

# Systemic therapy for hepatocellular carcinoma: beyond sorafenib

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**Abstract:** Hepatocellular carcinoma (HCC) remains the second leading cause of cancer mortality worldwide and the fifth leading cause of cancer-related deaths in the United States. In 2007, sorafenib became the first Food and Drug Administration (FDA) approved first line systemic treatment for HCC, however, it confers only modest benefit in median overall survival (mOS) and comes with significant side effects. This review article will explore systemic treatments for incurable HCC beyond sorafenib. It will pay particular emphasis to various kinase inhibitors, immunotherapies, and new data on combination therapies.

**Keywords:** Hepatocellular carcinoma (HCC); sorafenib; systemic therapy; immunotherapy; clinical trials; tyrosine kinase inhibitors

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## Introduction

Hepatocellular carcinoma (HCC) remains the third leading cause of cancer mortality worldwide. In the United States, HCC is the fifth leading cause of cancer-related deaths (1,2). Even with advances in therapy, HCC still confers significant mortality, with 5-year survival rates of only 18% from 2005 to 2011 (2). In its early stages, surgery and liver transplantation are a potentially curative treatment (3). However, up to 80% of patients present at an incurable stage (4). In such situations, local therapies including transarterial chemoembolization (TACE) usually are often used to control the disease when HCC is confined to the liver. For those patients who progress or are not candidates for local treatments, systemic therapies are the only option (4).

Sorafenib, a tyrosine kinase inhibitor, was the first Food and Drug Administration (FDA) approved first line systemic therapy for HCC in 2007. Sorafenib provides multiple sites of action, inhibiting vascular endothelial growth factor receptor 1 (VEGFR1), VEGFR2, VEGFR3, platelet-derived growth factor receptor beta (PDGFR- $\beta$ ), and RAF-family kinases (5). In the landmark phase III SHARP trial

including 602 HCC patients with mostly Child Pugh Class A, sorafenib improved median overall survival (mOS) compared to placebo (10.7 vs. 7.9 months;  $P < 0.001$ ) (6,7).

Even with modest improvement in survival, most patients have to be started on lower doses of sorafenib due to poor tolerance of side effects (8,9). It is clear that more effective and better-tolerated therapies are needed for this common and fatal disease.

## Protein kinase inhibitors—anti-angiogenics

To date, there are 538 known protein kinases in the human genome (10–12). These proteins are responsible for the phosphorylation of serine, threonine, or tyrosine residues on proteins in the cell, greatly modifying their functions. Moreover, protein kinases are closely involved in the mutagenesis and growth of human cancer cells (13).

Up to now, 37 different kinase inhibitors have been FDA approved for the treatment of cancer, including sorafenib (14). Additionally, over a hundred new drugs are in clinical trials and hundreds more are incubating in the preclinical ecosystem of the biopharma industry. Among

these, a significant number of agents beyond sorafenib have shown efficacy in the treatment of advanced HCC, all of which exhibit action against angiogenesis through inhibition of the VEGFR pathway (14).

### *First line therapy*

#### **Lenvatinib**

Lenvatinib, the most notable of these to date, is a multikinase inhibitor which affects VEGFR1–3, fibroblast growth factor receptor (FGFR) 1–4, PDGFR- $\alpha$ , RET, and KIT (15). In the phase III randomized control trial REFLECT, researchers compared lenvatinib to sorafenib in the treatment of Child Pugh Class A unresectable HCC in a cohort of 954 patients. Lenvatinib met its primary endpoint of non-inferiority compared to sorafenib, with a mOS of 13.6 *vs.* 12.3 months respectively [hazard ratio (HR) 0.92, 95% confidence interval (CI): 0.79–1.06] (16). It also achieved the secondary endpoints of progression free survival (PFS) of 7.4 *vs.* 3.7 months (HR 0.66, 95% CI: 0.57–0.77) and time to progression (TTP) of 8.9 *vs.* 3.7 months (HR 0.63, 95% CI: 0.53–0.73). Most notably, lenvatinib conferred an objective response rate (ORR) of 24.1% compared to 9.2% in the sorafenib arm per investigator review according to modified RECIST (mRECIST). This is the only tyrosine kinase inhibitor that showed non-inferiority compared to sorafenib in the 1<sup>st</sup> line treatment of HCC, providing an option for such patients beyond sorafenib, and has been recently approved in Japan, United States, and China.

### *Second line therapy*

#### **Regorafenib**

Regorafenib, another oral multikinase inhibitor, has a wide range of targets including VEGFR 1–3, tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2 (TIE-2), PDGFR- $\beta$ , c-KIT, RET, RAF-1, and BRAF (17,18). It was approved April 2017 by the FDA as a second line treatment in HCC patients previously treated on sorafenib. In the phase III RESORCE study comparing regorafenib to placebo with progression on sorafenib, the mOS for regorafenib *vs.* placebo was 10.6 *vs.* 7.8 months respectively (HR 0.63, 95% CI: 0.50–0.79) (19). The median PFS was 3.1 *vs.* 1.5 months (HR 0.43, 95% CI: 0.35–0.52). Similar to sorafenib, regorafenib has a common side effect, hand-foot skin reaction. In the RESORCE trial, patients who had hand-foot skin reaction during cycle

1 of regorafenib had better mOS of 14.1 *vs.* 6.6 months compared to those without (20). Of note, only patients who could tolerate and progress on sorafenib were enrolled in RESORCE trial and median duration of therapy of prior sorafenib in this study was 7.8 months, making regorafenib a good choice for patients who could stay on sorafenib for a relatively long period of time.

#### **Cabozantinib**

Cabozantinib is a tyrosine kinase inhibitor which inhibits VEGFRs, MET, AXL, RET, KIT, and FLT3 (21). In the recently published phase III CELESTIAL trial comparing cabozantinib to placebo in advanced HCC after sorafenib failure, cabozantinib and placebo achieved a mOS of 10.2 *vs.* 8.0 months respectively (P=0.005) (21). The median PFS was 5.2 *vs.* 1.9 months respectively (P<0.001). However, cabozantinib was associated with grade 3 or 4 adverse events in 68% of patients compared to 36% with placebo. The most common side effects were palmar-plantar erythrodysesthesia, hypertension, elevated transaminases, fatigue, and diarrhea. In the wake of this study, cabozantinib is poised to be a second line treatment option for HCC, though with a risk of high-grade adverse events nearly double that of placebo.

#### **Ramucirumab**

Ramucirumab is a monoclonal antibody (IgG1) which selectively inhibits VEGFR2 (22). The phase III REACH study compared ramucirumab to placebo as second line treatment for 565 HCC patients with Child Pugh Class A. There was no significant change in mOS between ramucirumab and placebo (9.2 *vs.* 7.6 months respectively) (22). However, ramucirumab achieved a higher ORR than placebo (7% *vs.* <1% respectively). In the prespecified retrospective analysis of the 250 patients with an alpha-fetoprotein (AFP)  $\geq$ 400 ng/mL, the mOS of ramucirumab was 7.8 months compared to 4.2 months of placebo. Thus, it is possible that AFP  $\geq$ 400 could be a potential biomarker predicting response to ramucirumab therapy. A subsequent phase III study, REACH-2, explored the mOS difference between ramucirumab and placebo in 2<sup>nd</sup> line patients with AFP  $\geq$ 400 ng/mL. This study was presented at ASCO 2018, indicating that ramucirumab improved mOS in patients who progressed on sorafenib with AFP  $\geq$ 400 ng/mL (23). Of the 292 patients with Child-Pugh A, ramucirumab improved mOS from 7.3 months in the placebo arm to 8.5 months (HR 0.71, 95% CI: 0.53–0.95). The most common side effects of ramucirumab therapy were hypertension and fatigue.

## Immunotherapy

It is well known that cancer utilizes multiple mechanisms to avoid detection by the immune system. One of these mechanisms is exerted through programmed death-ligand 1 (PD-L1), a ligand produced by tumor cells which binds to programmed death-1 (PD-1) receptor on T-cells (24). This interaction between PD-L1 and PD-1 inhibits T-cell activation and can lead to T-cell apoptosis. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibits T-cell activation through induction of regulatory T cells (Tregs), which creates an immunosuppressive environment. It also binds B7 on antigen-presenting cells to inhibit T-cell activation (25,26).

Both of the above mechanisms are targets for a new class of immune checkpoint inhibitors, either through interruption of the interaction between PD-1 and PD-L1 or between CTLA-4 and B7. By interfering with cancer's ability to ensure immune cell quiescence, these drugs can induce powerful immune responses to a diverse number of cancer, including melanoma, renal cell carcinoma, non-small cell lung cancers, and head and neck cancers (27-33). In fact, a number of these agents have shown significant promise in the treatment of advanced HCC.

### Second line therapy

#### Nivolumab

Nivolumab, a PD-1 inhibitor, is currently approved as second-line systemic treatment in advanced HCC patients who progressed on prior sorafenib treatment. In the associated phase I/II CHECKMATE 040 trial, 48 patients were treated in the dose-escalation phase and 214 in the dose-expansion phase (34). The ORR was 20% in the dose-expansion phase and 15% in the dose-escalation phase. For the 214 patients in the phase II study, the OS with nivolumab at 9 months was 74%. Such high ORR and long OS rate at 9 months in 2<sup>nd</sup> line HCC sets a new standard of care, allowing more patients to be eligible for such therapy regardless of the duration of prior sorafenib therapy.

A subgroup analysis in this study showed that patients with a PD-L1  $\geq 1\%$  achieved ORR of 26%, while patients PD-LA  $< 1\%$  showed ORR of 19%. Therefore, PD-L1 is not a predictive marker for response to PD-1 inhibitor therapy.

Finally, when researchers explored the subgroup of 56 patients who were sorafenib naïve, nivolumab showed ORR of 23% and OS rate of 82% at 9 months. This suggested that nivolumab might be beneficial as an alternative first

line treatment of HCC patients in lieu of sorafenib. A phase III trial of nivolumab *vs.* sorafenib as first line treatment for advanced HCC has been completed and we are eagerly awaiting the results.

#### Pembrolizumab

Another anti-PD-1 inhibitor is pembrolizumab (35). In the phase II trial, Keynote-224, pembrolizumab was assessed in 104 advanced HCC patients with Child Pugh Class A who had progressed on prior sorafenib therapy. Pembrolizumab met the primary endpoint of an ORR of 17% (34). In the study, there was also a 6-month PFS of 73% and 6-month OS rate of 77.9%. These results suggested that pembrolizumab might be a promising new therapy for patients with advanced HCC after sorafenib failure.

#### Tremelimumab

Tremelimumab is an anti-CTLA-4 agent which has shown promise in the treatment of advanced HCC. In a phase II trial, tremelimumab was explored in 21 patients with hepatitis C virus (HCV)-related HCC that included both treatment naïve and previously treated patients with both Child-Pugh Class A and B. Among 17 evaluable patients, tremelimumab achieved an ORR of 17.6%, with mOS of 8.2 months (13). Notably, one of the patients also exhibited a decreased HCV viral load over the course of the trial, suggesting that tremelimumab could have a role in the treatment of HCV in addition to its actions against advanced HCC. Such an observation makes immunotherapy particularly compelling in viral hepatitis related HCC, with its potential of not only providing disease control for HCC but also viral load reduction for hepatitis C.

## Combination therapies

In many other solid cancers, combination therapies of multiple systemic agents exhibit superior response and longer survival over single agents. However, these combination therapies also frequently come with increased toxicities. A number of trials combining multiple systemic treatment modalities are ongoing in advanced HCC.

In the phase I/II study of HCC patients treated with durvalumab (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor), 93% of patients had Child Pugh Class A and 30% were treatment naïve (36). Of these, a remarkable 20% achieved confirmed ORR. The subsequent phase III HIMALYA study is comparing durvalumab monotherapy, sorafenib, and the combination of tremelimumab and

**Table 1** An illustration of first- and second-line treatments for advanced HCC

Line of therapy	Drug class	Drug name
1 <sup>st</sup>	TKI	Sorafenib
1 <sup>st</sup>	TKI	Lenvatinib
1 <sup>st*</sup>	Immuno/combo	Nivolumab ± ipilimumab
1 <sup>st*</sup>	Combination	Nivolumab + cabozantinib ± ipilimumab
1 <sup>st*</sup>	Combination	Atezolizumab + bevacizumab
1 <sup>st*</sup>	Immunotherapy	Tremelimumab
1 <sup>st*</sup>	Immunotherapy	Durvalumab ± tremelimumab
1 <sup>st*</sup>	Combination	Pembrolizumab + cabozantinib
1 <sup>st*</sup>	Combination	Pembrolizumab + regorafenib
2 <sup>nd</sup>	Immunotherapy	Nivolumab
2 <sup>nd</sup>	TKI	Regorafenib
2 <sup>nd</sup> ^ (AFP ≥400)	TKI	Ramucirumab
2 <sup>nd</sup> ^	TKI	Cabozantinib
2 <sup>nd*</sup>	Immunotherapy	Pembrolizumab
2 <sup>nd*</sup>	Immunotherapy	Tremelimumab

\*, indicates ongoing research; ^, indicates completed trial, awaiting FDA approval. HCC, hepatocellular carcinoma; TKI, tyrosine kinase inhibitor; AFP, alpha-fetoprotein; FDA; Food and Drug Administration.

durvalumab. This study is being conducted as first line treatment in advanced HCC and we eagerly await the results.

Similarly, the anti-CTLA-4 agent, ipilimumab, is combined with the PD-1 inhibitor, nivolumab, in the fourth cohort of the Checkmate-040 trial (37). Combination therapies that target CTLA/PD-1 pathway have been successfully used in the treatment of advanced melanoma and advanced renal cell carcinoma, and are being explored in the treatment of non-small cell lung cancer (29,30,32).

In addition to combined immunotherapies, immunotherapy has been explored in combination with small molecular therapy. The rationale is that small molecules may help potentiate tumors to immunotherapeutic agents, either by priming the tumor microenvironment to allow better immune response, or by releasing antigens for immune recognition.

For example, at ASCO 2018, data was published with a combination of the PD-L1 antibody, atezolizumab, with bevacizumab, an anti-angiogenic agent. The study to date has a cohort of 26 patients with previously untreated, advanced HCC. In the 21 evaluable patients at the time of the presentation, confirmed partial responses occurred in 13 patients (63%). Calculations of PFS, TTP, and mOS are ongoing (38). Such impressive ORR suggests that atezolizumab plus bevacizumab in combination may be more

efficacious than the immunotherapeutic agent on its own.

In another combination regimen, cabozantinib is currently being explored with various immunotherapeutic agents. In fact, the Checkmate-040 trial includes a cabozantinib combination cohort. This cohort is evaluating the tolerability and safety in patients a nivolumab plus cabozantinib doublet regimen or nivolumab-ipilimumab-cabozantinib triple-therapy.

Finally, there are early trials involving pembrolizumab therapy, pairing with either regorafenib or lenvatinib, respectively (25,39).

## Conclusions

Hepatocellular carcinoma continues to confer significant morbidity and mortality in both the developed and the developing world. Since 2007, when sorafenib became the first systemic therapy approved by the FDA for treatment of advanced, unresectable HCC, a number of novel agents, including new protein kinase inhibitors, monoclonal antibodies, and new immunotherapeutic agents, have shown efficacy in the treatment of HCC (Table 1). Currently, lenvatinib, regorafenib and nivolumab are all FDA approved in the treatment of HCC.

Cabozantinib, ramucirumab, and pembrolizumab are in the process of obtaining FDA approval for the treatment of HCC. Ramucirumab marks the first time in the treatment of HCC that biomarker-derived therapy has shown efficacy. It is exciting to see benefit for a patient population with poor prognosis with AFP  $\geq 400$  ng/mL. Further research into new agents, combination therapies, and the identification of the appropriate patient populations for each intervention will likely continue to improve outcomes for this otherwise devastating disease. There is a vast future in the systemic treatment of HCC, beyond sorafenib.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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