



REVIEW ARTICLE

Targeting angiogenesis for liver cancer: Past, present, and future

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Abstract Liver cancer, mostly hepatocellular carcinoma (HCC), is the second leading cause of cancer mortality globally. Most patients were diagnosed at an advanced stage, and systemic therapy is the standard of care. All the approved systemic therapies for HCC are molecular targeted therapies with anti-angiogenic effects targeting the vascular endothelial growth factor signaling pathway. Sorafenib and lenvatinib are the first-line treatment, and regorafenib, ramucirumab, and cabozantinib are second-line treatment options. Although anti-PD-1 antibodies, including nivolumab and pembrolizumab, demonstrated promising anti-tumor effects as monotherapy for advanced HCC in phase II clinical trials, both failed in phase III studies. Anti-angiogenic treatment remains the backbone of systemic therapy for HCC. In this review, we summarized the approved anti-angiogenic medicines and discussed the potential strategies to improve the efficacy of anti-angiogenic therapy, including combination therapy with other treatments, and discussed the approaches to overcome the drawbacks of anti-angiogenic therapies.

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Abbreviations: HCC, hepatocellular carcinoma; TACE, transcatheter chemoembolization; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; ICI, immune checkpoint inhibitor; ORR, objective response rate; PR, partial response; CR, complete response; TKI, tyrosine kinase inhibitor; PD-1, program death-1; PD-L1, program death-1 ligand.

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Background of systemic therapy

Primary liver cancer is the second leading cancer-related death in China.¹ Although the incidence and mortality of liver cancer are declining in China,^{2,3} owing to the introduction of vaccination for newborns against the hepatitis B virus (HBV),⁴ it is increasing in the US and Europe.⁵ More than 90% of primary liver cancers are hepatocellular carcinoma (HCC). Survival after diagnosis of HCC is more miserable than many other types of cancer.⁵ In China, the 5-year survival of HCC is 12.1%, the second-lowest among all types of cancer.⁶ Only treatments for HCC are discussed in this Review. Most of the HCC patients were diagnosed at an advanced stage in most regions around the world including China,⁷ and systemic treatment is the standard of care for them. In most patients, HCC is associated with chronic liver injuries from chronic hepatitis virus infection, alcohol abuse or non-alcoholic liver steatosis hepatitis. These chronic liver injuries not only complicate treatment choice but also compete for the effect of tumor progression on patient survival.⁸ Treatment, therefore, needs to balance anti-tumor effects and harm to liver parenchyma. The result of systemic therapy for advanced-stage HCC was disappointing until the approval of sorafenib in 2008. Since then, no systemic treatment was found to be superior or equivalent to sorafenib until the approval, within the last two years, of several agents for systemic therapy of advanced-stage or unresectable HCC.⁹

Tumor angiogenesis in HCC and the rational of anti-angiogenic therapy

HCC is a typically hyper-vascular tumor. The characteristics of abundant and tortuous vessels distinguish HCC from benign lesions in angiography and imaging.¹⁰ With this feature, transcatheter chemoembolization (TACE), which is to starve tumors with embolism, is the standard of care for intermediate-stage HCC. Because of the genetic heterogeneity of tumor cells, anti-tumor cell therapy, e.g., chemotherapy, is not successful in HCC, to target the relatively stable vascular cells seems more rationale. Vascular endothelial growth factor (VEGF) is an essential angiogenic cytokine and plays a critical role in tumor angiogenesis.¹¹ VEGF signaling pathway also plays a vivid role in tumor angiogenesis and tumor progression in HCC.¹² Moreover, VEGF was found to be the common regulation of stromal cells, including fibroblasts, macrophages, and endothelial cells, by heterogeneous tumor cells.¹³ All the approved systemic therapies in the US, EU, and China are molecular targeted therapy with the primary mechanism of anti-angiogenesis targeting the VEGF and its receptors. Other signaling pathways with pro-angiogenic effects, such as platelet-derived growth factor (PDGF)/PDGF receptors (PDGFR), fibroblast growth factor (FGF)/FGF receptors (FGFR), angiopoietin/Tie, and endoglin (CD105), were also studied in HCC, and most multi-targeted tyrosine kinase inhibitors (TKIs) evaluated for the treatment for HCC covered these receptors.¹⁴

First-line

Sorafenib

Sorafenib is an oral TKI with anti-angiogenic and anti-proliferation effects by targeting VEGF receptors (VEGFRs), PDGFR, and Raf kinases.¹⁵ Sorafenib has been approved for the treatment of advanced-stage or unresectable HCC for more than 10 years in China and most parts of the world. Two trials conducted outside and within Asia have shown the efficacy of sorafenib in extending patient survival.^{16,17} Sorafenib became a standard of care recommended by the guidelines from almost all regions, and management of its toxicities, such as hand-foot syndrome, has improved its tolerance.¹⁸ After approval, It has been estimated that the overall survival (OS) of patients with advanced-stage HCC has been extended from 6.5 months to 8.5–8.9 months in Asian patients and from 10.7 months to 11.8–15.1 months in non-Asian patients, probably because of the improvement in the management of toxicities associated with sorafenib.¹⁹ Several reports demonstrated sorafenib-induced toxicities, such as diarrhea, hypertension, and hand-foot syndrome, were associated with better tumor response.²⁰ However, attempts to identify a molecular biomarker for selection of patients sensitive to sorafenib has failed. Monotherapy with other anti-angiogenic therapies (such as sunitinib,²¹ brivanib,²² and linifanib²³), or selective internal radiotherapy with yttrium-90 resin microspheres (SARAH and SIRveNIB studies^{24,25}) had been shown not to be superior to sorafenib in head-to-head phase III trials until the REFLECT trial²⁶ demonstrated that lenvatinib is not inferior to sorafenib in improving patient survival.

Combination treatment with sorafenib and locoregional therapy has been intensively investigated. However, most trials failed to demonstrate the additional benefit of sorafenib over TACE versus TACE alone in patients with intermediate-stage HCC, such as the SPACE study.²⁷ Also, adding TACE to sorafenib treatment did not further improve the OS with sorafenib monotherapy.²⁸ Recently, the results from the TACTICS trial demonstrated that TACE plus sorafenib is more effective in prolonging progression-free survival (PFS) than TACE alone in patients with unresectable HCC, but the overall survival (OS) data were not reported.²⁹ The major differences in trial design may be that the development of new lesions was not a criterion for stopping TACE as long as the lesion could be treated with TACE. This strategy gave patients more opportunities to receive TACE, which would prolong treatment duration for both arms.²⁹ A recent single-center randomized control trial (RCT) conducted in China demonstrated that the effect of sorafenib and hepatic arterial infusion chemotherapy (HAIC) using oxaliplatin, 5-fluorouracil, and leucovorin is better than sorafenib alone in patients with tumor invasion to portal vein in terms of OS and PFS and produced a much better objective response rate.³⁰ However, a similar regimen (HAIC plus sorafenib) was not proved to be more effective than sorafenib alone for patients with unresectable HCC (BCLC-B and C stages).³¹ Therefore, the effect of the combination of sorafenib with other locoregional treatment needs more investigations.

Lenvatinib

Lenvatinib is also a multi-kinase inhibitor targeting VEGFRs 1–3, PDGFR, FGFR, RET, and KIT.³² Lenvatinib was approved for advanced HCC in 2018 based on the REFLECT study, a non-inferior designed open-labeled control trial.²⁶ The objective response rate (ORR) of lenvatinib treatment was 18.8% (RECIST v1.1) or 40.6% (mRECIST) judged by masked independent image review.²⁶ A real-world study demonstrated that therapeutic response and adverse events after taking lenvatinib were similar to those of the REFLECT trial, regardless of previous TKI therapies,³³ and the immunomodulatory activity of lenvatinib has also been revealed in an experimental study³⁴ and a clinical study.³⁵

Although the trial demonstrated that lenvatinib provided a similar survival benefit to sorafenib, the higher ORR of lenvatinib is essential to encourage patients to stay on treatment and tolerate the toxicities and for physicians to monitor the effectiveness of treatment. The higher ORR also inspired the thought of down-staging treatment for initially unresectable HCC or neoadjuvant therapy for resectable HCC.

Second line

Regorafenib

Regorafenib is another multi-target TKI, targeting VEGFRs, Tie-2, PDGFR- β , FGFRs, Kit, and Ret. The RESORCE trial³⁶ was conducted in patients who tolerated sorafenib but progressed on sorafenib treatment. The median OS in regorafenib treated patients was 10.6 months compared to 7.8 months in the placebo group (HR = 0.61, $P < 0.0001$), and PFS was increased from 1.5 months to 3.1 months by regorafenib treatment (HR = 0.46, $P < 0.0001$); the ORR in regorafenib treated patients was 7% compared with 3% in the placebo group ($P = 0.020$, RECIST v1.1). Regorafenib is the first second-line treatment after sorafenib showing an OS benefit. The incidence of treatment-related grade 3 or 4 adverse events was 50%, including hand-foot syndrome, infection, hypertension, and fatigue.

One study showed sequential treatment using sorafenib and regorafenib may result in a median OS of 28 months in patients with advanced HCC.³⁷ For BCLC-B stage patients, TACE is the first recommended treatment, while refractory disease is commonly observed. At this time, sequential treatment with sorafenib and regorafenib may be introduced to TACE-resistant BCLC-B stage patients to achieve more prolonged survival.

Cabozantinib

Cabozantinib is a multi-kinase inhibitor targeting VEGFR-2, MET, and AXL. A randomized control study demonstrated cabozantinib treatment resulted in a longer OS (10.2 versus 8.0 months, HR = 0.76, $P = 0.005$) and PFS (5.2 versus 1.9 months, HR = 0.44, $P < 0.001$) compared with placebo in patients with advanced HCC as a second-line treatment.³⁸ An interesting finding from this study was that the HR for death was 0.69 in patients with HBV-related HCC and 1.11 in patients with HCV-related HCC, which suggests that anti-tumor effects of cabozantinib may be more potent for HBV-related HCC.

The molecular targets of cabozantinib, MET and AXL, have a role in treatment resistance to anti-angiogenesis therapies,³⁹ which is consistent with the effect of cabozantinib as a second-line treatment for HCC. Compared with regorafenib, cabozantinib resulted in longer PFS (5.2 vs. 3.4 months, per RECIST 1.1^{36,38}), while the grade 3 and 4 adverse events were more common, including hypertension, diarrhea, and hand-foot syndrome.

Ramucirumab

Ramucirumab is an antibody targeting VEGFR-2 but not a TKI. VEGFR-2 mainly expresses on endothelial cells and is the receptor for the ligand VEGF-A, C, D. VEGFR-2 mediates the majority of the downstream effects of VEGF in tumor angiogenesis.⁴⁰ In the REACH trial, in patients with advanced HCC who have been treated with sorafenib without success, prespecified subgroup analysis revealed that patients with serum alpha-fetoprotein (AFP) ≥ 400 ng/ml might benefit from ramucirumab treatment.⁴¹ The following REACH-2 trial was, therefore, explicitly conducted in patients with serum AFP ≥ 400 ng/ml, and the results demonstrated that OS and PFS were significantly better than the placebo arm.⁴²

The grade 3 or higher adverse events associated with ramucirumab treatment were very low. The median treatment intensity was 98% in the ramucirumab treated group, suggesting that most patients received a full dose of ramucirumab, and adverse events leading to treatment discontinuation occurred in only 11% of patients. Hypertension and hyponatremia were the only grade 3 or higher treatment-emergent adverse events that were noted in 5% or more of patients.⁴²

Other anti-angiogenic agents

Other agents were also evaluated for the treatment of advanced or unresectable HCC, including sunitinib as first-line,²¹ brivanib as first-line²² or second-line,⁴³ linifanib,²³ however, all the trials did not meet the primary endpoint because of lower anti-tumor effects or higher toxicity as compare with sorafenib or placebo (Fig. 1). Thalidomide is a proved drug with anti-angiogenic effect, however, its antitumor effects for HCC were modest in phase II clinical trials.^{44–47} Bevacizumab is a monoclonal antibody that blocks VEGF-A. In a phase II study, bevacizumab at 5–10 mg/kg every two weeks did show anti-tumor activity in HCC patients with an ORR of 13%, and 65% of patients were progression-free at six months.⁴⁸ However, severe bleeding occurred in 11% of the HCC patients and held back further phase III studies. However, in more carefully selected HCC patients, when combined with atezolizumab, an anti-PD-L1 antibody, bevacizumab at a dose of 15 mg/kg q3weeks showed acceptable tolerability with promising results; ORR was 29.9% (pooled analysis of arms A and F1) in a phase Ib clinical trial in 164 HCC patients.⁴⁹ The combination was further investigated as first-line treatment compared with sorafenib in a phase III study (IMbrave150 study, NCT03434379). Also, bevacizumab was in development with duravalumab (an anti-PD-L1 antibody) in combination with TACE (EMERALD-1, NCT03778957) or as adjuvant therapy (EMERALD-2 study, NCT03847428).

Three TKIs with antiangiogenic agents manufactured by Chinese pharmaceutical companies were also in clinical

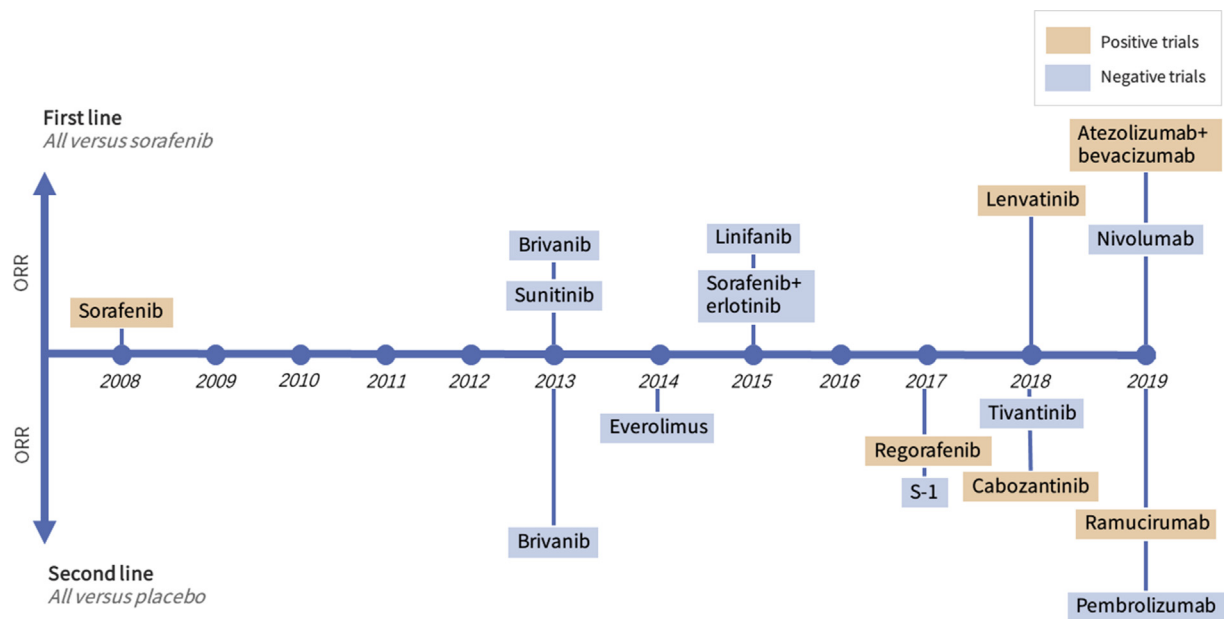


Figure 1 Timeline of phase III clinical trials evaluating systemic therapies for unresectable or advanced hepatocellular carcinoma in the last decade. ORR, objective response rate, the proportion of partial response and complete response per RECIST v1.1 criteria, except for brivanib which was evaluated by mRECIST criteria. Note that donafenib was also studied in a phase III trial, but the ORR was not reported.

development for HCC. Donafenib (targeting Raf and VEGFRs) (NCT02645981), apatinib (targeting VEGFR2) (NCT02329860) have been investigated in phase III studies. Most recently, the company announced that donafenib showed more potent anti-tumor efficacy than sorafenib in the phase 3 study for patients with advanced HCC.⁵⁰ Anlotinib (targeting VEGFRs, EGFR, and FGFR) also showed a durable anti-tumor activity (ORR 4.6% and median time to progression 4.0–5.5 months) and manageable toxicity in a phase II study.⁵¹

Anti-angiogenic therapy in early-stage HCC

The STORM trial to evaluate the effect of adjuvant sorafenib treatment after resection or ablation on early-stage HCC (BCLC stage 0-A) with a high risk of tumor recurrence did not reach its primary endpoint.⁵² The median treatment duration in the sorafenib arm was 12.5 months (22.2 months in the control arm), and 1-year discontinuation rate was 49% (35% in the control arm), suggesting long-term treatment with sorafenib is challenging, especially in the absence of a target lesion. Furthermore, more than 60% of patients were not the target population for receiving adjuvant anti-tumor treatment because the 2-year recurrence rate is less than 40% in the control arm. “Wrong stage and wrong dose” were the major criticisms for this trial.⁵³ However, a small trial demonstrated that sorafenib improved patient OS and decreased tumor recurrence rate only in patients with a higher risk of tumor recurrence.⁵⁴

Beyond anti-angiogenesis

In all phase III studies that led to the approval of molecular targeting therapies, the median OS for patients with

advanced or unresectable HCC was about one year,^{16,17,26} and there may be a ceiling of efficacy for anti-angiogenic treatments.⁵⁵ Strategies for improving the survival bar of these drugs are hot spots in clinical development. However, all combinational therapies with sorafenib, including systemic chemotherapy (doxorubicin,⁵⁶ or capecitabine and oxaliplatin⁵⁷), hepatic arterial infusion chemotherapy,³¹ tigatuzumab (a death receptor-5 agonist),⁵⁸ erlotinib (an EGFR inhibitor),⁵⁹ and TACE,²⁸ have failed to improve patient OS compared with sorafenib monotherapy.

The combination of anti-angiogenic therapy and an anti-PD-1 antibody

Immune checkpoint inhibitors (ICIs) may be promising for combination therapy with sorafenib and other anti-angiogenic drugs because the major toxicity profiles of TKIs and ICIs do not overlap. There’re early-phase clinical studies in HCC and late-phase studies in other solid tumors have shown that the toxicity of these two categories combination is manageable. More importantly, there may be synergistic biological effects between anti-angiogenesis and ICI agents. Intratumoral VEGF overexpression exerts an immunosuppression microenvironment in tumors by accumulation of regulatory T cells, myeloid-derived suppressor cells, immunosuppressive cytokines, inhibiting DC maturation and production of IDO,^{60,61} inhibiting T cell infiltration,⁶² and upregulating the expression of immune checkpoints on CD8⁺ T cells.⁶³ Most recently, VEGF was also found to reprogramming tumor microenvironment to promote an immune-suppressive environment that favors tumor progression and provides a rationale for combination therapy of ICI and anti-angiogenesis therapy.¹³ Anti-angiogenesis treatment may also increase the efficacy of immunotherapies by targeting angiopoietin-2 and

hepatocyte growth factor pathways, while immunotherapies may increase the effectiveness of anti-angiogenesis treatment by eliciting antibody-dependent cytotoxicity on endothelial cells followed by destructing tumor vasculature.⁶⁴ An animal study found that lenvatinib showed a more potent anti-tumor effect in immunocompetent mice than in immunodeficient mice, and the combination of lenvatinib and anti-PD-1 antibody resulted in a higher response rate compared with either treatment alone in immunocompetent mice.³⁴

In a phase Ib study evaluating the safety of lenvatinib in combination with pembrolizumab in 67 evaluable patients with unresectable HCC (NCT03006926)⁶⁵, no new adverse event was identified, with a confirmed ORR of 40.3% (27/67). Another phase I study combining SHR-1210 and apatinib in patients with advanced solid tumors, including HCC, showed manageable toxicity, with 50% of patients with evaluable HCC (8/16) achieving a PR.⁶⁶ Beyond acceptable safety and tolerability, a promising synergic effect of ICI and anti-angiogenic therapies has shown in several phase III studies in other solid tumors, like RCC, which is also characterized as a hyper-vascular tumor. TKIs, namely sunitinib or sorafenib, are standard treatments for advanced and metastatic RCC. The combination of axitinib (a TKI targeting VEGFRs) and pembrolizumab⁶⁷ or avelumab (a PD-L1 antibody)⁶⁷ showed superior anti-tumor effects to sunitinib in 2 phase III studies in RCC. The combination of lenvatinib and pembrolizumab showed promising anti-cancer activity in a phase II study in RCC, with the ORR as high as 66.7%, and the mPFS as 17.7 months.⁶⁸ The successful experience in RCC has shed light on drug development for HCC, and the combination of TKI and ICI can be anticipated to improve HCC outcomes further. The FDA has granted a breakthrough therapy designation for the combination of pembrolizumab and lenvatinib for the treatment of both RCC and HCC.⁶⁹ The highest ORR was reported in several small trials testing combination treatment of anti-angiogenesis agents with PD-1 antibodies, which are summarized in Table 1. Further evaluation of the efficacy and safety in phase III clinical trials is warranted as a top priority in drug development for advanced-stage or unresectable HCC by the pharmaceutical companies. The ongoing large phase III clinical trials, most of which

concerned combination therapy with anti-angiogenesis and ICI in HCC patients, are listed in Table 2. Most recently, the combination of atezolizumab and bevacizumab showed improved OS and PFS in compare with sorafenib in a phase III clinical trial (IMbrave150 study) both in global cohort of HCC patients⁷⁰ and in Chinese patients.⁷¹

Overcome the “opposite effects” of anti-angiogenic therapy

The “opposite effects”, rather than the “adverse effects”, is an off-target effect of an anti-tumor agent that increases the invasiveness of tumor cells and may partly counteract the antitumor effects. In preclinical studies, although anti-angiogenic therapies showed potent anti-tumor effects, they were also found to facilitate tumor metastasis.^{72,73} Our research found that sorafenib promotes invasiveness and the metastatic potential of orthotopic tumors in HCC mouse models by down-regulating the expression of HTA-TIP2,⁷⁴ and aspirin minimized the pro-metastasis effect of sorafenib by up-regulating HTATIP2 in tumor cells.⁷⁵ Anti-angiogenic therapy also acts upon the host,⁷⁶ and the changes in the host or metastatic target organ may facilitate tumor metastasis. Sorafenib was found to suppress host immune response by inhibiting NK cells’ proliferation and cytotoxic effects.⁷⁷ Sorafenib treatment in HCC mouse models recruits more macrophages by elevation of colony-stimulating factor-1, stromal-derived factor 1 α , and VRGF expression from tumor cells. The depletion of macrophages by clodrolip or zoledronic acid in combination with sorafenib significantly inhibited tumor progression compared with mice treated with sorafenib alone.⁷⁸ Host macrophages in organs other than liver may also affected by anti-angiogenic therapy. Our in vivo study found that two anti-angiogenic agents (sunitinib and sorafenib) facilitated tumor cell survival in blood stream and promoted lung metastasis by down-regulation the expression of interleukin-12b in macrophages and dendritic cells from host organs. Supplement with recombinant IL-12b or restoration of IL-12b expression by low-dose zoledronic acid alleviated the pro-metastasis effects of sorafenib or sunitinib.⁷⁹ To overcome the opposite effects of anti-angiogenic

Table 1 Safety and efficacy of combination treatment with anti-angiogenic therapy and anti-PD-1/PD-L1 antibody in patients with advanced HCC.

Combinations	Number of patients	ORR (RECIST v1.1)	mPFS (months)	Grade 3/4 AE
apatinib + camrelizumab ⁶⁶	16 (2nd line)	50%	5.8	NA
lenvatinib + pembrolizumab ⁶⁵	67 evaluable (63 as 1st line)	40.3%	9.5	80.6%
bevacizumab + atezolizumab ⁴⁹	104 (1st line) arm A	36%	7.3	38%
	60 (1st line) arm F1	20%	5.6	37%
axitinib + avelumab ⁸³	22 (1st line)	13.6%	5.5	72.7%
cabozantinib + nivolumab + ipilimumab ⁸⁴	35 (1st line)	26%	6.8	71%
cabozantinib + nivolumab ⁸⁴	36 (1st line)	17%	5.5	42%
lenvatinib + nivolumab ⁸⁵	30 (1st line)	54.2%	7.39	60%
regorafenib + pembrolizumab ⁸⁶	23 (1st line)	30%	NA	NA

ORR, objective response rate; mPFS, median progression-free survival; AE, adverse events; NA, not available.

Table 2 Ongoing phase 3 clinical trials of anti-angiogenic therapy with or without anti-PD-1/PD-L1 antibody for advanced or unresectable hepatocellular carcinoma.

Trial	Lines	Arms	Clinicaltrials.gov identifier	Sponsor
ZGDH3	First line	donafenib vs sorafenib	NCT02645981	Zelgen
LEAP-002	First line	lenvatinib + pembrolizumab vs lenvatinib	NCT03713593	MSD + Eisai
COSMIC-312	First line	cabozantinib + atezolizumab vs sorafenib vs cabozantinib	NCT03755791	Exelixis
SHR-1210-III-310	First line	camrelizumab + apatinib vs sorafenib	NCT03764293	Hengrui
ORIENT-32	First line	sintilimab + IBI305 vs sorafenib	NCT03794440	Innovent

therapy may become a promising approach to further increase the efficacy of anti-angiogenic therapy.

New targets for anti-angiogenic therapy

Most anti-angiogenic drugs are targeting the VEGF signaling pathway in tumor endothelial cells. However, emerging studies indicated that tumor endothelial cells are also heterogeneous. Our previous study found that CD105 (endoglin)-positive HCC endothelial cells showed increased apoptosis resistance, motility, and proangiogenic properties as compared with endothelial cells from non-tumor liver tissue. These cells acquired more resistance to chemotherapeutic agents and sorafenib than their counterparts without CD105 expression in normal liver tissue.⁸⁰ The combination of TRC105 (an anti-endoglin antibody) and sorafenib demonstrated encouraging evidence of efficacy, including a 25% partial response rate and a durable response in HCC patients with measurable disease in an early-phase clinical trial.^{81,82}

Prospective

Nowadays, anti-angiogenic therapy is the backbone of systemic treatment for advanced or unresectable HCC. Based on the ongoing clinical trials, anti-angiogenic treatment will remain the first-line therapy in the near future. The combination of anti-angiogenic therapy with an anti-PD-1 antibody showed promising efficacy in the early phase clinical trials, and will hopefully be the first-line treatment in the future. For Chinese patients, drug development by local pharmaceuticals will provide them with more affordable medications. Based on the ongoing clinical trials (Table 2), not only the systemic therapy for patients with advanced HCC will be changed by combinational therapy or novel molecular targeted therapy, the treatment of early-stage and intermediate-stage HCC will also be largely changed with the emerging agents or strategies. For the patients with early-stage HCC, a first widely-accepted adjuvant therapy may be an ICI or an anti-angiogenic treatment with low toxicity shortly, and the efficacy of TACE for the patients with intermediate-stage HCC will be also improved by the combination with ICIs and an anti-angiogenic agent.

Conflict of interest

HCS received a lecture fee from Bayer, Eisai, and MSD.

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