



# New Therapeutic Options for Advanced Hepatocellular Carcinoma

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## Abstract

Hepatocellular carcinoma (HCC), one of the most common lethal diseases in the world, has a 5-year survival rate of only 7%. Hepatocellular carcinoma has no symptoms in the early stage but obvious symptoms in the late stage, leading to delayed diagnosis and reduced treatment efficacy. In recent years, as the scope of HCC research has increased in depth, the clinical development and application of molecular targeted drugs and immunotherapy drugs have brought new breakthroughs in HCC treatment. Targeted therapy drugs for HCC have high specificity, allowing them to selectively kill tumor cells and minimize damage to normal tissues. At present, these targeted drugs are mainly classified into 3 categories: small molecule targeted drugs, HCC antigen-specific targeted drugs, and immune checkpoint targeted drugs. This article reviews the latest research progress on the targeted drugs for HCC.

## Keywords

HCC, targeted therapy, immune checkpoint, small molecule drugs, sorafenib

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Liver cancer is one of the most common fatal diseases in the world.<sup>1</sup> Early-stage liver cancer has no symptoms, whereas late-stage symptoms become obvious, leading to delays in diagnosis and reduced therapeutic efficacy.<sup>2</sup> There are more than 850 000 new cases of liver cancer every year worldwide, 90% of which are hepatocellular carcinoma (HCC).<sup>3</sup> In China in particular, due to the high incidence of hepatitis B, the number of HCC deaths in 2015 reached roughly 422 000, accounting for 57% of the global HCC deaths.<sup>4</sup> At present, surgery is still an effective way to improve the survival rate of patients with HCC.<sup>5</sup> However, incomplete resection, high recurrence rate, and high metastasis rate are the main problems affecting HCC's clinical therapeutic efficacy.

In recent years, with advances in understanding of HCC's molecular biology, the clinical development and application of molecular targeted drugs and immunotherapy drugs have brought new breakthroughs in HCC treatment, greatly improving its diagnosis and treatment efficacy, prolonging the survival of patients with HCC, and improving their quality of life.<sup>6</sup> However, HCC's morbidity and mortality have not decreased, and they are still increasing year by year. In this

article, the latest research progress in targeted therapy for HCC from recent years is briefly reviewed, including small molecule targeted inhibitors, targeted drugs designed based on specific antigens for HCC, and immune checkpoint inhibitors.

## Small Molecule Targeted Drugs

In recent years, molecular targeted therapy has emerged as a new cancer treatment method.<sup>7</sup> Compared with traditional therapy,

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**Table 1.** Characteristics of Agents Approved for Second-Line Treatment of Patients With Advanced HCC.

	Regorafenib	Cabozantinib	Ramucirumab	Nivolumab	Pembrolizumab	Ipilimumab plus nivolumab
Drug class	Multitarget kinase inhibitor	Multitarget kinase inhibitor	Monoclonal antibody	Monoclonal antibody	Monoclonal antibody	Monoclonal antibody
Molecular targets	VEGFR-1–3, TIE2, KIT, RET, RAF1, BRAF, BRAFV600E, PDGFR, FGFR	VEGFR-2, MET, RET, AXL, FLT3, c-KIT	VEGFR-2	PD-1	PD-1	CTLA-4/PD-1
Route of administration	Oral	Oral	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion
Study	RESORCE (NCT01774344) (NCT01908426) (NCT02435433) (NCT01658878) (NCT02702414) (NCT01658878)	CELESTIAL REACH-2 CheckMate 040 KEYNOTE-224 CheckMate 040				
Design	Phase 3	Phase 3	Phase 3	Phase 1-2	Phase 2	Phase 1-2
Primary end point	OS	OS	OS	ORR	ORR	ORR

Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen 4; BRAF, B-Raf Proto-Oncogene; PDGFR, Platelet Derived Growth Factor Receptor Beta; ORR, Objective Response Rate; OS, overall survival; FGFR, fibroblast growth factor receptor; FLT3, fms-like tyrosine kinase-3; PD, programmed cell death; RET, ret proto-oncogene; VEGFR, vascular endothelial growth factor receptor.

molecular targeted therapy has improved targeting, can specifically kill tumor cells and reduce damage to normal tissues, has low rates of drug resistance, and is safer and better tolerated by patients.<sup>8</sup> In 1906, Enrich first proposed the concept of targeted drug delivery, that is, to use a specific carrier to selectively deliver drugs or other antitumor active substances to the target site, therefore limiting the therapeutic effect or drug effect to specific target cells, tissues, or organs as far as possible, without affecting the function of their normal counterparts, so as to improve efficacy and reduce adverse reactions.<sup>9</sup>

Molecular targeted therapy targets overexpressed cell receptors, key genes, and some marker molecules of tumor cells by selecting specific blockers to inhibit tumor growth, progress, and metastasis.<sup>10</sup> The principle of molecular targeted therapy is to target key genes and signaling pathways in the process of tumor development, or the proto oncogene, tumor suppressor gene, and suicide gene, among others, by designing small molecule inhibitors to reverse the biological behavior of tumor cells at the molecular level, so as to inhibit the proliferation and metastasis of tumor cells.<sup>11</sup> At present, there are dozens of molecular targeted drugs both on the market and in the clinical research stage, including sorafenib, regorafenib, lenvatinib, cabozantinib, and other drugs, which have achieved significant results (Figure 1) (Table 1).

### Sorafenib

Sorafenib is a broad-spectrum, small molecule inhibitor that can inhibit the expansion, angiogenesis, and apoptosis of many tumor cells.<sup>12</sup> Sorafenib primarily targets serine/threonine kinase, vascular endothelial growth factor receptor (VEGFR), Platelet-derived growth factor receptor beta (PGFR $\beta$ ), Kit,

fms-like tyrosine kinase-3 (FLT3), ret proto-oncogene (RET), and other receptor tyrosine kinases to inhibit tumor cell proliferation and angiogenesis, which subsequently inhibits tumor growth.<sup>13</sup> In 602 patients with advanced HCC who had not received systematic treatment before, the median survival time of the sorafenib group was 2.8 months longer than that of placebo group (44%). There was a significant difference between the sorafenib group and the placebo group.<sup>13</sup> The patients with advanced HCC had good tolerance to sorafenib, indicating that sorafenib can be used as a first-line drug to treat patients with advanced HCC.

### Regorafenib

The molecular structures of regorafenib and sorafenib are very similar, as are their mechanisms of action.<sup>8</sup> However, regorafenib has higher biological activity than sorafenib, capable of widely inhibiting the kinases related to angiogenesis and tumorigenesis, such as VEGFR 1-3, tyrosine protein kinase receptor Tie, RET, PDFGR, basic fibroblast growth factor receptor (FGFR), serine/threonine protein kinase RAF, mitogen-activated protein, and kinase p38, so as to play an antitumor role.<sup>14</sup>

The researchers tested regorafenib as a second-line drug in 573 patients with HCC who had been treated with sorafenib, 194 of whom received placebo.<sup>15</sup> The final data showed that, compared with the placebo group, regorafenib significantly improved the overall patient survival time from 7.8 months in the placebo group to 10.6 months in the experimental group. In 2 of the patients treated with regorafenib, the tumor shrank to an undetectable state.<sup>16</sup> These data indicate that regorafenib has a good therapeutic effect in patients with HCC who have been treated with sorafenib.

### Lenvatinib

Lenvatinib is an inhibitor of VEGFR1-3, FGFR1-4, PDGFR $\alpha$ , and tyrosine protein kinase receptor RET and Kit.<sup>17</sup> In June 2017, the annual meeting of the American Society of Clinical Oncology reported the phase III clinical research results of lenvatinib in the first-line treatment of unresectable liver cancer.<sup>18</sup> It was found that the total survival time of the main clinical end point in the lenvatinib group was longer than that of the sorafenib group (13.6 vs 12.3 months), and the secondary clinical end point in the lenvatinib group was also significantly better than that of the sorafenib group, including progression-free survival time (7.4 vs 3.7 months), disease progression time (8.9 vs 3.7 months), and objective remission rate (24% vs 9%). Although the main clinical end point overall survival of the lenvatinib group and sorafenib group did not reach statistical difference, progression-free survival of the lenvatinib group was twice as long as that of the sorafenib group, and time to progress was nearly 3 times longer than that of sorafenib group (Figure 2).<sup>19</sup>

In addition, 83% of the Asian patients (288 cases) in the REFLECT study had been infected with the hepatitis B virus (HBV). Among the patients with HBV-related HCC, the effective rate of the lenvatinib group was 21.5%, which was 2.6 times higher than that of the sorafenib group (8.3%). The median overall survival time of the lenvatinib group (15.0 months) was significantly longer than that of the sorafenib group (10.2 months), and the median progression-free survival time and median time to progression in the lenvatinib group were significantly better than those of the sorafenib group.<sup>18,20</sup>

It has been confirmed that lenvatinib is not inferior to sorafenib in the first-line treatment of advanced liver cancer, especially in patients with HBV-related HCC.<sup>8</sup> This shows that lenvatinib has good application prospects in Asia, especially in China, and is expected to become the latest standard for the treatment of advanced HCC.

### Cabozantinib

Cabozantinib is an effective multireceptor tyrosine kinase inhibitor, which can target VEGFR2, c-Met, Kit, Axl, and FLT3 with 0.035, 1.3, 4.6, 7, and 11.3 nM half-maximal inhibitory concentration, respectively. In the second-line phase III CELESTIAL trial, cabozantinib significantly improved overall survival in patients with liver cancer and was approved for use in patients with unresectable liver cancer.<sup>21,22</sup>

### Inhibitors of VEGF

Vascular endothelial growth factor is the only known growth factor that specifically acts on vascular endothelial cells.<sup>23,24</sup> Studies have shown that VEGF was expressed in both hepatocytes and HCC cells, and its expression intensity gradually increased with the development of HCC.<sup>25</sup> Vascular endothelial growth factor and its receptor are powerful factors for inducing angiogenesis. When combined, they can strongly induce

endothelial cell proliferation and tubular formation, which is an important part of angiogenesis.<sup>26</sup> Furthermore, HCC is a vascular-rich cancer.<sup>27</sup> Vascular endothelial growth factor and microvessel density in HCC are significantly increased,<sup>27,28</sup> and the high expression of VEGF in HCC indicates poor prognosis.<sup>29</sup> At each stage of HCC progression, the proliferation of vascular endothelial cells is active, and the expression of VEGFR molecules on the cell surface is significantly upregulated.<sup>30</sup> Angiogenesis in cancer tissues has an important impact on the biological invasion abilities of the tumor.<sup>31</sup> Therefore, blocking VEGF/VEGFR and reducing angiogenesis in the tissues are considered a novel idea for targeted therapy in HCC.

Bevacizumab is a recombinant human-mouse chimeric monoclonal antibody against VEGF.<sup>32</sup> The humanization process prolongs the half-life of the drug and weakens its immunogenicity.<sup>33</sup> Through competitive binding with VEGF in the circulation, bevacizumab can prevent the binding of VEGF to the corresponding receptor, thus blocking the formation of new blood vessels in HCC.<sup>24</sup> At the same time, bevacizumab can normalize the distribution of blood vessels in HCC and its surrounding tissues, which improves the delivery of chemotherapy drugs by reducing the interstitial pressure.<sup>34</sup>

The efficacy of bevacizumab in advanced HCC treatment has been initially confirmed.<sup>35</sup> Zhu et al reported a GE2MOX2B scheme for the treatment of advanced liver cancer in a phase II clinical study.<sup>36</sup> All of the 33 patients were enrolled into the group, 30 of whom were evaluable, with an effective rate of 20% and a disease stability rate of 27%; the median survival time was 9.6 months, the median progression-free survival time was 5.3 months, and the disease-free survival times at 3 and 6 months were 70% and 48%, respectively. Therefore, the scheme has certain antitumor activity as well as a high disease-free survival rate in 6 months, which is worth further study. Siegel et al also used bevacizumab in a phase II clinical drug trial.<sup>37</sup> The results showed that 65% of the 46 patients had a median progression-free survival time of 6 months. Adverse reactions included hypertension, thrombosis, and bleeding. Through dynamic contrast-enhanced nuclear magnetic resonance imaging of the tumor, it could be observed that the concentration of VEGF in patients' plasma was decreased, and the vasoactivity was also decreased.

Ramucirumab is an anti-VEGF monoclonal immunoglobulin G (IgG) antibody. It was first evaluated in the REACH trial, a second-line phase III trial in patients with progression or intolerance leading to the failure of sorafenib.<sup>38-40</sup> Ramucirumab significantly improved the overall survival rate to 8.5 months (hazard ratio: 0.71, 95% CI: 0.5-0.95), compared with the median survival rate of 7.3 months in the placebo group. Ramucirumab is the first approved systemic therapy for liver cancer in a biomarker selection population. Ramucirumab has demonstrated survival benefits in patients having unresectable HCC with  $\alpha$ -fetoprotein (AFP)  $\geq$  400 ng/dL.<sup>41,42</sup>

Thalidomide can inhibit angiogenesis by interfering with the effect of VEGF and fibroblast growth factor.<sup>43</sup> Several clinical trials discussed the therapeutic effect of thalidomide on patients with HCC whose cancer could not be resected or treated

locally.<sup>44</sup> It was found that the objective response rate of thalidomide was about 5%, and 10% to 30% of patients demonstrated disease stability for 2 months after thalidomide single drug treatment.<sup>45</sup>

### Matrix Metalloproteinase Inhibitors

Metastasis is one of the characteristics of cancer.<sup>46-49</sup> One of the important steps is the degradation of extracellular matrix (ECM), which is especially important for liver cancer.<sup>50-52</sup> The invasion and metastasis that result after ECM degradation are largely related to integrin and matrix metalloproteinases (MMPs).<sup>53-55</sup> Integrin not only mediates the adhesion of HCC cells to other HCC cells and HCC cells to the ECM but also participates in the chemotaxis, proliferation, and apoptosis of tumor cells, and thus, integrin involvement extends nearly throughout the entire process of HCC cell invasion and metastasis.<sup>56-60</sup> The monoclonal antibodies LM609 and Vitaxin of integrin  $\alpha V\beta 3$  also showed good antiangiogenic effects in vitro and in vivo, and Vitaxin has subsequently entered phase II clinical trials.<sup>61</sup>

Matrix metalloproteinase is a type of proteolytic enzyme involved in the degradation of the ECM and basement membrane.<sup>62-65</sup> Its structure, function, and regulatory level are closely related to the growth, invasion, and metastasis of liver cancer.<sup>66-69</sup> A large number of studies have shown that MMPs, including MMP-7, MMP-9, and MMP-2, are highly expressed in liver cancer cells and tissues.<sup>70-73</sup> Marimastat is a synthetic MMP inhibitor.<sup>74</sup> Like tissue inhibitor of metalloproteinases-2, Marimastat can inhibit the invasion induced by hepatocyte growth factor (HGF).<sup>75</sup> Clinically related drugs also include Bamalabaster, Novartis, BAY12-9566, AG-3340, OPB-3206, KBR07785, and KBR-8301.<sup>76-78</sup> At present, it is suggested that the response rate of these drugs is low, and they may be used as chemopreventive drugs for liver cirrhosis and other patients with a higher risk of developing liver cancer.

## Liver Cancer-Specific Antigen Targeting Drugs

### $\alpha$ -Fetoprotein Targeted Drugs

$\alpha$ -Fetoprotein is a sensitive serum marker of HCC.<sup>79-81</sup> A clinical study of Japanese chronic hepatitis showed that the sensitivity, cutoff, and specificity of AFP were 79%, 78 ng/mL, and 78%, respectively.<sup>82</sup> In small liver cancer, the sensitivity of AFP is relatively low (33%-65%),<sup>83</sup> and the level of AFP in serum seems to be related to the size and differentiation of HCC.<sup>84</sup> In a considerable number of patients with chronic liver disease, AFP (20-200 ng/mL) increased significantly.<sup>85</sup> Therefore, AFP has long been used in the clinical diagnosis of HCC.

With the development of new research, tumor immunology researchers are increasingly interested in the antitumor immune response of AFP.<sup>86</sup> In a phase I/II clinical trial, 4 kinds of AFP-activated dendritic cells were used to treat patients with HCC to

test their immune response.<sup>87</sup> The results of ELISPOT showed that interferon  $\gamma$  (IFN- $\gamma$ ) increased in 6 of 10 individuals after inoculation with at least 1 AFP polypeptide, resulting in AFP-specific T-cell response.<sup>88</sup> In addition, studies of AFP-DNA vaccines and adenovirus-driven immunotherapy in 2 pretreated AFP-positive HCC patients reported expected safety and immunogenic T-cell responses.<sup>89</sup>

### Glypican-3 Targeted Drugs

Glypican-3 is a heparin sulfate proteoglycan anchored to the cell surface by glycosylphosphatidylinositol.<sup>90</sup> Glypican-3 is a carcinoembryonic antigen, and its abnormal overexpression in 81% of patients with HCC is related to poor prognosis.<sup>91</sup> Therefore, it may be an ideal target for HCC targeting therapy.

So far, many research institutions have invented 4 high-affinity antibodies, GCC-3, HN3, HS20, and YP7, for GPC-3 using phage display and hybridoma technology.<sup>92</sup> A phase I clinical study of GCC3 showed that patients with high GPC-3 expression had significantly higher progression-free survival than those with low GPC-3 expression.<sup>93</sup> HN3 and YP7 can fuse with the fragment pe38 of *Pseudomonas* exotoxin A to produce immunotoxin.<sup>94</sup> The heterotopic tumor of Hep3B and HepG2 can be eliminated using HN3-PE38 alone or combined with chemotherapy.<sup>95</sup> The immunotoxin produced by YP7-PE38 has better antitumor activity than that produced by HN3-PE38.<sup>96</sup> Therefore, GPC-3 is expected to be a new potential target for HCC treatment.

### Hepatocyte Growth Factor and Its Receptor Inhibitors

Hepatocyte growth factor is an important liver regeneration factor.<sup>97</sup> Its receptor is c-Met, which belongs to the tyrosine kinase receptor family.<sup>98</sup> c-Met is highly expressed or mutated in many tumor cells, including HCC.<sup>99</sup> Hepatocyte growth factor combined with c-Met, through a series of signal transduction pathways, is closely related to cell growth, differentiation, angiogenesis, and other processes, and promotes the infiltration and metastasis of HCC cells.<sup>100-103</sup> This indicates that HGF may become an effective target for the treatment of HCC.

At present, the inhibitors and antagonists of HGF include the following: (1) NK4, an endogenous fragment truncated by HGF, which can bind to the c-Met receptor, but cannot activate it, thus antagonizing the interaction between HGF and c-Met, and in turn inhibiting HCC cell invasion and metastasis<sup>104</sup>; (2) small molecule c-Met selective inhibitors, such as SOMCL-863, PHA.665752, and SU11274<sup>105</sup>; (3) tivantinib (ARQ 197), which mainly binds to retinoic acid receptor and can downregulate the expression of c-Met protein, inhibit HGF-induced invasion, and inhibit the intrahepatic spread of HCC cells and liver metastasis of other types of cancer by inhibiting transcription factor subunit (API) activity.<sup>106</sup> Clinical trials have confirmed that tivantinib is a drug with better efficacy and less adverse reactions, and thus, it may become a new anti-HCC drug.

## Drugs Targeted at Immuno Checkpoint

Immuno checkpoint blocking therapy has recently become a promising treatment for many kinds of malignant tumors, including HCC.<sup>107</sup> At present, cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death (PD) 1, T-cell immunoglobulin and mucin domain-containing protein 3, and B- and T-lymphocyte attenuator are the most studied immuno checkpoint receptors.<sup>108</sup> Blocking the above negative regulatory immune regulatory targets can significantly improve the median overall survival and response rate of patients and improve the prognosis of patients with melanoma, renal cancer, and non-small cell lung cancer.<sup>109</sup> The blocking monoclonal antibodies of CTLA-4 and PD-1/PD-L1 have been approved by the Food and Drug Administration (FDA) for melanoma treatment.<sup>110</sup>

### Cytotoxic T-lymphocyte Antigen 4 Targeted Drugs

Cytotoxic T-lymphocyte antigen 4 is expressed in activated T cells and Treg cells and also in the initial T cells.<sup>111</sup> Compared with CD28, CTLA-4 has higher affinity to CD80 and CD86.<sup>112</sup> Therefore, CTLA-4 can inhibit the binding of CD28, CD80, and CD86, and thus inhibit T-cell activation.<sup>113</sup> Cytotoxic T-lymphocyte antigen 4 signaling may also stimulate the expression of transforming growth factor  $\beta$  in CD4-positive T cells.<sup>114</sup> In addition, inhibition of CD28 binding to CD80 and CD86 in Regulator Of WNT Signaling Pathway (APC) may result in a decrease in T-cell activation.<sup>115</sup> Specific knockout or blocking of CTLA-4 can activate the autoimmune response and improve anticancer immunity.<sup>116</sup> In 2011, the US FDA approved a randomized phase III clinical trial using the monoclonal antibody ipilimumab blocking CTLA-4 for the treatment of melanoma.<sup>117</sup>

The phase I clinical trial (NCT01008358) of human IgG2 monoclonal antibody tremelimumab against CTLA-4 in patients with HCC showed that 21 patients with advanced liver cirrhosis (liver function grade of Child-Pugh A or B) who were not suitable for percutaneous ablation or transarterial embolization had good tolerance to tremelimumab, and there were no treatment-related deaths.<sup>112</sup> About 17.6% of the patients had partial reactions, and 45% of them were stable for more than 6 months. Interestingly, patients with stable IFN- $\gamma$  during treatment had a better response than those with decreased IFN- $\gamma$ , which indicated that patients with stable IFN- $\gamma$  had active anti-tumor immunity. A phase I clinical trial of tremelimumab in patients undergoing radiofrequency ablation or arterial therapy is currently in progress (NCT01853618).<sup>118</sup> Another phase II clinical trial (NCT01649024), in which tremelimumab was used to treat patients with advanced HCC, showed that among the 17 evaluable cases, 3 had partial remission, 10 had stable tumor control, and the disease control rate was as high as 76.4%.<sup>119</sup>

### Programmed Cell Death 1 Targeted Drugs

As a member of the CD28 superfamily, PD-1 was first discovered by Professor Yoshio Benschu of Kyoto University in

1992.<sup>120</sup> At present, PD-1, as a significant target of immunotherapy, has attracted wide attention in the field of tumor-targeted therapy.<sup>121</sup> Programmed Cell Death 1 was mainly expressed in CD8-positive T cells but could also be detected in Treg cells and myeloid-derived suppressor cells (MDSCs).<sup>122</sup> Programmed Cell Death 1 not only mediates the differentiation and proliferation of Treg but also regulates peripheral blood tolerance and autoimmunity.<sup>123</sup> Long-term antigen exposure leads to overexpression of PD-1 in T cells, leading to T-cell depletion or nonresponse.<sup>124</sup>

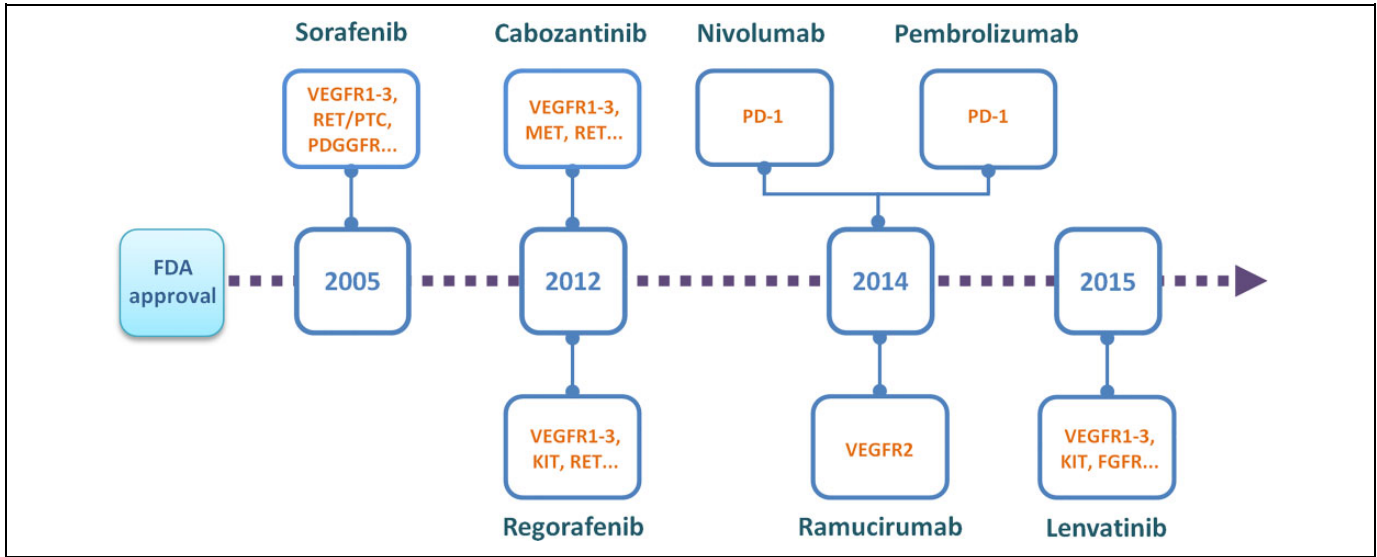
Tumor cells can express PD-L1 or PD-L2 to activate the expression of PD-1 in tumor-infiltrating lymphoid tissue and escape from immune surveillance.<sup>8</sup> The clinical study results showed that the PD-1/PDL-1 pathway may induce immune tolerance for HCC. At the same time, the expression levels of PD-1 and PD-L1 are closely related to the development stage, local recurrence rate, and poor HCC prognoses.<sup>125</sup> Similarly, the level of PD-1 and CD8 positive T cells in the tumor is related to HCC progression and postoperative recurrence.<sup>126</sup>

In addition, in the HBV-positive HCC patients who received cryoablation, the prognosis of those who expressed PD-1 and PD-L1 on circulating tumor cells was poor.<sup>127</sup> In vitro, Treg cells, MDSCs, and PD-1-positive T cells from the peripheral blood of patients with advanced HCC were consumed simultaneously to restore the activation of CD8-positive T cells.<sup>128</sup>

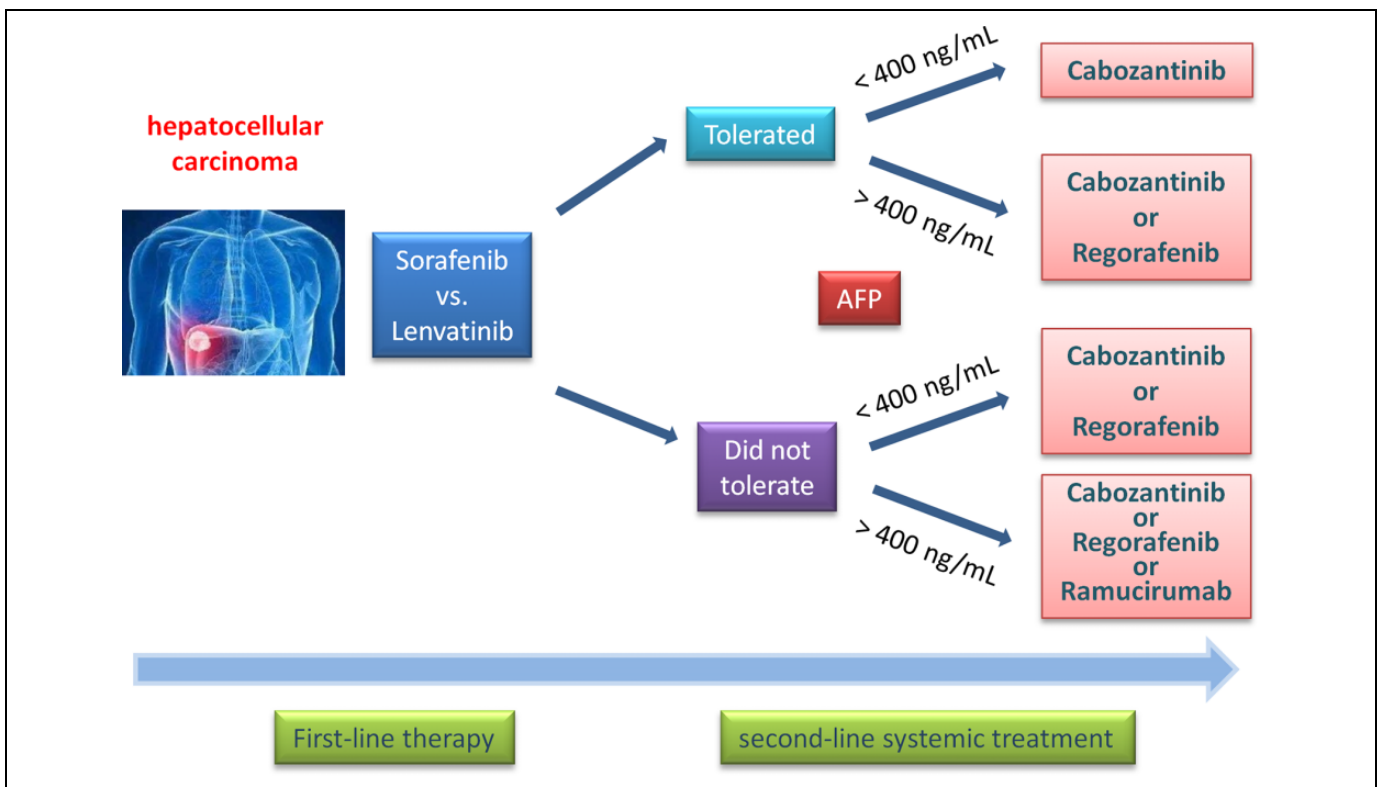
In 2017, El Khoueiry et al released the latest data of nivolumab, a PD-1 inhibitor, in the treatment of patients with advanced HCC.<sup>129</sup> In the dose extension stage, 42 (20%) patients observed objective response, 96 (45%) patients observed stable disease, 138 (64%) patients observed disease control, 28 (67%) patients had sustained response, and the median response time was 9.9 months. Most of the diseases were stable for at least 6 months, and 79 (57%) of 138 patients demonstrated disease control. At the dose extension stage, the median progression time was 4.1 months, and the overall survival rate was 83% at 6 months and 74% at 9 months. The 6-month progression-free survival rate was 37%, and the 9-month progression-free survival rate was 28%.<sup>130,131</sup>

## Outlook

Multiple combination regimens, including immunotherapy, multireceptor kinase inhibitors, and anti-VEGF agents likely portend the future of HCC treatment, in which combination therapies will hopefully increase objective responses and overall survival. In recent years, PD-1 antibody has made great achievements in further promoting the application and research of various drugs targeting immunoassay sites in HCC, and liver cancer treatments targeting immunoassay sites have entered development. Although the available treatment methods of advanced liver cancer are greatly expanding at present, single administration treatment methods do not yield satisfactory results. Therefore, it is necessary to increase the development of new targeted drugs and to simultaneously promote the research and application of targeted drugs combined with other treatment methods or multiple targeted drugs combined with each other. These



**Figure 1.** Overview of various targeted drugs. Molecular targeted therapy selects specific blockers to effectively intervene in the regulation of cell receptors, key genes, and marker molecules, in order to achieve tumor-inhibiting effects.



**Figure 2.** Second-line systemic treatment options in patients with hepatocellular carcinoma. PD-1 inhibitors can be considered given objective response rates of 15% to 20%, although phase III studies have failed to demonstrate statistically significant survival benefit compared to other agents in phase III studies. PD-1 indicates programmed cell death 1.

combinations may include targeted therapy combined with surgical resection, radiotherapy, chemotherapy, interventional therapy, and immunotherapy, and even targeted therapy combined with cell therapy, gene therapy, and other conventional or

emerging treatment methods for liver cancer. As research broadens and deepens in scope, targeted therapy will likely continue to demonstrate its advantages of high specificity, good therapeutic effects, long-lasting benefits, and less adverse reactions.

## Authors' Note

YSM and DF designed the study. YSM, JBL, and TMW contributed equally to this work. All authors performed the statistical analyses and interpreted the data. D.F. wrote the manuscript. All authors contributed to the final version of the manuscript and approved the final manuscript. Our study did not require an ethical board approval because it did not contain human or animal trials.

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