

# Research Progress on Anti-angiogenesis Drugs in Hepatocellular Carcinoma

Yihui Yang<sup>1</sup>, Liwen Ren<sup>1</sup>, Hong Yang<sup>1</sup>, Binbin Ge<sup>2</sup>, Wan Li<sup>1</sup>, Yumin Wang<sup>3</sup>, Hongquan Wang<sup>3</sup>, Guanhua Du<sup>1\*</sup>, Bo Tang<sup>4\*</sup>, Jinhua Wang<sup>1\*</sup>

<sup>1</sup>Beijing Key Laboratory of Drug Target Identification and Drug Screening, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China

<sup>2</sup>School of Pharmacy, Weifang Medical University, Weifang 261053, China

<sup>3</sup>Aerospace Center Hospital, School of Aerospace Clinical Medicine, Peking University, Beijing 100049, China

<sup>4</sup>Department of Hepatobiliary Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, 530021, Guangxi, China

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## \*CORRESPONDING AUTHORS

Jinhua Wang  
E-mail: wjh@imm.ac.cn  
Bo Tang  
E-mail: dr\_sntangbo@163.com  
Guanhua Du  
E-mail: dugh@imm.ac.cn

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**Abstract:** Primary liver cancer is the sixth most prevalent cancer worldwide and ranked in third for cancer-related mortality rate. Hepatocellular carcinoma (HCC) accounts for about 90% of all primary liver cancers. High vascularization of HCC implies the significance of angiogenesis in the development and pathogenesis of HCC. Several angiogenic pathways have been identified as being dysregulated in HCC, highlighting potential therapeutic targets for the treatment of HCC. In 2007, sorafenib was approved as the standard first-line treatment for advanced HCC, catapulting the therapeutic approach of HCC into the avenue of targeted therapy. In recent years, the approval of several novel targeted drugs and the progress in combination of immunotherapy and targeted therapies provide more alternatives for the treatment of HCC. The progress of anti-angiogenesis therapies in HCC over the past few decades is reviewed and the future prospect of anti-angiogenesis therapy for HCC is also discussed.

**Keywords:** Hepatocellular carcinoma, Anti-angiogenesis, Targeted therapy, Combination treatment, Research progress

## 1. Introduction

Liver cancer is one of the most common gastrointestinal neoplasms worldwide. Global Cancer Statistics 2020 (GLOBOCAN 2020) estimated that there were about 910,000 new cases of liver cancer in 2020, and it was ranked 6<sup>th</sup> after female breast, lung, colorectal, prostate, and stomach cancers and remained the 3<sup>th</sup> most common cause for global cancer-related deaths<sup>[1]</sup>. Liver cancer, which is very common in China, has become a great threat against Chinese public health, accounting for almost half of the new cases and dead cases of liver cancer<sup>[2]</sup>. Liver cancer mainly comprises primary liver cancer and secondary liver cancer. Primary liver cancer is a kind of malignant carcinoma transformed from hepatocytes and cholangiocytes after sequential genomic damage, and consists of three major subtypes, namely, hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and mixed HCC-ICC tumors. HCC and ICC make up of 99% of primary liver cancer cases<sup>[3]</sup>.

Nearly 800,000 new cases of HCC, which is the most common subtype of primary liver cancer, were reported annually, accounting for more than 90% of primary liver cancer cases<sup>[3]</sup>. With a 5-year survival of 12%, HCC is considered one of the most aggressive malignancies due to its propensity for metastasis and invasion as well as poor prognosis. Higher incidence rates of HCC have been reported in Asia and Sub-Saharan, and major risk factors of HCC include HBV/HCV infection, alcohol abuse, and non-

alcoholic fatty liver diseases<sup>[4]</sup>. The Barcelona Clinic Liver Cancer staging system is widely used for the management of HCC. Patients with HCC are classified as five stages and corresponding treatment therapies for each stage are recommended. Treatments for HCC are mainly divided into curative therapies containing surgical resection, liver transplantation, ablative therapies, and palliative therapies, including chemoembolization and targeted therapies<sup>[5]</sup>. However, more than 70% of HCC patients are diagnosed with unresectable HCC and could only receive palliative therapies. Besides, cytotoxic drugs have poor efficacy in HCC patients and increase their toxicity due to the change of liver function in patients with HCC<sup>[4]</sup>.

Tumor angiogenesis is an important hallmark of tumors. HCC is characterized by hypervascularization, which exhibits apparent microvascular abnormality<sup>[6]</sup>. The expression of multiple proangiogenic growth factors is upregulated in HCC; these growth factors include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), basic fibroblast growth factor, and transforming growth factor- $\beta$ , which activate subsequent downstream signaling pathways involved in cell proliferation and angiogenesis, such as mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinases pathways<sup>[7,8]</sup>. Thus, as a highly vascularized tumor, anti-angiogenic therapy is a major strategy for treating patients with HCC. Several newly approved therapies for advanced HCC targeting angiogenesis pathway have brought new hopes for the treatment of advanced HCC in recent years. Here, the latest new treatment options in first- and second-line drugs as well as the combination of anti-angiogenic drugs and immune drugs for HCC are reviewed in this article.

## 2. First-line anti-angiogenic drugs for HCC

### 2.1. Sorafenib (Nexavar)

In 2007, sorafenib was approved by the US Food and Drug Administration (FDA) as the first systemic treatment for advanced HCC. Sorafenib is an oral multi-kinase inhibitor (MKI), which targets VEGF receptor-1 (VEGFR-1), VEGFR-2, VEGFR-3, PDGF receptor (PDGFR- $\beta$ ), c-Kit, FLT-3, and RET, and blocks downstream RAF/MEK/ERK signaling pathway to directly inhibit tumor proliferation as well as interferes with the process of angiogenesis. The efficacy of sorafenib was evaluated in two large-scale, placebo-controlled, randomized, Phase III studies, including Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) and Asia-Pacific studies that involved patients with advanced HCC previously untreated with systemic treatment. In SHARP study, patients taking sorafenib had a better median overall survival (OS) compared with placebo group (10.7 vs. 7.9 months; hazard ratio [HR]=0.69,  $P=0.00058$ ). In Asia-Pacific study, patients on sorafenib also demonstrated a significant increase in median OS

as a mirror clinical trial of SHARP study carried out in Asian population (6.5 vs. 4.2 months, HR=0.68,  $P=0.014$ ). Treatment-related adverse effects (TRAEs) were reported more frequently in sorafenib treatment group, including hand-foot syndrome, diarrhea, weight loss, and fatigue<sup>[9-12]</sup>. Following the two critical clinical studies, sorafenib was the first approved first-line drug for the treatment of advanced HCC. However, sorafenib has modest treatment benefit to patients as demonstrated by the low tumor regression rate and short median OS in clinical setting. The primary and acquired drug resistance also limited the clinical benefit of sorafenib to patients with HCC<sup>[13]</sup>. Due to the unsatisfactory clinical benefit and complexity of the cancer's molecular pathogenesis, combination of sorafenib with surgical resection, chemoembolization, and other targeted drugs was evaluated whether the combination therapies could improve the clinical efficacy of sorafenib but no combination therapies containing sorafenib were successful in Phase III trials to date<sup>[14]</sup>.

### 2.2. Lenvatinib (Lenvima)

Lenvatinib is an oral MKI preferably targeting VEGFR1–3, FGFR1–4, PDGFR $\alpha$ , KIT, and RET. Lenvatinib has been approved for the treatment of thyroid cancer. In 2018, REFLECT trial, a Phase III study was carried out to evaluate the efficacy of lenvatinib versus sorafenib for the first-line treatment of advanced HCC. Compared with sorafenib, lenvatinib exhibited similar efficacy on the basis of median OS (13.6 vs. 12.3 months, HR=0.92) but demonstrated significant improvement in specified secondary endpoints, including median progression-free survival (PFS) (7.4 months vs. 3.7 months; HR=0.66;  $P<0.0001$ ), objective response rate (ORR) (24.1% vs. 9.2%, odds ratio=3.13,  $P<0.0001$ ), and time to progression (TTP) (8.9 vs. 3.7 months, HR=0.66,  $P<0.0001$ ). In terms of TRAEs, lenvatinib showed more favorable toxicity profiles than sorafenib with the most common TRAEs being hypertension, diarrhea, loss of appetite, and weight loss. Based on the non-inferior results, lenvatinib was approved as the second first-line treatment for advanced HCC in 2018<sup>[15]</sup>. As an alternative to sorafenib, Japanese economists considered that lenvatinib was comparably cost effective than sorafenib<sup>[16]</sup>.

### 2.3. Donafenib

Donafenib is an oral small-molecule multitarget kinase inhibitor developed by Suzhou Zelgen Biopharmaceuticals Co., Ltd. (Jiangsu Province, China). It can inhibit multiple receptor tyrosine kinases, such as VEGFR, PDGFR, Raf, and the downstream Raf/MEK/ERK signaling pathway, thus inhibiting tumor cell proliferation and tumor angiogenesis<sup>[17]</sup>. Donafenib is the first domestically made anti-angiogenic agent for the first-line treatment of advanced HCC in China. The results of the open-label, randomized, parallel-controlled Phase II/III clinical trial

study ZGDH3 showed that donafenib was more effective and safer than sorafenib for the treatment of advanced liver cancer. The study was conducted simultaneously in 37 centers and included a total of 668 patients with unresectable or metastatic HCC. The research data showed that in terms of effectiveness, the primary endpoint of the experimental group was significantly better than the control group (12.1 months vs. 10.3 months, HR=0.831,  $P=0.0363$ ). However, there was no significant difference in the secondary endpoints of the two groups, such as mPFS and ORR. In terms of safety, TRAEs with Grade  $\geq$  grade r, there was no significant difference in the secondary endpoints. Donafenib group were significantly lower than that in the sorafenib group. The above results indicated that donafenib was safer and more efficient than sorafenib. Donafenib is a deuterated derivative obtained by replacing the methyl group of sorafenib with a tri-deuterium methyl group. Given that the deuterium-carbon bond is more stable than the hydrogen-carbon bond, donafenib is hard to be metabolized by liver drug enzymes. Therefore, donafenib can reach higher plasma exposure with less toxic metabolites, thereby achieving efficacy and safety improvement at lower dose<sup>[18]</sup>. Although donafenib has not been approved for marketing, the 2020 version of the Chinese Society of Clinical Oncology (CSCO) Guidelines for the Diagnosis and Treatment of Primary Liver Cancer has officially included donafenib as a first-line treatment for advanced HCC<sup>[19]</sup>.

### 3. Second-line anti-angiogenic therapies for HCC

#### 3.1. Regorafenib (Baiwango)

In May 2017, the US FDA approved to repurpose regorafenib as the second-line treatment for patients with advanced HCC who had previously been treated with sorafenib. As a structural analogue of sorafenib, regorafenib which is also an oral MKI can target a variety of kinases related to tumor angiogenesis, tumor growth, and metastasis, including VEGFR1~3, TIE-2, KIT, RET, RAF-1, BRAF, PDGFR, FGFR, and CSF1R. The large international multicenter Phase III RESORCE study evaluated the efficacy and safety of regorafenib in HCC patients with tumor progression after sorafenib treatment. The results suggested that regorafenib significantly improved the OS of patients (median OS: 10.6 months vs. 7.8 months, HR=0.63,  $P<0.0001$ ). Compared with the placebo group, the risk of death of patients in the regorafenib group was significantly reduced by 37%. Regorafenib group also had significant improvement in terms of PFS (median PFS: 3.1 months vs. 1.5 months, HR=0.46,  $P<0.0001$ ). All subjects in the regorafenib group had adverse reactions. The most common third-degree and fourth-degree TRAEs include hypertension (15% in the regorafenib group vs. 5% in the placebo group), hand-foot-skin reactions

(13% vs. 1%), fatigue (9% vs. 5%), and diarrhea (3% vs. 0%)<sup>[20]</sup>. Although the structures of the two molecules are relatively similar, the exact mechanism through which regorafenib can benefit patients after the treatment of sorafenib therapy is still unclear. In addition to its ability to continuously inhibit VEGFR signaling and anti-angiogenic effects, regorafenib is also believed to directly inhibit the signaling pathways of tumor cell proliferation, metastasis, and can regulate tumor microenvironment<sup>[21]</sup>.

#### 3.2. Cabozantinib

Cabozantinib was approved by the US FDA in 2012 for the treatment of medullary thyroid cancer. In 2019, the US FDA approved cabozantinib for the treatment of HCC patients with acquired resistance to sorafenib. Cabozantinib is a tyrosine kinase inhibitor, which can inhibit proteins involved in tumorigenesis and angiogenesis, such as VEGFR1-3, MET, AXL, and angiopoietin receptors TIE-2, RET, c-Kit, and FLT-3<sup>[22]</sup>. The results of the large international multicenter Phase III clinical trial CELESTIAL showed that cabozantinib can significantly prolong the survival time of patients with advanced HCC and reduce the risk of death or progression by 56%. The clinical trial recruited 707 patients with HCC who were pathologically diagnosed as unacceptable to radical therapy. About 70% of the patients had received at least one systemic treatment (such as sorafenib) before the disease progressed, and about 30% of the patients had undergone two treatments. The subjects were randomly divided into two groups according to the ratio of two to one, and received cabozantinib (60 mg/day) and placebo, respectively. The clinical trial was stopped in the second interim analysis. The data of the entire test population revealed that the median OS of the two groups of patients was 10.2 months and 8 months, respectively (HR=0.76,  $P=0.005$ ), and the median PFS was 5.2 months and 1.9 months (HR=0.44,  $P<0.001$ ), as shown in **Table 1**. For the group of subjects who had previously received sorafenib treatment, the median OS of the cabozantinib group and the placebo group was 11.3 months and 7.2 months, respectively (HR=0.70, 95% CI=0.55–0.88), the median PFS was 5.5 months and 1.9 months (HR=0.40, 95% CI=0.32–0.50). About 68% of patients in the cabozantinib treatment group and 36% of the placebo group had Grade 3 or 4 TRAEs. Hand-foot syndrome, hypertension, fatigue, elevated aspartate aminotransferase levels, and diarrhea were the most common TRAEs<sup>[23]</sup>.

#### 3.3. Apatinib (Aitan)

Apatinib was developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd., a Chinese domestic pharmaceutical enterprise. As a novel small molecule of VEGFR2 tyrosine kinase inhibitor, apatinib can block the proliferation and migration of vascular endothelial cells, reduce tumor microvessel density, and inhibit tumor tissue angiogenesis. Apatinib can significantly prolong the

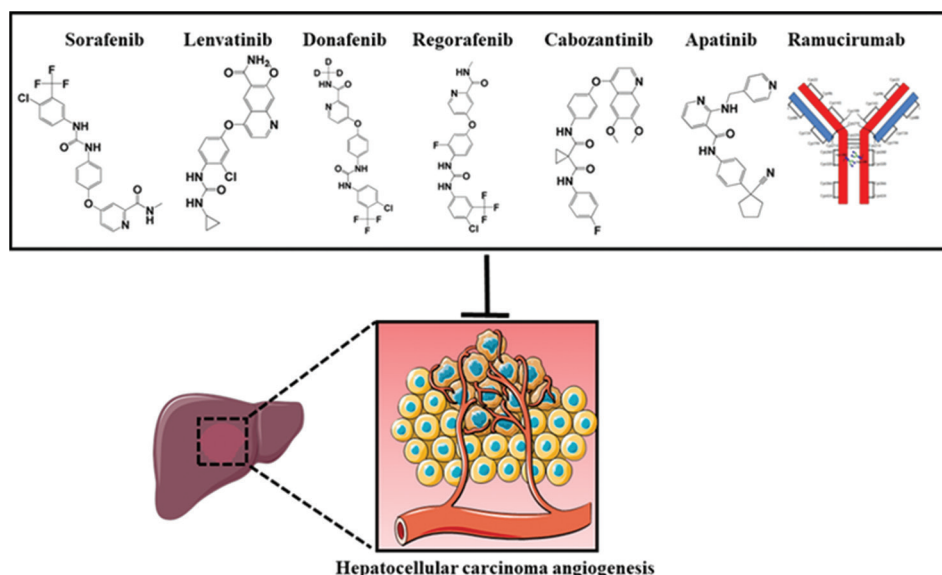
survival time of patients with advanced gastric cancer. It was approved in December 2014 as the third-line therapy for patients with advanced gastric adenocarcinoma or gastric-esophageal junction adenocarcinoma who had undergone at least two systemic chemotherapies in the past and had disease progression or recurrence<sup>[24]</sup>. On December 31, 2020, the Chinese National Medical Products Administration (NMPA) approved apatinib as the second-line treatment of advanced HCC for patients who have failed after receiving or was intolerable to at least one first-line systemic treatment in the past. The approval of apatinib was based on the results of a prospective, randomized, double-blind, placebo-controlled national multicenter Phase III clinical trial AHELP. The results showed that apatinib can significantly prolong the median OS of patients to 8.7 months, which is significantly higher

than the 6.8 months of the placebo group (HR=0.785,  $P=0.0476$ ). The median PFS of the apatinib group was 4.5 months, while that of the placebo group was 1.9 months (HR=0.471,  $P<0.0001$ ). At the same time, the ORR of the apatinib group reached 10.7%, which was significantly higher than that of the control group of 1.5%. The above results indicated that the apatinib treatment not only has high objective efficiency but also has significant survival benefit. In terms of safety, the adverse events related to apatinib treatment are similar to that of the treatment for advanced gastric cancer. There are no new safety issues and all the patients are well tolerated<sup>[25]</sup>. At present, the 2020 version of the CSCO Guidelines for the Diagnosis and Treatment of Primary Liver Cancer has officially included apatinib as the single agent for the second-line treatment of advanced HCC<sup>[19]</sup>.

**Table 1.** Summary of clinical trials of anti-angiogenic therapies in patients with advanced HCC

Drug	Clinical trial	Phase	N	Regimen	Median overall survival	Median progression-free survival	Objective response rate
Sorafenib	SHARP <sup>[11]</sup>	III	602	First line versus placebo	10.7 months versus 7.9 months ( $P<0.001$ )	5.5 months versus 2.8 months ( $P<0.001$ )	2% versus 1% ( $P=0.05$ )
	Asia-Pacific <sup>[12]</sup>	III	226	First line versus placebo	6.5 months versus 4.2 months ( $P=0.014$ )	2.8 months versus 1.4 months ( $P<0.001$ )	3.3% versus 1.3%
Lenvatinib	REFLECT <sup>[15]</sup>	III	954	First line versus sorafenib	13.6 months versus 12.3 months ( $P=0.70$ )	7.4 months versus 3.7 months ( $P<0.001$ )	24.1% versus 9.2% ( $P<0.001$ )
Donafenib	Feng Bi et al. <sup>[18]</sup>	II/III	668	First line versus sorafenib	12.1 months versus 10.3 months ( $P=0.0363$ )	3.7 months versus 3.6 months ( $P=0.2824$ )	4.6% versus 2.7% ( $P=0.2448$ )
Regorafenib	RESORCE <sup>[20]</sup>	III	573	Second line versus placebo	10.6 months versus 7.8 months ( $P<0.001$ )	3.1 months versus 1.5 months ( $P<0.001$ )	11% versus 4% ( $P=0.0047$ )
Cabozantinib	CELESTIAL <sup>[23]</sup>	III	707	Second line versus placebo	10.2 months versus 8.0 months ( $P=0.005$ )	5.2 months versus 1.9 months ( $P<0.001$ )	4% versus less than 1% ( $P=0.009$ )
Apatinib	Qiu Li et al. <sup>[25]</sup>	III	393	Second line versus placebo	8.7 months versus 6.8 months ( $P=0.0476$ )	4.5 months versus 1.9 months ( $P<0.001$ )	10.7% versus 1.5%
Ramucirumab	REACH-2 <sup>[28]</sup>	III	292	Second line versus placebo	8.5 months versus 7.3 months ( $P=0.0199$ )	2.8 months versus 1.6 months ( $P<0.001$ )	5% versus 1% ( $P=0.1697$ )





**Figure 1.** Anti-angiogenic drugs for hepatocellular carcinoma

### 3.4. Ramucirumab (Cyramza)

In 2019, ramucirumab was approved by the US FDA as the second-line treatment for HCC patients with disease progression after being treated with sorafenib and serum alpha fetoprotein (AFP)  $\geq 400$  ng/ml. Ramucirumab is also the first biomarker-driven therapy for liver cancer approved by the US FDA. AFP is a plasma glycoprotein, mainly formed in the liver during early fetal development. About 40% of advanced HCC patients had AFP  $\geq 400$  ng/ml, which was related to the poor prognosis. The increase of AFP level had a strong correlation with the high microvascular density and high VEGF level in HCC<sup>[26]</sup>. Ramucirumab is a humanized recombinant IgG1 monoclonal antibody that specifically binds to VEGF receptor 2 (VEGFR-2) to block the binding of VEGF-A, VEGF-C, and VEGF-D and inhibits the proliferation and migration of endothelial cells induced by ligands connected with tumor angiogenesis<sup>[27]</sup>. This approval is based on the results of Phase III REACH-2 study, an international, double-blind, placebo-controlled, multicenter clinical trial. Although the previous REACH trial did not ultimately reach the primary endpoint, a subgroup analysis showed that ramucirumab could significantly benefit patients with AFP levels no less than 400 ng/ml (median OS: 7.8 months vs. 4.2 months,  $P=0.006$ ). Based on this, adult HCC patients who had AFP  $\geq 400$  ng/ml and developed resistance or disease progression after receiving sorafenib treatment were enrolled in REACH-2 trial. The results showed that the median OS of the ramucirumab group was 8.5 months, while that of the placebo group was 7.3 months (HR=0.71,  $P=0.0199$ ). In addition, the median PFS was 2.8 months, which is longer than 1.6 months in the control group (HR=0.452,  $P<0.0001$ ). The most important TRAEs in the ramucirumab group were asthenia (27%), peripheral edema (25%), and anorexia (23%)<sup>[28]</sup>.

The structures and details of the above-mentioned drugs and their relevant clinical outcomes are shown in **Figure 1** and **Table 1**.

## 4. Combination of anti-angiogenic therapies and immunotherapies

### 4.1. Combination treatment of lenvatinib and pembrolizumab

The positive effect of the combination of lenvatinib and pembrolizumab has previously been reported in the treatment of patients with recurrent endometrioma, advanced gastric cancer, and advanced renal cancer<sup>[29-31]</sup>. In 2020, a multicenter open-label Phase IB clinical trial aimed to evaluate the use of lenvatinib in combination with pembrolizumab in patients with unresectable or metastatic HCC. The clinical trial was a single-arm trial, involving 104 patients in total. Patients took 12 mg (for those with body weight  $\geq 60$  kg) or 8 mg (for those with body weight  $< 60$  kg) of lenvatinib orally every day and received an intravenous injection of 200 mg pembrolizumab every 3 weeks. According to independent imaging review analysis, in the combination of lenvatinib and pembrolizumab group, the ORR was 40% (based on modified Response Evaluation Criteria in Solid Tumors or mRECIST) and 36% (based on Response Evaluation Criteria in Solid Tumors 1.1 or RECIST version 1.1), the median PFS was 9.3 months (based on mRECIST) and 8.6 months (based on RECIST v1.1), and the median OS was 22 months (based on mRECIST). Furthermore, lenvatinib combined with pembrolizumab achieved a sustained response in patients with a duration of response (DOR) of 8.6 months (based on mRECIST) and 12.6 months (based on RECIST v1.1). The adverse reactions of the combination therapy were similar

to those using monotherapy, mainly including hypertension, diarrhea, and hypothyroidism. About 67% of the patients had third-degree or fourth-degree TRAEs. Compared with lenvatinib or sorafenib monotherapy, the ORR of patients taking lenvatinib combined with pembrolizumab was significantly improved. Based on the data of this study, lenvatinib combined with pembrolizumab was approved by the US FDA as the first-line treatment for patients with unresectable HCC. At present, Phase III clinical trials of lenvatinib combined with pembrolizumab are in progress (LEAP-002, NCT03713593)<sup>[32]</sup>.

#### 4.2. Combination treatment of cabozantinib and nivolumab or combination treatment of cabozantinib, nivolumab, and ipilimumab

For the treatment of metastatic urothelial tumors and other genitourinary tract tumors, combination treatment of cabozantinib and nivolumab or combination treatment of cabozantinib, nivolumab, and ipilimumab has controllable toxicity and potential efficacy. These combinations were also evaluated in patients with HCC<sup>[33]</sup>. In the CheckMate040 study, 71 patients with advanced HCC, regardless of their prior treatment history of sorafenib, were randomly divided into two groups: The first group (36 patients) that received 240 mg of nivolumab intravenously every 2 weeks and 40 mg of cabozantinib orally every day, and the second group (35 patients) that received 3 mg/kg of nivolumab intravenously every 2 weeks, 40 mg of cabozantinib orally every day, and 1 mg/kg of ipilimumab intravenously every 6 weeks. In the dual-therapy group and the triple-therapy group, the ORR was 17% and 26% and the median PFS was 5.5 months and 6.8 months, respectively. Neither group achieved the median OS ultimately. Besides, the triple-therapy group experienced more Grades 3 and 4 TRAEs compared with the dual-therapy group (71% vs. 42%). Although higher rate of TRAEs occurred in triple-therapy group, all the TRAEs were controllable and reversible<sup>[34]</sup>.

#### 4.3. Combination treatment of apatinib and camrelizumab

On March 4, 2020, PD-1 inhibitor camrelizumab injection, which was developed domestically, was officially approved by the Chinese NMPA for the treatment of advanced HCC in patients who had received sorafenib treatment and/or systemic chemotherapy with oxaliplatin-containing regimens. Subsequently, the efficacy and safety of camrelizumab combined with apatinib in the treatment of patients with advanced HCC was evaluated in a non-randomized open-label Phase II clinical trial RESCUE. The study enrolled 190 patients with advanced HCC, of which 70 patients who had not received other treatments were regarded as the first-line treatment group, and the other 120 patients who were intolerant to first-line targeted therapies were regarded as the second-line treatment

group. The patients were treated with 200 mg (body weight  $\geq 50$  kg) or 5 mg/kg (body weight  $< 50$  kg) of intravenous camrelizumab every 2 weeks, and 250 mg of oral apatinib every day. The ORR was 34.3% (95% CI=23.3–46.6) in the first-line treatment group and 22.5% (95% CI 15.4–31.0) in the second-line treatment group. The median PFS of the two groups was 5.7 months (95% CI=5.4–7.4) and 5.5 months (95% CI=3.7–5.6). The incidence of Grade 3 and above TRAEs was 77.4% (147/190), among which hypertension was the most common (34.2%). Besides, two treatment-related deaths occurred<sup>[35]</sup>.

### 5. Discussion

Drugs targeting tumor angiogenesis plays an important role in the treatment of patients with advanced HCC and they become an appropriate option for HCC patients with preserved liver function<sup>[8]</sup>. Before sorafenib was approved in 2007, no drug targeting tumor angiogenesis is available. Sorafenib has brought new hope for patients with advanced HCC who have lost the opportunity of treatments such as surgery and ablation. However, in the following decade, many small-molecule kinase inhibitors, including sunitinib, brivanib, linifanib, and sorafenib, have undergone head-to-head trials, which were unfortunately ended up in failure. During the period, sorafenib has been the only anti-angiogenic drug approved for the first-line treatment of advanced HCC. Recently, significant progress has been made in the field of anti-angiogenic drugs for HCC, and a number of first-line or second-line therapies have been approved for HCC, of which small-molecule kinase inhibitors (sorafenib, lenvatinib, donafenib, regorafenib, and cabozantinib) and the monoclonal antibody ramucirumab targeting VEGFR-2 have also been approved for treatment of HCC<sup>[36]</sup>. In addition, Phase III clinical trial ZGDH3 of donafenib, which is developed in China with independent intellectual property rights, is the first large-scale Phase III clinical trial that has achieved success in monotherapy head-to-head comparison of HCC anti-angiogenic therapy in the recent 13 years<sup>[18]</sup>. The results of this study were included in the report of the 2020 American Society of Clinical Oncology annual meeting, indicating that the effectiveness and safety of donafenib are promising.

In the past few decades, a better and gradual understanding of the molecular mechanisms of tumorigenesis and development has allowed for tremendous development of anti-angiogenic therapy for HCC. However, low response rate and drug resistance still limit the clinical benefits of these drugs to the patients with HCC. In recent years, immunotherapy has achieved breakthroughs and rapid development, providing more treatment options for HCC patients. Anti-angiogenic therapy and immunotherapy, as two important directions in the research of HCC treatment in recent years, have both achievements and some limitations. Therefore, a combination of anti-

angiogenic therapy and immunotherapy has also emerged. Many clinical trials of immunotherapy combined with anti-angiogenic therapy as the first-line or second-line treatment of advanced HCC are currently in progress<sup>[37]</sup>. In addition, since HBV and HCV infections are the main risk factors of HCC, the popularization of antiviral treatment strategies in the developing areas and the improvement of public health awareness may contribute to a decrease in the global incidence of HCC<sup>[5]</sup>. With the continuous development of multi-omics technology and precision medicine, the development of new prognostic biomarkers and new treatment strategies will provide more effective treatments for HCC patients and will also contribute to a steady stream of strength to the global anti-tumor efforts.

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## Conflicts of interest

The authors declare that they have no competing interest.

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