase (18.6%), fatigue (18.6%)

Abbreviations: AE, adverse event; AFP, alpha-fetoprotein; HR, hazard ratio; OS, overall survival.

and weight loss, diarrhea, hypertension, proteinuria, and hand-foot skin reaction. Ramucirumab can relate most of its side effects to its specific interaction with the VEGFR and has more fluid retention/ascites and some increase in encephalopathy, possibly from vascular shunting.

Both the PD-1 inhibitors nivolumab and pembrolizumab received accelerated approval on the basis of single-arm trials after prior sorafenib in the phase I/II Checkmate 040 and phase II KEYNOTE 224 trials, respectively.[13,40] Both showed response rates of approximately 15%-20% and were well tolerated. Importantly, these early studies confirmed the safety of these agents in a population of patients with underlying liver disease. Although these patients were all well-compensated with Child-Pugh A liver disease, the side effect profile and incidence of immune-related adverse events (AEs) really did not differ significantly from those seen in other cancer populations. The confirmatory phase III trial Checkmate 459 evaluated nivolumab compared with sorafenib in the first-line setting. The study confirmed the ORRs, long duration of response, and overall safety of nivolumab in this population but did not meet its primary end point of improving OS (median OS with nivolumab, 16.4 months [95% CI, 13.9 to 18.4] *v* 14.7 months with sorafenib [95% CI, 11.9 to 17.2], HR 0.85 [95% CI, 0.72 to 1.02]; *P* value = .075).[41] Because of this finding, in late April 2021, the FDA's Oncologic Drug Advisory Committee voted five to four against continuing the accelerated approval for nivolumab as monotherapy in patients previously treated with sorafenib and the approval was voluntarily withdrawn. Similarly, the phase III trial KEYNOTE 240 comparing pembrolizumab with placebo in the second-line setting also confirmed pembrolizumab's safety and activity in this population, but it did not meet the statistical threshold for its coprimary end point of increasing OS (13.9 months [95% CI, 11.6 to 16.0] for pembrolizumab *v* 10.6 months [95% CI, 8.3 to 13.5]) for placebo (HR 0.781; 95% CI, 0.611 to 0.998; $P = .0238$, $P = .0174$ needed for significance).[16] In April 2021, the Oncologic Drug Advisory Committee voted nine to zero to continue its accelerated approval, citing that pembrolizumab may fill a void for patients who may not be candidates for an immuno-oncology agent (IO)–based regimen in the frontline setting and that there were ongoing confirmatory studies. KEYNOTE 394, which had a similar trial design as KEYNOTE 240 but accrued patients exclusively from Asia, was recently presented.[15] The study reported an improvement in OS with pembrolizumab versus placebo of 14.6 months (12.6-18.0) versus 13.0 months (10.5-15.1) with a HR of 0.79 (95% CI, 0.63 to 0.99; $P = .018$). It improved the PFS from 2.3 months to 2.6 months (HR 0.74; 95% CI, 0.60 to 0.92; $P = .0032$) and ORRs from 1.3% to 13.7% with a median duration of response of 23.9 months in the pembrolizumab arm. There were no new safety signals reported. It is critical to note that, for all the single-agent data discussed above, none were generated in the era of first-line options other than sorafenib.

VEGF TARGETING/MONOCLONAL ANTIBODY AND IMMUNOTHERAPY

The challenges with phase III studies of single-agent ICI and the evidence that targeting the VEGF axis may promote a favorable microenvironment for an immune response paved the way for combination approaches. A phase Ib study of the PD-L1 antibody atezolizumab and the anti-VEGF antibody bevacizumab established the safety and provided an efficacy signal for this combination.[42] The IMbrave 150 study evaluated this combination versus sorafenib in an open-label global phase III study.[43] Earlier studies of bevacizumab alone in HCC suggested that it might have single-agent antitumor activity, but there were concerns about bleeding risk in a cirrhotic population.[44] To mitigate that, IMbrave 150 required upper endoscopy within six months of starting study drug and varices had to be managed per institutional guidelines. Varices that were felt to be of high risk for bleeding were excluded. In the primary analysis, median OS and PFS were significantly improved versus sorafenib with HRs of 0.58 (95% CI, 0.42 to 0.79; $P < .001$) and 0.59 (95% CI, 0.47 to 0.76; $P < .001$), respectively. Although the median OS was not reached in the treatment arm in the primary analysis, with additional follow-up, it was established to be 19.2 months.[45] These survival end points are supported by an ORR of 30% by RECIST 1.1 and a disease control rate of 74% with a median duration of response over 18 months. Importantly, the regimen was well-tolerated with similar all-grade and grade 3-5 AEs as sorafenib. Fewer patients on the combination arm needed to stop both drugs as compared with sorafenib for AEs (7% for the combination *v* 10.3% for sorafenib). Common immune-related AEs were seen in the experimental arm, but there were no new safety concerns or liver-specific toxicities. In regard to bleeding events, all-grade bleeding events were higher with the combination (25.2%) as compared with sorafenib (17.3%), but grade 3/4 events were similar (6.4% *v* 5.8%, respectively) and grade 5 GI bleeding events were rare with atezolizumab and bevacizumab (four total). These data are supported by the more favorable quality-of-life readouts and patient-reported outcomes with the combination as well.[46] The approach has since been validated in a similar phase III study (ORIENT-32) performed in China, which compared the combination of the PD-1 antibody sintilimab and a bevacizumab biosimilar (IBI305) with sorafenib, yielding very similar results.[10] Specifically, HRs were 0.57 (95% CI, 0.43 to 0.75; $P < .0001$) and 0.56 (95% CI, 0.46 to 0.70; $P < .0001$) for OS and PFS, respectively, and the ORR was 20.5% for the combination.

VEGF TARGETING/MULTIKINASE INHIBITOR AND IMMUNOTHERAPY

In regard to potentiating ICI activity, besides VEGF, there are several other kinase targets that may be relevant including the FGFR, the TAM receptors (Tyro3, *AXL*, and Mer), tyrosine kinase with Ig, and EGF homology domains (tyrosine kinase with Ig and EGF homology domains), among others.[47,48]

Table 2 illustrates the wide, active clinical trial landscape exploring these combinations. A consensus of the completed phase I studies demonstrates the safety of these combinations.[49-54] Although most of these studies are in the frontline setting, the question of whether an IO + TKI approach could overcome resistance in patients who do not respond or progress on IO + VEGF antibody is being evaluated and could provide insight into sequencing strategies in the future (ClinicalTrials.gov identifiers: NCT04770896 and NCT04696055).

There are several combinations now in phase III studies. The combination of pembrolizumab and lenvatinib in the single-arm phase Ib KEYNOTE 524 trial/Trial 116 showed a promising ORR of 36%, a PFS of 8.6 months, and an OS of 22 months, without unexpected toxicities.[49] Again, although immune-mediated AEs were reported, they were not increased as compared with single-agent pembrolizumab. The majority of AEs were driven by lenvatinib. This combination is now being evaluated in the ongoing phase III study LEAP-002 comparing lenvatinib plus pembrolizumab with lenvatinib plus placebo (ClinicalTrials.gov identifier: NCT03713593).

The combination of atezolizumab and cabozantinib was advanced into phase III without significant preliminary data in HCC. The COSMIC-312 trial randomly assigned 877 patients between atezolizumab and cabozantinib or sorafenib in patients with advanced HCC without prior treatment.[8] The study met its primary end point of improving the PFS from 4.2 months with sorafenib to 6.8 months in the treatment arm (HR, 0.63; 95% CI, 0.44 to 0.91; $P = .0012$). However, at the time of this analysis, there was

TABLE 2. VEGF Targeting/Multikinase Inhibitor and Immunotherapy Combination Studies

PD-1/PD-L1 Agent and TKI Used	Comparator Group	Disease Setting	No.	Name	NCT Identifier
Atezolizumab/cabozantinib	Sorafenib	Frontline treatment of advanced HCC	740	COSMIC-312	NCT03755791
Atezolizumab/lenvatinib or atezolizumab/sorafenib	Lenvatinib or sorafenib	Second-line after progression on atezolizumab/bevacizumab	554	IMbrave251	NCT04770896
Avelumab/regorafenib	None	Locally advanced or unresectable	362 (HCC cohort)	REGOMUNE	NCT03475953
Avelumab/axitinib	None	Frontline treatment of advanced HCC	22	VEGF Liver 100	NCT03289533
Nivolumab/regorafenib	None	Second-line treatment	60	GOING	NCT04170556
Nivolumab/regorafenib	None	Frontline treatment of advanced HCC	42	RENOBATE	NCT04310709
Nivolumab/lenvatinib	None	Frontline treatment of advanced HCC	30	—	NCT03418922
Nivolumab/sorafenib	None	Frontline treatment of advanced HCC	40	—	NCT03439891
Nivolumab/cabozantinib	None	Neoadjuvant before resection	15	—	NCT03299946
Nivolumab/lenvatinib	None	Frontline treatment of advanced HCC	50	IMMUNIB	NCT03841201
Nivolumab/APL-101	None	Advanced HCC, any line	20 (HCC cohort)	—	NCT03655613
Pembrolizumab/lenvatinib	None	Frontline treatment of advanced HCC	104	KEYNOTE 524/ Trial 116	NCT03006926
Pembrolizumab/lenvatinib	Placebo/lenvatinib	Frontline treatment of advanced HCC	750	LEAP-002	NCT03713593
Pembrolizumab/sorafenib	None	Frontline treatment of advanced HCC	27	—	NCT03211416
Pembrolizumab/regorafenib	None	Frontline treatment of advanced HCC	57	—	NCT03347292
Pembrolizumab/regorafenib	None	After progression on PD-1/PD-L1 therapy	119	—	NCT04696055
Pembrolizumab/cabozantinib	None	Frontline treatment of advanced HCC	29	—	NCT04442581
Durvalumab/lenvatinib	None	Frontline treatment of advanced HCC	20	DULECT2020-1	NCT04443322
Durvalumab/cabozantinib	None	Locally advanced or unresectable	29 (HCC = 1 cohort)	CAMILLA	NCT03539822
Durvalumab/tivozanib	None	Frontline treatment of advanced HCC	42	—	NCT03970616
Tislelizumab/regorafenib	Regorafenib (phase II portion)	Frontline treatment of advanced HCC	125	—	NCT04183088
Tislelizumab/lenvatinib	None	Frontline treatment of advanced HCC	66	—	NCT04401800
Tislelizumab/sitravatinib	None	Frontline treatment or refractory HCC	111	—	NCT03941873
Pembrolizumab or nivolumab/ vorolanib	None	No other standard-of-care options available aside from pembrolizumab or nivolumab	36 (HCC cohort)	—	NCT03511222

Abbreviations: HCC, hepatocellular carcinoma; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

no difference in median OS with combination, and although ORRs were improved from 3.7% with sorafenib to 11% with cabozantinib and atezolizumab, this is less than the 17% rate reported with single-agent atezolizumab in earlier phase studies (n = 59).[42] AEs with the combination were generally in line with those seen with single-agent cabozantinib and checkpoint inhibitors. Grade 3/4 toxicities were higher with the combination (54% *v* 32%), but only 6.1% of patients had to discontinue treatment because of toxicity. Consistent with single-agent cabozantinib studies, high-grade bleeding events were not reported.

The RESCUE study evaluated the combination of the PD-1 antibody camrelizumab and the VEGFR-2 TKI apatinib in a single-arm study in China in mostly hepatitis B virus–related liver cancers in the first- and second-line setting. The study reported an ORR of 34.3% (24 of 70; 95% CI, 23.3 to 46.6) in the first-line and 22.5% (27 of 120; 95% CI, 15.4 to 31.0) in the second-line cohort per independent review. The median PFS in both cohorts was 5.7 months (95% CI, 5.4 to 7.4) and 5.5 months (95% CI, 3.7 to 5.6), respectively. The 12-month survival rate was 74.7% (95% CI, 62.5 to 83.5). Grade ≥ 3 treatment-related AEs (TRAEs) were reported in 77.4% of patients, with the most common being hypertension (34.2%). The regimen is now in a global randomized phase III study versus sorafenib in the frontline setting (ClinicalTrials.gov identifier: NCT03764293).

IO-IO COMBINATIONS: PD-1/PD-L1 AND CTLA-4 COMBINATIONS

There is rationale for the dual targeting of both the CTLA-4 and PD-1/PD-L1 pathways given their distinct points in the regulation of adaptive immunity[55]: (1) reversing the CTLA-4–induced inhibition of early T-cell activation and (2) preventing PD-1 effects on T-cell exhaustion.

In HCC, this approach was first studied in a 3-arm expansion of the CheckMate 040 study.[36] Patients who had previously received sorafenib were randomly assigned 1:1:1 to nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, administered once every 3 weeks (four doses), followed by nivolumab 240 mg once every 2 weeks (arm A); nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, administered once every 3 weeks (four doses), followed by nivolumab 240 mg once every 2 weeks (arm B); or nivolumab 3 mg/kg once every 2 weeks plus ipilimumab 1 mg/kg once every 6 weeks (arm C).

With about 50 patients per arm, the median investigator-assessed ORR was 32% (95% CI, 20 to 47) in arm A, 27% (95% CI, 15 to 41) in arm B, and 29% (95% CI, 17 to 43) in arm C. Interestingly, despite the very similar ORRs, the median OS in arm A was longest, 22.8 (9.4 to NE) versus 12.5 (7.6 to 16.4) and 12.7 (7.4 to 33) for arms B and C, respectively. Although this combination demonstrated a higher response rate than single-agent nivolumab, it also increased side effects; any-grade TRAEs were reported in 46 of 49 patients (94%) in arm A, 35 of 49 patients (71%) in arm B, and 38 of 48 patients (79%) in arm C, and immune-mediated AEs were increased in all arms as well, most commonly rash, hepatitis, and adrenal insufficiency, with the highest rates in arm A. Systemic corticosteroids were used to manage TRAEs in 25 patients (51%) in arm A, 12 patients (24%) in arm B, and 11 patients (23%) in arm C. These efficacy and safety data were used to support the FDA decision to grant arm A accelerated approval in March 2020 for the second-line treatment of HCC after prior sorafenib. The CheckMate 9DW study is a global phase III confirmatory study evaluating ipilimumab and nivolumab versus either sorafenib or lenvatinib in the first-line setting of advanced HCC (ClinicalTrials.gov identifier: NCT04039607).

Tremelimumab and durvalumab were first evaluated in a randomized phase II study of patients intolerant to or progressing on sorafenib.[56] This study evaluated both single-agent durvalumab (1,500 mg once every 4 weeks) or tremelimumab (750 mg once every 4 weeks [seven doses] and then once every 12 weeks) and two different combinations, T300 + D (tremelimumab 300 mg once plus durvalumab 1,500 mg once followed by durvalumab 1,500 mg once every 4 weeks) and T75 + D (n = 84, tremelimumab 75 mg once every 4 weeks plus durvalumab 1,500 mg once every 4 weeks [four doses] followed by durvalumab 1,500 mg once every 4 weeks). ORRs were (95% CI) 24.0% (14.9 to 35.3), 10.6% (5.4 to 18.1), 7.2% (2.4 to 16.1), and 9.5% (4.2 to 17.9), for T300 + D, durvalumab, tremelimumab, and T75 + D, respectively. All-grade AEs across arms occurred in 98.6%, 94.1%, 97.1%, and 97.6%, any-grade TRAEs occurred in 82.4%, 60.4%, 84.1%, and 69.5%, and grade > 3 TRAEs occurred in 37.8%, 20.8%, 43.5%, and 24.4%, respectively. Common immune-related AEs were observed and were higher in the tremelimumab-containing arms, 31.1%, 24.6%, and 26.8% for T300 + D, tremelimumab alone, T75 + D, respectively, as compared with durvalumab alone (15.8%). TRAEs requiring systemic steroids were also reported at higher frequency in the tremelimumab-containing arms (T300 + D: 24.3%, tremelimumab 26.1%, and T75 + D 24.4% *v* durvalumab 9.9%). The longest survival was seen in the T300 + D arm, 18.73 months (95% CI, 10.78 to 27.27), as compared with 13.57 (95% CI, 8.74 to 17.64), 15.11 (95% CI, 11.33 to 20.50), and 11.30 (95% CI 8.38 to 14-95) for the durvalumab alone, tremelimumab alone, and the T75 + D arms, respectively. The phase III HIMALAYA study randomly assigned 1,324 patients to three arms in a 1:1:1 fashion to receive the so-called STRIDE regimen (the T300 + D arm), single-agent durvalumab, or sorafenib. The primary end point was median OS in the T300 + D arm versus sorafenib with a key secondary objective of durvalumab alone versus sorafenib, and other typical end points were PFS, ORR, duration of response, and safety. The durvalumab versus sorafenib arm was powered for noninferiority with the same noninferiority margin of 1.08 as used in the REFLECT study. Also similar to REFLECT, and different from the other IO

combination studies, HIMALAYA excluded the poor prognostic group of patients with main portal vein invasion. The study met its primary end point with a median OS of 16.6 months in the combination arm versus 13.8 months in the sorafenib arm (HR 0.86; 96% CI, 0.65 to 0.92; $P = .0035$). The study also met its secondary end point of establishing noninferiority of durvalumab versus sorafenib with the median OS of 16.6 months (14.1 to 19.1) versus sorafenib with 13.8 months (12.3 to 16.1) and a HR 0.86 (95.67% CI, 0.73 to 1.03). Unlike the other two combination studies, HIMALAYA did not demonstrate an improvement in PFS for either of the experimental arms with medians of 3.78 (3.68 to 5.32), 3.65 (3.19 to 3.75) and 4.07 (3.75 to 5.49) months for the combination, durvalumab, and sorafenib arms, respectively. ORRs were higher with the durvalumab-containing arms, 20.1% for T300 + D, 17.0% for durvalumab, and 5.1% for sorafenib. The median duration of response was 22.34 months for T300 + D and 16.82 months for durvalumab. There were no new safety events seen in this study. Grade 3/4 TRAEs were reported in 25.8%, 12.9%, and 36.9% of patients in the combination, durvalumab, and sorafenib arms, respectively. There were more all-grade immune-mediated AEs in the combination arm (35.8%) versus durvalumab (16.5%). High-grade bleeding events were uncommon. Quality-of-life data are awaited.

CONSIDERATIONS FOR PATIENT SELECTION

On the basis of the data presented to date, it would appear that atezolizumab and bevacizumab is the most active regimen in the frontline setting for patients eligible for systemic therapy. The IMbrave 150 study reported the longest median survival and the highest ORR in the treatment arm while improving quality of life. For patients who are not eligible for bevacizumab because of its side effect profile, the combination of durvalumab and tremelimumab would be an option once approved given its improvements in median OS and ORRs and side effect profile. In addition, atezolizumab and cabozantib met its primary end point of improving PFS and did have a higher response rate than sorafenib, but OS has not shown a significant improvement at this time. For patients who are not candidates for a doublet because of concerns for side effects, when approved, single-agent durvalumab demonstrated noninferiority to sorafenib. For patients who are not candidates for IO therapy, either sorafenib or lenvatinib is an appropriate choice. There have been intense efforts to identify biomarkers of response to IO therapy. Although there are ongoing efforts, to date, no single assay has been validated and none are used in clinical practice.[57] Currently, there is no tissue-based biomarker or clinical selection marker to point us toward one regimen or another. A recent study[58] has suggested less survival benefit of IO regimens in patients with nonviral-related liver disease, but this has not been evaluated prospectively and studies have not demonstrated a difference in ORRs on the basis of etiology.

There are several groups of patients who are not typically included in clinical trials of HCC, which require clinical judgment. For one, many patients seen in clinic do not meet all the inclusion and exclusion criteria of clinical studies. This includes patients with less compensated liver disease and/or poorer performance status (> ECOG 1). For these groups, there are really two issues: (1) can we even improve survival with treatment or is their survival limited by comorbidities and (2) is treatment safe. Although we do not

TABLE 3. Available Data on the Current Regimens in Global Phase III Studies in the Frontline Setting

Study Name (combo)	Class	Phase	HR mOS (95% CI)	mOS, mo	HR PFS (95% CI)	mPFS, mo	ORR, %	All TRAEs, %	Grade 3/4 TRAE, %	Discontinuation Rate for AE, %
IMbrave 150 (atezolizumab bevacizumab)	PD-L1 VEGF	III	0.58 (0.42 to 0.79)	19.2	0.59 (0.47 to 0.76)	6.8	30	83.9	35.6	7
HIMALAYA (durvalumab-tremelimumab)	PD-L1 CTLA-4	III	0.78 (0.65 to 0.92)	16.4	0.90 (0.77 to 1.05)	3.78	20.1	75.8	25.8	8.2
COSMIC-312 (atezolizumab-cabozantinib)	PD-L1 TKI	III	0.90 (96% CI, 0.69 to 1.18), IA	15.4 (IA)	0.63 (0.44 to 0.91)	6.8	11	NR	53.8	6.1
KEYNOTE 524 (pembrolizumab-lenvatinib)	PD-1 TKI	Ib	—	22	—	8.6	36	95.0	67	6
CheckMate040 (nivolumab-ipilimumab)	PD-1 CTLA-4 (arm A)	I/II	—	22.8	—	NR	32	94.0	53	22

Abbreviations: AE, adverse events; CTLA, cytotoxic T-lymphocyte–associated protein; HR, hazard ratio; IA, interim analysis; mOS, median overall survival; mPFS, median progression-free survival; NR, not reported; ORR, objective response rate (RECIST); PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event; VEGF, vascular endothelial growth factor.

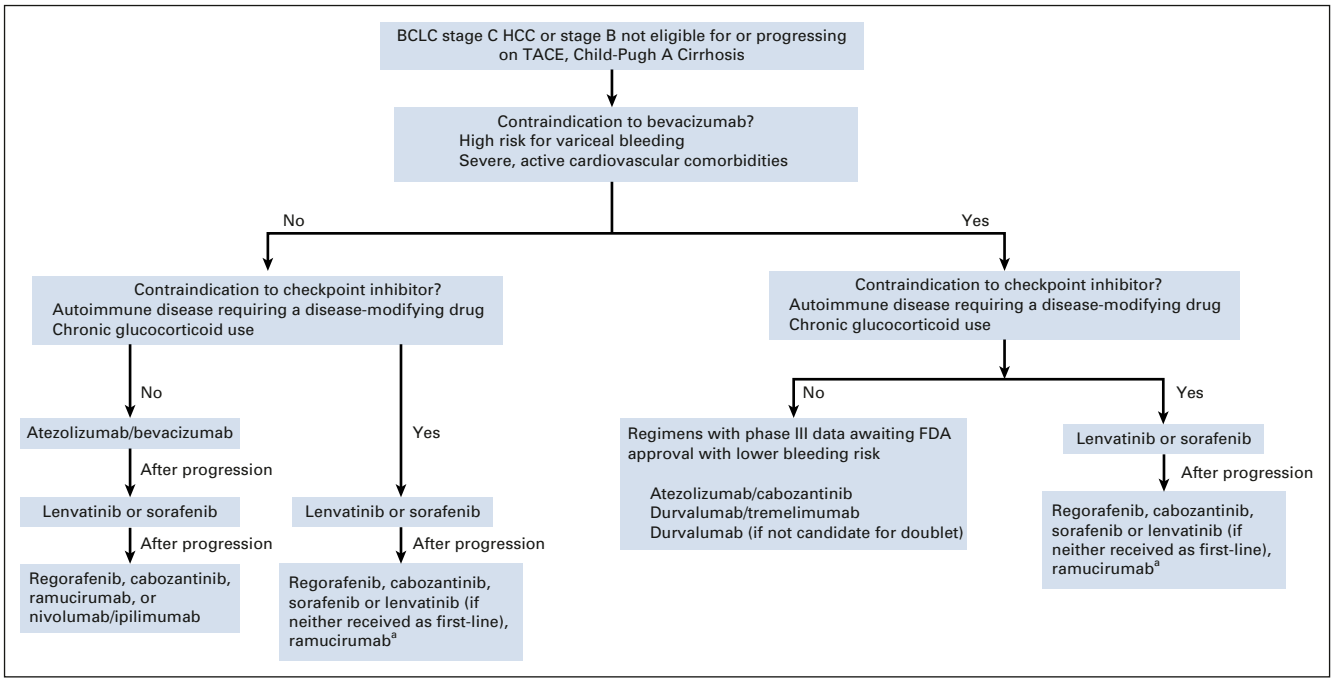

FIG 2. A proposed treatment algorithm for patients who are candidates for systemic treatment. [a]Single agent pembrolizumab or nivolumab/ipilimumab could be considered if prior contraindication to checkpoint inhibitor has resolved. BCLC, Barcelona Clinic Liver Cancer; FDA, US Food and Drug Administration; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

have data on the efficacy of most of the drugs that are approved in these populations, a balanced discussion with patients regarding the unknown benefit and chance for increased toxicity may be appropriate if they are able to come to clinic. This may be especially relevant for patients whose liver function and performance status are compromised from a large tumor burden, and now that we have regimens that have higher ORRs, their clinical condition may improve with treatment. Another population is the subset of patients who undergo liver transplant and recur with HCC. In these patients, the use of immunotherapy should be considered contraindicated given the high risk of graft failure.[59] The tyrosine kinase inhibitors or ramucirumab can be used with close follow-up and attention as there is likely a higher risk of AEs.

In conclusion, we have seen numerous new agents approved in the past few years that are improving outcomes for our patients and now with positive data from phase III studies with ICIs, we are seeing significant gains in survival in the frontline setting with side effect profiles that are more favorable than TKIs. Currently, atezolizumab and bevacizumab is the most active FDA-approved regimen for advanced liver cancer. We have new data emerging from two completed phase III studies of atezolizumab and cabozantinib and tremelimumab and durvalumab. Although these regimens will carry the same risks for patients with contraindication to ICIs, they could be an option for those patients at high risk of bleeding. For patients who cannot receive ICIs, single-agent sorafenib or lenvatinib is an appropriate first-line option. Table 3 shows available data on the current regimens in global phase III studies in the frontline setting, and Figure 2 provides a suggested algorithm for sequencing.

In the end, the successes that we are seeing are generating more questions that will take time to answer (Table 4). Results of several ongoing phase III studies evaluating these novel regimens in earlier stages of HCC are ongoing, including in the adjuvant setting after curative resection or ablation and in patients with BCLC B, intermediate-stage HCC in combination with locoregional treatments. This is

TABLE 4. Future Questions for Systemic Therapy in Hepatocellular Carcinoma

What regimen will be the next step forward in frontline that will beat the TKI/VEGF-IO and IO-IO doublets?
Can we identify a biomarker to guide the best regimen for a given patient?
For patients who progress on IO-based combinations frontline, what is the best second-line option?
Will there be activity for a TKI-IO or IO-IO combination after atezolizumab and bevacizumab in the frontline?
If a patient gets an IO-IO combination, will they benefit from a TKI-based regimen in second-line?
Patients who may get a TKI-IO regimen in frontline, how do they respond to sequential TKIs after?

Abbreviations: IO, immuno-oncology agent; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

certainly an exciting time in the HCC field, and despite our progress, we must continue to work together in a multidisciplinary manner to offer our patients the most appropriate treatment for their condition and maintain a commitment to research and biomarker development to keep things moving ahead.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.02605.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71:209-249, 2021
2. Sanyal AJ, Van Natta ML, Clark J, et al: Prospective study of outcomes in adults with nonalcoholic fatty liver disease. N Engl J Med 385:1559-1569, 2021
3. Llovet JM, Bru C, Bruix J: Prognosis of hepatocellular carcinoma: The BCLC staging classification. Semin Liver Dis 19:329-338, 1999
4. Llovet JM, Ricci S, Mazzaferro V, et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378-390, 2008
5. Bruix J, Qin S, Merle P, et al: Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 389:56-66, 2017
6. Kudo M, Finn RS, Qin S, et al: Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. Lancet 391:1163-1173, 2018
7. Finn RS, Ducreux M, Qin S, et al: IMbrave150: A randomized phase III study of 1L atezolizumab plus bevacizumab vs sorafenib in locally advanced or metastatic hepatocellular carcinoma. J Clin Oncol 36, 2018 (abstr TPS4141)
8. Kelley RK, Yau T, Cheng AL: Cabozantinib plus atezolizumab versus sorafenib as first-line systemic treatment for advanced hepatocellular carcinoma: Results from the randomized phase III COSMIC-312 trial. Presented at the ESMO Virtual Plenary, November 20, 2021
9. Abou-Alfa GK, Chan, SL, Kudo, M, et al: Phase 3 randomized, open-label, multi-center study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. Presented at the ASCO Gastrointestinal Symposium, 2022
10. Ren Z, Xu J, Bai Y, et al: Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): A randomised, open-label, phase 2-3 study. Lancet Oncol 22:977-990, 2021
11. Abou-Alfa GK, Meyer T, Cheng AL, et al: Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 379:54-63, 2018
12. Zhu AX, Kang YK, Yen CJ, et al: Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein concentrations (REACH-2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 20:282-296, 2019
13. Zhu AX, Finn RS, Edeline J, et al: Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): A non-randomised, open-label phase 2 trial. Lancet Oncol 19:940-952, 2018
14. Yau T, Kang Y-K, Kim T-Y, et al: Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): Results from CheckMate 040. J Clin Oncol 37, 2019 (abstr 4012)
15. Qin S, Chen, Z, Fang, W, et al: Pemrbolizumab plus best supportive care (BSC) versus placebo plus BSC as second-line therapy in patients in Asia with advanced hepatocelluar carcinoma (HCC): Phase 3 KEYNOTE-394 study. Presented at the ASCO Gastrointestinal Cancers Symposium, 2022
16. Finn RS, Ryoo BY, Merle P, et al: Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: A randomized, double-blind, phase III trial. J Clin Oncol 38:193-202, 2020
17. Moustafa AS, Abdel Aal AK, Ertel N, et al: Chemoembolization of hepatocellular carcinoma with extrahepatic collateral blood supply: Anatomic and technical considerations. Radiographics 37:963-977, 2017
18. Zhu AX, Duda DG, Sahani DV, et al: HCC and angiogenesis: Possible targets and future directions. Nat Rev Clin Oncol 8:292-301, 2011
19. Yang ZF, Poon RT: Vascular changes in hepatocellular carcinoma. Anat Rec (Hoboken) 291:721-734, 2008
20. Guo Y, Xiao Z, Yang L, et al: Hypoxiainducible factors in hepatocellular carcinoma (Review). Oncol Rep 43:3-15, 2020
21. Morse MA, Sun W, Kim R, et al: The role of angiogenesis in hepatocellular carcinoma. Clin Cancer Res 25:912-920, 2019
22. Hato T, Zhu AX, Duda DG: Rationally combining anti-VEGF therapy with checkpoint inhibitors in hepatocellular carcinoma. Immunotherapy 8:299-313, 2016
23. Terme M, Colussi O, Marcheteau E, et al: Modulation of immunity by antiangiogenic molecules in cancer. Clin Dev Immunol 2012:492920, 2012
24. Lucas T, Abraham D, Aharinejad S: Modulation of tumor associated macrophages in solid tumors. Front Biosci 13:5580-5588, 2008
25. Oura K, Morishita A, Tani J, et al: Tumor immune microenvironment and immunosuppressive therapy in hepatocellular carcinoma: A review. Int J Mol Sci 22: 5801, 2021
26. Zongyi Y, Xiaowu L: Immunotherapy for hepatocellular carcinoma. Cancer Lett 470:8-17, 2020
27. Chang H, Jung W, Kim A, et al: Expression and prognostic significance of programmed death protein 1 and programmed death ligand-1, and cytotoxic T lymphocyte-associated molecule-4 in hepatocellular carcinoma. APMIS 125:690-698, 2017
28. Inarrairaegui M, Melero I, Sangro B: Immunotherapy of hepatocellular carcinoma: Facts and hopes. Clin Cancer Res 24:1518-1524, 2018

29. Prieto J, Melero I, Sangro B: Immunological landscape and immunotherapy of hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 12:681-700, 2015
30. Kalathil SG, Lugade AA, Miller A, et al: PD-1(+) and Foxp3(+) T cell reduction correlates with survival of HCC patients after sorafenib therapy. JCI Insight 1: e86182, 2016
31. Kudo M: Scientific rationale for combined immunotherapy with PD-1/PD-L1 antibodies and VEGF inhibitors in advanced hepatocellular carcinoma. Cancers (Basel) 12:1089, 2020
32. Noman MZ, Desantis G, Janji B, et al: PD-L1 is a novel direct target of HIF-1alpha, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. J Exp Med 211:781-790, 2014
33. Venniyoor A: Synergism between anti-angiogenic and immune checkpoint inhibitor drugs: A hypothesis. Med Hypotheses 146:110399, 2021
34. Wallin JJ, Bendell JC, Funke R, et al: Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. Nat Commun 7:12624, 2016
35. Curran MA, Montalvo W, Yagita H, et al: PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci USA 107:4275-4280, 2010
36. Yau T, Kang YK, Kim TY, et al: Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: The CheckMate 040 randomized clinical trial. JAMA Oncol 6:e204564, 2020
37. Cheng AL, Kang YK, Chen Z, et al: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 10:25-34, 2009
38. Kudo M, Finn RS, Qin S, et al: Analysis of survival and objective response (OR) in patients with hepatocellular carcinoma in a phase III study of lenvatinib (REFLECT). J Clin Oncol 37, 2019 (abstr 186)
39. Qin S, Bi F, Gu S, et al: Donafenib versus sorafenib in first-line treatment of unresectable or metastatic hepatocellular carcinoma: A randomized, open-label, parallel-controlled phase II-III trial. J Clin Oncol 39:3002-3011, 2021
40. 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 389:2492-2502, 2017
41. Sangro B, Park J, Finn RS, et al: LBA-3 CheckMate 459: Long-term (minimum follow-up 33.6 months) survival outcomes with nivolumab versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma. Presented at the ESMO Virtual 2020, July 1, 2020
42. Lee MS, Ryoo BY, Hsu CH, et al: Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): An open-label, multicentre, phase 1b study. Lancet Oncol 21:808-820, 2020
43. Finn RS, Qin S, Ikeda M, et al: Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 382:1894-1905, 2020
44. Siegel AB, Cohen EI, Ocean A, et al: Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. J Clin Oncol 26:2992-2998, 2008
45. Finn RS, Qin S, Ikeda M, et al: IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). J Clin Oncol 39, 2021 (abstr 267)
46. Galle PR, Finn RS, Qin S, et al: Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): An open-label, randomised, phase 3 trial. Lancet Oncol 22:991-1001, 2021
47. Fukumura D, Kloepper J, Amoozgar Z, et al: Enhancing cancer immunotherapy using antiangiogenics: Opportunities and challenges. Nat Rev Clin Oncol 15: 325-340, 2018
48. Msaouel P, Genovese G, Gao J, et al: TAM kinase inhibition and immune checkpoint blockade—A winning combination in cancer treatment? Expert Opin Ther Targets 25:141-151, 2021
49. Finn RS, Ikeda M, Zhu AX, et al: Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. J Clin Oncol 38: 2960-2970, 2020
50. Iyer RV, Li D, Dayyani F, et al: DEDUCTIVE: A study of tivozanib in combination with durvalumab in subjects with untreated advanced hepatocellular carcinoma—Phase Ib results. J Clin Oncol 39, 2021 (abstr 294)
51. Kim RD, Harris WP, Sung MW, et al: Results of a phase Ib study of regorafenib (REG) 80 mg/day plus pembrolizumab (PEMBRO) for first-line treatment of advanced hepatocellular carcinoma (HCC). J Clin Oncol 39, 2021 (abstr 323)
52. Kudo M, Ikeda M, Motomura K, et al: A phase Ib study of lenvatinib (LEN) plus nivolumab (NIV) in patients (pts) with unresectable hepatocellular carcinoma (uHCC): Study 117. J Clin Oncol 38, 2020 (abstr 513)
53. Kudo M, Motomura K, Wada Y, et al: Avelumab in combination with axitinib as first-line treatment in patients with advanced hepatocellular carcinoma: Results from the phase 1b VEGF liver 100 trial. Liver Cancer 10:249-259, 2021
54. Yarchoan M, Zhu Q, Durham JN, et al: Feasibility and efficacy of neoadjuvant cabozantinib and nivolumab in patients with borderline resectable or locally advanced hepatocellular carcinoma (HCC). J Clin Oncol 39, 2021 (abstr 335)
55. Kyi C, Postow MA: Immune checkpoint inhibitor combinations in solid tumors: Opportunities and challenges. Immunotherapy 8:821-837, 2016
56. Kelley RK, Sangro B, Harris W, et al: Safety, efficacy, and pharmacodynamics of tremelimumab plus durvalumab for patients with unresectable hepatocellular carcinoma: Randomized expansion of a phase I/II study. J Clin Oncol 39:2991-3001, 2021
57. Greten TF, Abou-Alfa GK, Cheng AL, et al: Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of hepatocellular carcinoma. J Immunother Cancer 9:e002794, 2021
58. Pfister D, Nunez NG, Pinyol R, et al: NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature 592:450-456, 2021
59. Au KP, Chok KSH: Immunotherapy after liver transplantation: Where are we now? World J Gastrointest Surg 13:1267-1278, 2021

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Hepatocellular Carcinoma: Pick the Winner—TK Versus Immuno-oncology Agent–Based Combinations

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Consulting or Advisory Role: Pfizer, Bayer, Novartis, Bristol Myers Squibb, Merck, Eisai, Lilly, Genentech/Roche, AstraZeneca, Exelixis, CStone Pharmaceuticals, Hengrui Therapeutics
Research Funding: Pfizer (Inst), Bayer (Inst), Novartis (Inst), Eisai (Inst), Lilly (Inst), Merck (Inst), Bristol Myers Squibb (Inst), Roche/Genentech (Inst)
Expert Testimony: Bayer

No other potential conflicts of interest were reported.