

Combination Antiangiogenic and Immunotherapy for Advanced Hepatocellular Carcinoma: Evidence to Date

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Alison L Raybould
Hanna Sanoff

Department of Medicine, Division of Hematology-Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

Abstract: For over a decade, sorafenib remained the only systemic agent with proven clinical efficacy for patients with advanced hepatocellular carcinoma (HCC). Recent years have seen a proliferation of agents. In the first line, lenvatinib was found to be non-inferior to sorafenib in terms of overall survival (OS), with significantly better progression-free survival and objective response rate. Meanwhile, encouraging efficacy signals were observed in phase I/II studies of immune checkpoint inhibitors as monotherapy in HCC. Although subsequent phase III trials failed to demonstrate statistically significant benefit in OS, other clinically meaningful outcomes were observed, including long-term disease control with a favorable toxicity profile. In addition, a synergistic response has been postulated based on the interplay between antiangiogenic molecular targeted agents and immunotherapy. On this basis, interest has turned toward combination strategies of immunotherapy with these standard-of-care medications in the hope of improving treatment efficacy for advanced HCC, while maintaining tolerable safety profiles. Indeed, preliminary results from phase I studies of lenvatinib plus pembrolizumab and atezolizumab plus bevacizumab have proved favorable, prompting phase III investigations in the frontline setting, and for atezolizumab plus bevacizumab, these positive findings have been substantiated by recent reporting of phase III data from IMbrave150. In this review, we will present the currently available data on combination therapy atezolizumab plus bevacizumab in advanced HCC, and compare these findings to other promising combination treatments, most notably that of lenvatinib plus pembrolizumab.

Keywords: advanced hepatocellular carcinoma, combination therapy, antiangiogenic treatment, immunotherapy

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and a major leading cause of cancer death, being responsible for more than 700,000 deaths annually.¹ In the USA, HCC represents the fastest rising cause of cancer-related death.^{2,3} The prognosis of HCC remains dismal, with a 5-year survival of 18.1% across all stages and 2.3% for advanced disease.⁴ For patients with advanced HCC, for whom options are limited to systemic therapy, the 1-year survival rate has been less than 50% following diagnosis.⁵ Without major driver mutations in HCC, treating with medications that impair hepatic functional reserve has proven quite difficult.

Prior to 2007, there were no effective treatment options for patients diagnosed at an advanced stage or those who progressed after locoregional therapy.⁶ The advent of sorafenib, a multikinase inhibitor that targets the vascular endothelial growth factor

Correspondence: Alison L Raybould
Division of Hematology/Oncology,
Physicians Office Building, 3rd Floor, 170
Manning Drive, CB #7305, Chapel Hill,
NC 27599, USA
Tel +1-919-966-4431
Fax +1-919-966-6735
Email Alison.Raybould@unhealth.unc.edu

receptor (VEGFR), among others, provided the first breakthrough in treatment of advanced HCC following the results of two large phase III randomized control trials (SHARP trial⁷ and Asia-Pacific trial⁸). The SHARP trial demonstrated that sorafenib resulted in a nearly 3-month survival benefit compared to placebo in patients with advanced HCC, leading to FDA approval in the first-line setting (10.7 vs 7.9 months; HR 0.69; $p < 0.0001$).⁷ This survival benefit was similarly borne out in a trial evaluating patients with advanced HCC from the Asia-Pacific region, which showed that the median improvement in overall survival (OS) compared to placebo was 2.3 months (6.5 vs 4.2 months; HR 0.68; $p = 0.014$).⁸ Both trials restricted enrollment to patients with Child–Pugh class A cirrhosis and Eastern Cooperative Oncology Group (ECOG) performance status 2 or less. Post-marketing data, including the prospective non-interventional GIDEON study, have demonstrated an acceptable safety profile in patients with Child–Pugh class B7 cirrhosis.⁹

In the 10 years that followed, several global phase III trials failed to prove non-inferiority¹⁰ or superiority in terms of OS in the first-line setting.^{11–18} Without therapeutic alternatives or second-line agents available, sorafenib remained the only FDA-approved therapy for a decade. The 2-year period from 2017 to 2018 brought on a dramatic boon in available therapies, with approval of multitarget inhibitors regorafenib, lenvatinib, and cabozantinib; single-target ramucirumab; and immune checkpoint inhibitors nivolumab and pembrolizumab, which were granted FDA approval based on phase I/II data despite negative phase III studies.

Oral multikinase inhibitor regorafenib was the first systemic treatment shown to provide survival benefit in HCC patients who had progressed on sorafenib. In the phase III RESORCE trial, treatment with regorafenib led to improved OS for patients with disease progression on sorafenib compared to placebo (median OS 10.6 vs 7.8 months; HR 0.63 [95% CI 0.50–0.79]).¹⁹

Shortly thereafter, the phase III CELESTIAL trial showed improved survival with oral molecular kinase inhibitor cabozantinib versus placebo in advanced HCC patients previously treated with sorafenib (median OS 10.2 vs 8.0 months; HR 0.76 [95% CI 0.36–0.52]; $p < 0.001$). The study included patients who had received up to two lines of systemic therapy and progressed after at least one. In the subgroup of patients who had received sorafenib as their only prior systemic treatment, median OS was 11.3 months with cabozantinib versus 7.2 months with placebo (HR 0.70 [95% CI 0.55–0.88]).²⁰

The phase III REACH-2 trial evaluated the efficacy of ramucirumab, a human monoclonal antibody VEGFR-2 antagonist, versus placebo in the second-line setting for patients with advanced HCC and baseline elevated alpha-fetoprotein (AFP) levels ≥ 400 ng/mL. This population was selected based on positive results from the REACH trial,²¹ which showed OS benefit in this prespecified subgroup. In REACH-2, treatment with ramucirumab significantly improved OS compared to placebo (median OS 8.5 vs 7.3 months; HR 0.710 [95% CI 0.531–0.949]; $p = 0.0199$), while also having a tolerable toxicity profile.²² While these advances provided more treatment options in the second-line setting, sorafenib remained the only FDA-approved first-line therapy until lenvatinib entered the scene.

Lenvatinib is an oral multikinase inhibitor that inhibits VEGFR-1–3, fibroblast growth factor receptors (FGFR)-1–4, platelet-derived growth factor receptor (PDGFR)- α , KIT, and RET, thereby suppressing the activity of factors important in angiogenesis and tumor growth. Based on phase II efficacy signal,²³ the multicenter, randomized, open-label, phase III REFLECT trial investigated the efficacy and safety of lenvatinib versus standard-of-care sorafenib as first-line treatment in 954 patients with advanced HCC.²⁴ The REFLECT trial met its primary endpoint, demonstrating non-inferiority of lenvatinib to sorafenib in OS (13.6 months on lenvatinib vs 12.3 months on sorafenib; HR 0.92 [95% CI 0.79–1.06]). In addition, lenvatinib showed a statistically significant improvement versus sorafenib for all secondary efficacy endpoints, including progression-free survival (PFS) (7.4 vs 3.7 months; HR 0.66 [95% CI 0.57–0.77]), time to progression (TTP) (8.9 vs 3.7 months; HR 0.63 [95% CI 0.53–0.73]), and objective response rate (ORR) by mRECIST (24.1% vs 9.2%; OR 3.1 [95% CI 2.2–4.6]). The results of the REFLECT trial led to FDA approval of lenvatinib as first-line therapy for patients with advanced HCC in August 2018.²⁵

Until very recently, sorafenib and lenvatinib represented the two available first-line options for advanced HCC, but these have now been joined by combination atezolizumab plus bevacizumab, which was granted FDA approval on May 29, 2020, based on positive phase III data from IMbrave150.²⁶ These phase III data substantiate promising early phase data of durable objective responses in a subset of patients treated with anti-programmed cell death-1 (PD-1) therapy.^{27,28}

Immune Checkpoint Inhibition

Immuno-oncology has drastically changed the treatment landscape of a number of malignancies, and its potential

has been investigated in the treatment of advanced HCC. Two immune checkpoint inhibitors, nivolumab and pembrolizumab, received conditional accelerated approval from the FDA for use in the second-line setting of advanced HCC based on phase I/II data demonstrating durable objective responses observed in nearly 20% of patients.^{29,30} Although subsequent phase III data failed to demonstrate statistically significant improvement in OS, clinically meaningful outcomes were observed, and it remains to be seen whether the FDA will withdraw its conditional approval.

In CheckMate-040, a phase I/II, open-label, non-comparative, dose-escalation and expansion trial, 262 patients with advanced HCC who were sorafenib naïve, sorafenib intolerant, or sorafenib refractory were treated with anti-PD-1 monoclonal antibody nivolumab at doses of 0.1–10 mg/kg once every 2 weeks (dose-escalating cohort) or at a dose of 3 mg/kg once every 2 weeks (expansion cohort).²⁷ This trial yielded a manageable safety profile with promising efficacy, including an ORR of 20% (95% CI 15–26) in the dose-expansion phase, with three complete responses (CRs) and 39 partial responses (PRs); 91% of responders had responses lasting for 6 months or longer.

Based on these encouraging results, the follow-up randomized, multicenter, phase III study CheckMate-459 investigated nivolumab against sorafenib in the frontline setting for advanced HCC patients. Nivolumab failed to meet its primary endpoint of improved OS (median OS 16.4 months for nivolumab vs 14.7 months for sorafenib; HR 0.85 [95% CI 0.72–1.02]; $p=0.0752$).³¹ Although the predetermined statistically significant OS was not met, clinically meaningful improvements in ORR were observed, with 14 CRs (4%) and 43 PRs (12%) in the nivolumab arm compared to five CRs (1%) and 21 PRs (6%) in the sorafenib arm. A detailed analysis of the study results is not yet available, which may further help guide the role of nivolumab monotherapy in advanced HCC therapy.

A later stage of CheckMate-040 evaluated the role of nivolumab in combination with ipilimumab at various dose levels in 148 patients with advanced HCC who had previously been treated with sorafenib.³² A total of 49 patients received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses, followed by nivolumab 240 mg every 2 weeks. After 28 months' follow-up, the ORR was 33% (95% CI 20–48) in this arm, with four CRs and 12 PRs. The median duration of response (DOR) was 17.5 months (range 4.6–30.5+ months), with 56% lasting for at least 12 months

and 31% for at least 24 months. This combination was well tolerated, with rash and pruritis as the most common any-grade treatment-related adverse events (TRAEs). Grade 3–4 TRAEs occurred in 38% of patients, with aspartate aminotransferase (AST) elevation being the most common (33%); among the grade 3–4 TRAEs, 5% led to discontinuation of treatment. Based on this study, the FDA granted accelerated approval of combination therapy of nivolumab plus ipilimumab in March 2020.³³

The utility of the anti-PD-1 monoclonal antibody pembrolizumab has also been explored for the treatment of patients with advanced HCC. KEYNOTE-224, a non-randomized, single-arm, multi-center, open-label, phase II study, evaluated the efficacy and safety of pembrolizumab in 104 patients with advanced HCC who had progressed on or been intolerant to sorafenib, with preserved ECOG and Child–Pugh class A liver disease.²⁸ Exclusion criteria included those with autoimmune disease or an immunosuppressed state. Eighteen of 104 patients (17% [95% CI 11–26]) achieved the primary endpoint of an objective response, with one CR (1%) and 17 PRs (16%). Response was independent of causation of HCC and appeared to be durable, with duration ranging from 3.1 to 16.7 months; 89% of responders had a response duration of 6 months or greater and 56% of responders had a response duration of 12 months or greater. TRAEs were observed in 76 patients (73%), with grade 3 toxicities in 25 patients (24%) and immune-mediated events in 15 patients (14%), including three cases (3%) of immune-mediated hepatitis. There were no cases of viral hepatitis flares. These results led to accelerated FDA approval for pembrolizumab in the second-line setting, with continued approval potentially contingent upon further confirmatory trials of clinic efficacy. This has been subsequently explored in KEYNOTE-240, a phase III, double-blind, placebo-controlled trial.

In KEYNOTE-240, 413 patients with advanced HCC who had been previously treated with sorafenib were randomized in a 2:1 ratio to receive 200 mg of pembrolizumab every 3 weeks plus best supportive care (BSC) or placebo with BSC.³⁴ Those who had received prior immunotherapy or any systemic therapy for HCC other than sorafenib were excluded. The primary endpoints were OS and PFS. Median OS was 13.9 months (95% CI 11.6–16 months) in the pembrolizumab group and 10.6 months (95% CI 8.3–13.5 months) in the placebo group. Median PFS was 3 months (95% CI 2.8–4.1 months) versus 2.8 months (95% CI 2.5–4.1 months), respectively.

Although the pembrolizumab arm had longer OS (HR 0.78 [95% CI 0.61–0.99]) and longer PFS (HR 0.78 [95% CI 0.61–0.99]), it did not reach statistical significance per the planned analysis. Failure to meet primary co-endpoints was postulated to be due to a better OS in the placebo group than predicted, likely related to unanticipated availability of other effective post-study second-line therapies, including regorafenib and nivolumab. Nevertheless, similarly to KEYNOTE-224, there were observed improvements in ORR in those treated with pembrolizumab compared to placebo (18.3% [95% CI 14–23.4] vs 4.4% [95% CI 1.6–9.4]), and a subset of patients derived long-term benefit, with more than 19% of pembrolizumab-treated patients remaining without progression for more than 1 year.

The toxicity profile remained similar to KEYNOTE-224, with grade 3 adverse events occurring in 147 patients (52.7%) in the pembrolizumab-treated arm versus 62 patients (46.3%) in the placebo arm. Immune-mediated adverse events occurred in 51 patients (18.3%) in the pembrolizumab group and 11 patients (9.2%) in the placebo group. Among these, 10 patients (3.6%) experienced immune-mediated hepatitis in the pembrolizumab group versus no events of immune-mediated hepatitis observed in the placebo group. Similarly, there were no identified cases of viral hepatitis flares. Despite not meeting either primary endpoint, pembrolizumab remains FDA approved in the second-line setting for those who have failed sorafenib therapy.³⁵ Its efficacy continues to be investigated in KEYNOTE-394, a phase III trial in Asia, as second-line therapy for patients with advanced HCC (NCT03062358). The results of that study were not available at time of publication but are expected to be reported in the coming months.³⁶ Even though neither nivolumab nor pembrolizumab monotherapy demonstrated statistically significant improvement in OS compared with either sorafenib in the first-line or placebo in the second-line setting, it is clear that a subset of patients with advanced HCC experience considerable clinical benefit from PD-1 inhibition, prompting further investigation of immunotherapy in the treatment arsenal for advanced HCC via combination therapy.

Atezolizumab and Bevacizumab Combination Therapy

Multikinase inhibitors with antiangiogenic properties have been the mainstay of standard first-line therapy for advanced HCC. Lenvatinib, along with the other three multikinase

inhibitors for HCC (sorafenib, regorafenib, and cabozantinib), also has immunomodulatory effects on the tumor microenvironment. These immunomodulating effects include the promotion of dendritic cell maturation, upregulation of T-cell trafficking and function, and reversal of immunosuppression cell expression caused by tissue hypoxia.^{37–39} In preclinical HCC models, single-cell RNA sequencing demonstrated that treatment of lenvatinib with or without anti-PD-1 antibody led to decreased monocyte and macrophage populations and increased CD8⁺ T-cell populations. Further, immunocompetent mice treated with lenvatinib plus anti-PD-1 antibody had greater tumor regression and a higher response rate compared with either treatment alone.⁴⁰ These observations suggest a potentially synergistic effect of combining immunotherapy with standard-of-care therapies known to exhibit immunomodulatory activity. In advanced HCC, the most extensively studied combination regimen consists of anti-PD-1 or anti-PD-L1 plus antiangiogenic agents.⁴¹ One such regimen involving an anti-PD-L1 monoclonal antibody, atezolizumab, plus a VEGF inhibitor, bevacizumab, has emerged as a practice-changing treatment option, with recent FDA approval in the frontline setting based on positive findings from the phase III study IMbrave150.⁴²

This combination first showed promise in a phase Ib study of patients with advanced HCC and preserved liver function (Child–Pugh class A) treated with atezolizumab 1200 mg IV every 3 weeks and bevacizumab 15 mg/kg IV every 3 weeks. This study demonstrated durable responses, with 12 of 23 responses (52%) lasting for 6 months or more and 6 of 23 responses (26%) lasting for 12 months or more.⁴³ Responses were observed across all clinically relevant subgroups, irrespective of etiology, geographic region, baseline AFP, or tumor burden. The ORR was 32% per investigator-assessed mRECIST. Median PFS was 14.9 months (range 0.5–23.9+). Among 103 safety-evaluable patients, TRAEs occurred in 82%, with decreased appetite (28%), fatigue, rash, and pyrexia (20% each) being the most common. Five deaths were reported, two of which were considered treatment related (one grade 4 drug-induced liver injury with hepatic decompensation and one pneumonitis). Overall, adverse events were felt to be consistent with the known safety profile of each drug, and no new safety signals were identified.

These favorable results have been further substantiated by the multicenter, open-label, randomized, phase III study IMbrave150, leading to recent FDA approval of atezolizumab plus bevacizumab as first-line therapy. This trial randomized 501 treatment-naïve patients with advanced HCC and preserved liver function (Child–Pugh class A) in a 2:1 ratio to

receive experimental atezolizumab 1200 mg IV infusion every 3 weeks plus bevacizumab 15 mg/kg every 3 weeks (n=336) versus standard-of-care sorafenib 400 mg orally twice a day (n=165).^{4,44} Co-primary endpoints were PFS and OS, as assessed by an independent review facility (IRF) per RECIST 1.1 criteria. This study showed a significantly longer median PFS in the combination arm compared to the sorafenib arm (6.8 vs 4.3 months; HR 0.59 [95% CI 0.47–0.76]; $p<0.0001$). Similarly, the median OS was not reached in the combination arm compared to 13.2 months in the sorafenib arm (HR 0.58 [95% CI 0.42–0.79]; $p=0.0006$). This makes it the first therapy in over a decade to demonstrate improved survival for patients with advanced HCC who have not yet received treatment. The ORR was more than double in the combination group versus the sorafenib group per RECIST 1.1 criteria (27% vs 12%; $p<0.0001$) and nearly threefold increased per IRF-assessed mRECIST criteria (33% vs 13%; $p<0.0001$). The median duration of treatment was 7.4 months with the combination and 3 months for sorafenib. Grade 3–4 adverse events occurred at similar rates across the two groups (57% combined vs 55% sorafenib), as did grade 5 adverse

events (5% combined vs 6% sorafenib). The investigators noted that atezolizumab plus bevacizumab also delayed deterioration of quality of life compared to sorafenib. The combination of atezolizumab plus bevacizumab appeared to have a tolerable safety profile and yielded both statistically significant and clinically meaningful improvement in OS and PFS for untreated patients with unresectable HCC. In May 2020, the FDA approved atezolizumab plus bevacizumab as first-line therapy for patients with advanced HCC.⁴² It is currently the only combination regimen with positive phase III data and is expected to become the new standard of care in the first-line setting. Table 1 demonstrates the efficacy and safety results of atezolizumab plus bevacizumab from IMbrave150 and provides a comparison to data from other available combination regimens.

Lenvatinib and Pembrolizumab Combination Therapy

Lenvatinib plus pembrolizumab is another combination therapy for advanced HCC with promising early phase data. KEYNOTE-524, an open-label, multicenter, phase Ib trial,

Table 1 Results of Phase I Trials of Antiangiogenics Plus Immune Checkpoint Inhibitors for HCC

Setting	Lenvatinib + Pembrolizumab ³⁶	Atezolizumab + Bevacizumab ⁴²	Nivolumab + Cabozantinib ⁴⁶	Nivolumab + Cabozantinib ± Ipilimumab ⁴⁶
	First-Line	First-Line	First- or Second-Line	First- or Second-Line
Efficacy results*	n=67 (%)	n=73 (%)	n=36 (%)	n=35 (%)
Objective response rate	30 (44.8)	23 (32)	6 (17)	9 (26)
Complete response	4 (6.0)	1 (1)	0	0
Partial response	26 (38.8)**	22 (30)	6	9
Disease control rate	na	56 (77)	29 (81)	29 (83)
≥16 weeks		48 (66)		
≥24 weeks		34 (47)		
Median DOR (months)	18.7 (6.9–NE)	NR (1.6–22)	8.3	NR
≥6 months		12/23 (52)		
≥12 months		6/23 (26)		
Median PFS (months)	na	14.9 (0.5–23.9+)	5.5 (3.2–10.9)	6.8 (4.0–14.3)
6-month PFS (%)	na	71%		
Median OS (months)	na	NR (0.8–24+)	21.5 (13.1–NR)	NR (15.1–NR)
Safety results	n=30 (%)	n=103 (%)	n=36 (%)	n=35 (%)
Any AEs	30 (100)	95 (92)		
Treatment-related AEs	28 (93.3)	84 (82)		
Grade ≥3	18 (60)	46 (45)	17 (47)	25 (71)
Serious AEs	8 (26.7)	36 (35)		
Grade 5	3 (10)***	5 (5)***		
Dose interruptions/reductions	18 (60)/18 (60)	na		
Discontinuation	5 (16.7)	24 (24)	4 (11)	7 (20)

Notes: *Investigator-assessed per modified RECIST in the lenvatinib plus pembrolizumab trial and per RECIST 1.1 in the bevacizumab plus atezolizumab trial. **Includes unconfirmed PRs (2 patients); ***Two grade 5 AEs in each trial were deemed treatment related.

Abbreviations: AEs, adverse events; DOR, duration of response; HCC, hepatocellular carcinoma; na, not applicable; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival.

evaluated the tolerability and safety of lenvatinib (12 mg/day if weight >60 kg or 8 mg/day if weight ≤60 kg, orally) plus pembrolizumab (200 mg IV every 3 weeks) in 104 patients with BCLC stage B or C HCC, Child–Pugh class A, ECOG 0 or 1, and no prior systemic therapies.⁴⁵ No dose-limiting toxicities (DLTs) were observed, and enrollment was expanded to 104 patients (DLT, n=6; escalation, n=98). At median follow-up of 10.6 months, 37 patients remained on treatment (lenvatinib only, n=3; combination, n=34). ORR was 36% (95% CI 26.6–46.2), including one CR (1%) and 35 PRs (35%) by RECIST v1.1. These results compare favorably to the lenvatinib arm of the REFLECT trial, in which the ORR was 24.1% with CR in six patients (1%) and PR in 109 patients (23%).¹⁹ Median PFS was 8.6 months (95% CI 7.1–9.7), and median DOR was 12.6 months (95% CI 6.9–not estimable).

Updated safety data will be forthcoming, but available safety analysis reported that any-grade treatment-emergent adverse events (TEAEs) occurred in 99 patients (99%), with 85% representing grade ≥3 TEAEs. Among these, hypertension was the most common, seen in 18% of patients. Three treatment-related deaths were reported (one acute respiratory distress syndrome, one intestinal perforation, one abnormal hepatic function). Based on these results of tolerable toxicities and promising efficacy, the FDA granted a breakthrough therapy designation for the combination of lenvatinib and pembrolizumab in the treatment of patients with newly diagnosed, advanced HCC in July 2019.⁴⁶

A multicenter, double-blinded, phase III trial, LEAP-002 (NCT03713593), is currently underway to examine this combination in the frontline setting for patients with advanced HCC and well-preserved liver function (Child–Pugh class A).⁴⁷ Approximately 750 patients will be randomized to receive either standard-of-care lenvatinib (12 mg if weight ≥60 kg or 8 mg if weight <60 kg) orally daily plus pembrolizumab 200 mg IV every 3 weeks in the experimental arm or lenvatinib plus placebo in the control arm. The co-primary endpoints include OS and PFS, and secondary endpoints include ORR, DOR, disease control rate (DCR), TTP per RECIST 1.1, adverse events, and pharmacokinetics.

In addition, a single-arm phase IIb trial is investigating the safety and efficacy of lenvatinib and pembrolizumab in the second-line setting for patients with advanced hepatobiliary malignancies, including HCC, while also exploring potential biomarkers of therapeutic response (NCT03895970).⁴⁸ Eligible patients must have preserved liver function (Child–Pugh class A or mild class B), BCLC stage B–C, and ECOG 0–2. Primary outcomes include ORR, DCR, and PFS, while

secondary outcomes include OS, DOR, stable disease, and TEAEs.

Studies are beginning to expand combination treatment regimens to include locoregional liver-directed therapies for incurable, non-metastatic disease. A phase III, multicenter, randomized, double-blinded, controlled trial of lenvatinib and pembrolizumab in combination with transarterial chemoembolization (TACE) in patients with incurable, non-metastatic HCC was recently announced.⁴⁹ The experimental arm will receive lenvatinib (12 mg orally daily if weight ≥60 kg or 8 mg if weight <60 kg) and pembrolizumab 400 mg IV every 6 weeks with TACE. The control arm will receive oral and IV placebo with TACE.

Alternative Combination Therapy

It is worth mentioning recently updated results from CheckMate-040, which, based on favorable data from earlier cohorts, trialed combination cabozantinib and nivolumab with or without ipilimumab for advanced HCC.⁵⁰ Stratification was based on prior sorafenib exposure, and 171 patients were randomized to receive nivolumab 240 mg every 2 weeks and cabozantinib 40 mg orally daily (n=36) or nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks and cabozantinib 40 mg orally daily (n=35). After median follow-up of 19 months, ORR was 17% in the nivolumab and cabozantinib group (six PRs) and 26% (nine PRs) in the nivolumab, ipilimumab, and cabozantinib group. This is in contrast to prior studies of combination ipilimumab and nivolumab in which ORR was greater than 30%.³² Median PFS was 5.5 months in the doublet arm and 6.8 months in the triplet arm. Triplet therapy had a high rate of grade 3–4 TRAEs, occurring at a rate of 71% compared to 47% in the doublet arm. These most commonly consisted of AST increase (23%), lipase increase (17%), ALT increase (17%), hypertension (17%), and palmar–plantar erythrodysesthesia (9%). Longer duration of follow-up may be useful in revealing the true risk–benefit ratio of either combination group.

There remains great enthusiasm to explore other combination therapies, particularly in the frontline setting. **Figure 1** highlights the main targets of systemic treatment for advanced HCC, which have been combined with the goal of potentiating a synergistic response. The open-label, phase Ib COSMIC-021 study (NCT03170960) seeks to assess the safety and preliminary efficacy of cabozantinib plus atezolizumab across several gastrointestinal tumor types, including untreated advanced HCC patients with well-preserved liver function (Child–Pugh class A).⁵¹ In the multicenter, open-label, phase III trial COSMIC-312 (NCT03755791), patients with untreated

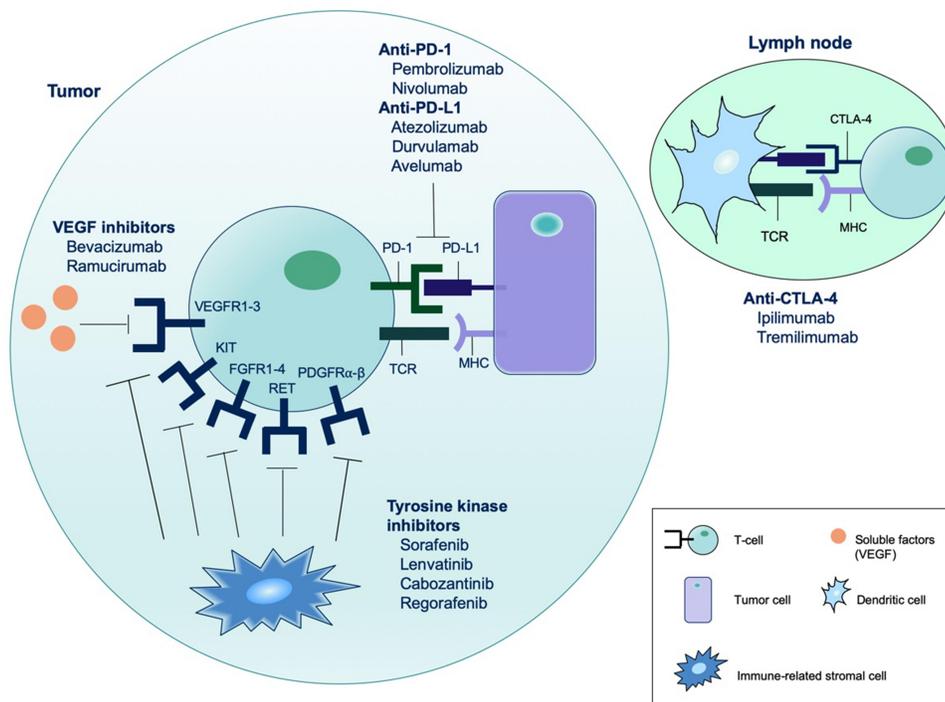


Figure 1 Main targets of systemic treatment for advanced HCC. VEGF inhibitors (bevacizumab and ramucirumab) prevent binding of circulating VEGF to the VEGF receptor, thereby inhibiting angiogenesis of tumor blood vessels. Tyrosine kinase inhibitors (TKIs) (sorafenib, lenvatinib, cabozantinib, regorafenib) block the intracellular kinase domain of the transmembrane receptor, preventing activation of downstream signal transduction cascades that lead to cell proliferation. Each multikinase inhibitor may act upon a diverse set of receptors, thereby suppressing activity of factors important in angiogenesis and tumor growth. VEGF receptors (VEGFR)-1–3, fibroblast growth factor receptors (FGFR)-1–4, platelet-derived growth factor receptor (PDGFR)- α - β , KIT, and RET are examples of some high-affinity targets of TKIs, but this is not a complete list. Immune checkpoint inhibitors (anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies) act by blocking checkpoint proteins from binding with partner proteins, preventing the silencing of immune cells, thereby restoring the ability of the immune system to detect and kill cancer cells. These treatment modalities have been combined to potentiate a synergistic effect in tumor cell death.

advanced HCC have been randomized to an experimental arm of cabozantinib (40 mg orally daily) plus atezolizumab (1200 mg IV infusion every 3 weeks) versus a control arm of sorafenib (400 mg orally twice daily).⁵² Co-primary endpoints include OS and PFS, while secondary endpoints include ORR, safety, pharmacokinetics, and correlation of biomarker analyses with clinical outcomes. Other ongoing phase I/II combination therapy trials include regorafenib plus pembrolizumab as first-line treatment for advanced HCC (NCT 03347292),⁵³ regorafenib plus anti-PD-L1 antibody avelumab in patients with advanced solid tumors (NCT03475953),⁵⁴ and cabozantinib plus anti-PD-L1 antibody durvalumab in patients with gastrointestinal malignancies, including both treated and untreated advanced HCC (NCT03539822).⁵⁵ In the phase Ib study of ramucirumab plus durvalumab in previously treated patients with advanced malignancies, an ORR was observed in three of the 28 patients (11%) in the HCC cohort, with a median OS of 10.7 months.⁵⁶ The compares to a median OS of 8.5 months in REACH-2.²¹ Table 2 depicts the FDA approval status of current immunotherapy regimens for advanced HCC.

Conclusions

Advanced HCC remains a deadly disease; however, with the emergence of multiple new treatment options, median survival is now reported at longer than a year. Further, results from combination antiangiogenic therapy and checkpoint inhibitor trials offer patients a realistic hope for some additional years of life. Combination therapy with antiangiogenic treatments and immunotherapy provides new promise for a disease with an otherwise grim prognosis. Preclinical studies suggest that the immunomodulatory effects of antiangiogenic therapy may be potentiated by the addition of immunotherapy, and this has been well illustrated in much of the available clinical trial data. As the first treatment to demonstrate superiority in the front-line setting for advanced HCC in over a decade, the combination of atezolizumab and bevacizumab is expected to change clinical practice, and with its recent FDA approval, it now represents an overwhelming improvement on the other currently FDA-approved first-line treatment options, sorafenib and lenvatinib. Similarly, phase I data from combination lenvatinib and pembrolizumab as first-line therapy appear extremely promising. While we anticipate combination

Table 2 FDA Approval Status of Immunotherapy for Advanced HCC*

Regimen	Setting	Study	Approval Status
Pembrolizumab	Second-line	KEYNOTE-224 ²⁴	Conditional
Nivolumab	Second-line	CheckMate-040 ²³	Conditional
Nivolumab + ipilimumab	Second-line	CheckMate-040 ²⁷	Conditional
Pembrolizumab + lenvatinib	First-line	KEYNOTE-524 ³⁸	Breakthrough therapy designation
Atezolizumab + bevacizumab	First-line	IMbrave150 ⁴⁵	Submitted and pending
Nivolumab + cabozantinib ± ipilimumab	First- or second-line	CheckMate-040 ⁴⁶	Ongoing
Cabozantinib + atezolizumab	First-line	NCT03755791 (COSMIC-312) ⁴⁸	Ongoing
Regorafenib + avelumab	First-line	NCT03347292 ⁵⁰	Ongoing
Cabozantinib + durvalumab	Second-line	NCT03539822 (CAMILLA) ⁵¹	Ongoing
Ramucirumab + durvalumab	Second-line	NCT02572687 ⁵²	Ongoing

Note: *FDA approval status for treatment of advanced HCC involving immunotherapy as of April 2020.

therapy to alter the treatment landscape for patients with advanced HCC, it also raises important questions regarding treatment selection as well as optimal sequence strategy. Our current second-line agents have proven benefit only in sorafenib-experienced patients, and we cannot infer conclusions about their efficacy following treatment with various combination strategies. Future areas of investigation should work on isolating predictive biomarkers that can identify the subset of patients who may benefit from immunotherapy most, and on understanding the appropriate sequence of combination treatment with current standard-of-care first- and second-line agents.

Disclosure

Dr Hanna Sanoff reports grants from Bayer, outside the submitted work. The authors report no other conflict of interest in this work.

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