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**Mechanisms of resistance to sorafenib and** **the** **corresponding strategies in hepatocellular carcinoma**

Zhai B*et al.* Sorafenib resistance in HCC

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**Abstract**

Sorafenib, the unique drug as first-line treatment for advanced hepatocellular carcinoma (HCC), has opened a window of hope after searching effective agents to combat HCC for decades. However, the overall outcomes are far from satisfaction. One of the explanations is genetic heterogeneity of HCC, which has led to identifying predictive biomarkers for primary resistance to sorafenib, and then applying the concept of personalized medicine, or seeking therapeutic strategies, such as combining sorafenib with other anticancer agents. Some of the combinations have demonstrated a better effectiveness than sorafenib alone with good tolerance. The acquired resistance to sorafenib has also drawn attention. Sorafenib, as a multilkinase inhibitor, targets several cell signaling pathways, but simultaneously or sequentially the addiction switches and compensatory pathways are activated. Several mechanisms are involved in the acquired resistance to sorafenib, such as crosstalks involving PI3K/Akt and JAK-STAT pathways, hypoxia-inducible pathways, epithelial-mesenchymal transition, *etc.* Based on the investigated mechanisms, some other molecular targeted drugs have been applied as second-line treatment to treat HCC after the failure of sorafenib therapy, and more are under evaluation in clinical trials. However, the exact mechanisms accounting for sorafenib resistance remains unclear. Further investigation on the crosstalk and relationship of associated pathways will better our understanding of the mechanisms, and help seeking effective strategies for overcoming sorafenib resistance in HCC.

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**Key words:** Hepatocellular carcinoma; Sorafenib; Drug resistance; Cellular signaling pathway; Clinical trials

**Core tip:** The primary resistance of hepatocellular carcinoma (HCC) to sorafenib is due to genetic heterogeneity, thus seeking predictive biomarkers and combining sorafenib with other anticancer agents for HCC have been launched with varying degrees of success. Sorafenib inhibits several kinase targets, but it can also simultaneously or sequentially activate the addiction switches and compensatory pathways, inducing the acquired resistance. Some other molecular targeted drugs have been used as second-line treatment for advanced HCC after the failure of sorafenib therapy. Further investigation on the crosstalk and relationship of associated pathways will better our understanding of the mechanisms accounting for sorafenib resistance in HCC.

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**INTRODUCTION**

Liver cancer is the second most frequent cause of cancer death in men worldwide, and hepatocellular carcinoma (HCC) accounts for 70%-85% of the total liver cancer burden[[1](#_ENREF_1)]. Many lines of clinical investigation indicate that none of the adjuvant therapies is particularly effective in treating HCC after surgery, and systemic traditional chemotherapy has a very low response rate for HCC. Recently emerging molecular targeted drugs (MTD) have been demonstrated to be promising agents in prolonging the overall survival (OS) of late stage HCC patients. Particularly, sorafenib has been uniquely recommended as the first-line treatment for advanced HCC[[2](#_ENREF_2)]. Despite of the encouraging achievement, the worry about drug resistance to sorafenib is increasing as the OS of HCC patients after sorafenib treatment was only 2-3 mo longer than placebo, and sorafenib was shown to result in a limited increase in median time to symptomatic progression and a low partial response rate due to drug resistance[[3](#_ENREF_3), [4](#_ENREF_4)]. Although the exact rate of resistance to sorafenib has not been reported, considering the dilemma that no effective systemic therapy is available so far for patients after failure of sorafenib therapy, the studies on the mechanisms of sorafenib resistance are urgently required[[5-7](#_ENREF_5)]. The present article aims to review the latest progress in this field, by focusing the mechanisms of resistance to sorafenib and the strategies in HCC.

**PREDICTION OF SORAFENIB SENSITIVITY**

Due to genetic heterogeneity, some HCC cells are initially resistant to sorafenib which is termed primary resistance[[8](#_ENREF_8)]. The IC50 values of growth inhibition of different HCC cell lines by sorafenib*in vitro* showed big variations[[9](#_ENREF_9), [10](#_ENREF_10)]. Thus, it is important to indentify predictive biomarkers for primary resistance to sorafenib.

The activation of RAF/ mitogen-activated protein kinase (MAPK)/ extracellular signaling-regulated kinase (ERK) signal pathway is commonly observed in HCC[[11](#_ENREF_11)]. Sorafenib executes its anti-tumor activity partially through targeting the Raf-1 and B-Raf, thus inhibiting the RAF/MEK/ERK signaling pathways. It was reported that sorafenib inhibited the phosphorylated ERK (pERK) in HCC PLC/PRF/5 and HepG2 cells[[9](#_ENREF_9)]. Zhang *et al*[[12](#_ENREF_12)] reported that the effects of sorafenib on cell proliferation were significantly correlated with basal pERK levels, and the U0126, a selective inhibitor of ERK1/2 could reduce the sensitivity of HCC cells to sorafenib through downregulation of pERK. In a phase II clinical study of sorafenib, the pERK levels in tumor samples from 33 patients showed the correlation with median time to progress (TTP)[[13](#_ENREF_13)]. However, the correlationship was not validated in the phase III trial[[14](#_ENREF_14)]. It has recently reported that the c-Jun N-terminal kinase (JNK), another member of MAPK family, can serve as a biomarker to predict the sensitivity to sorafenib[[15](#_ENREF_15)]. Hagiwara *et al*[[15](#_ENREF_15)] examined the JNK activity in 39 tumor specimens from advanced HCC before sorafenib treatment, and found that the tumors from the non-responder group had higher expression of phospho-c-Jun and JNK activity. Moreover, the JNK activation was correlated with decreased TTP and poor OS. A recent study on patients enrolled in SHARP trial (the phase III, randomized, controlled Sorafenib HCC Assessment Randomized Protocol) investigated predictive biomarkers to sorafenib, and showed that the angiogenesis biomarkers Ang2 and VEGF, among ten assessed plasma biomarkers, were independent predictors of the survival of advanced HCC patients. Although the patients with higher soluble c-KIT or lower hepatocyte growth factor (HGF) in sera at baseline showed enhanced survival benefit, neither of them predicted the response to sorafenib[[16](#_ENREF_16)].

The current available data indicate that candidate biomarkers for sorafenib sensitivity are still of uncertain value. Well-designed prospective clinical studies are required to judge their exact roles in predicting the primary resistance to sorafenib in HCC. In addition, more preclinical studies are also needed to clarify whether the currently known biomarkers are the downstream events of the latent key biomarkers or these biomarkers vary in individual patients.

**MECHANISMS OF ACQUIRED RESISTANCE TO SORAFENIB**

Long-term exposure to antitumor drugs often results in reduced sensitivity of the tumor cells to the drug, leading to acquired resistance. Many mechanisms account for acquired resistance to antitumor drugs, such as addiction switching, compensatorypathway because of pathway loops or crosstalk, epithelial-mesenchymal transition (EMT), cancer stem cells, disabling of pro-apoptotic signals, hypoxic microenvironment, *etc*[[17-19](#_ENREF_17)]. Recently, some studies have also indicated the correlation between these mechanisms and resistance to sorafenib in HCC.

***PI3K/Akt pathway*** ***and sorafenib resistance***

The phosphatidylinositol 3-kinase (PI3K)/Aktand MAPK pathways are most critical pathways involved in the development and progression of HCC, and are activated or overexpressed in a high proportion of HCC tissues. The parallelPI3K/Akt pathway remains unscathed, when sorafenib targets the MAPK pathway and tyrosine kinases by inhibiting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), Ret and c-kit[[3](#_ENREF_3)]. Considering the existing crosstalk between the PI3K/Aktand MAPK pathways[[20](#_ENREF_20)], the latent compensatory mechanism of PI3K/Akt pathways in drug resistance to sorafenib has been attracting attention. Sorafenib has demonstrated to activate Akt, and upregulate the phosphorylation of its downstream targets such as S6K and 4EBP1 in HCC cells[[21](#_ENREF_21), [22](#_ENREF_22)]. A study by Chen *et al*[[7](#_ENREF_7)] has shown that sorafenib-resistant HCC cells, which were established by long-term exposure to sorafenib, had increased expression of phosphorylated Akt and p85, a regulatory subunit of PI3K, compared with the parental cells. Similarly, the HCC cells with ectopic expression of constitutive Akt also showed the resistance to sorafenib. In addition, the resistance to sorafenib could be reversed by gene knockdown of Akt and Akt inhibitor MK-2206. These results indicate that activation of PI3K/Akt pathway may contribute to sorafenib resistance and call for the further study in clinical trials.

***JAK-STAT pathway and sorafenib resistance***

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway participates in the regulation of cell proliferation, differentiation, survival, motility, and apoptosis in many organs including liver[[23](#_ENREF_23), [24](#_ENREF_24)]. STAT3 plays a critical role in transcriptional regulation of genes and is also activated by many cytokines and growth factor receptors such as PDGFR, fibroblast growth factor receptor (FGFR), epidermal growth factor receptor (EGFR) through JAK[[25](#_ENREF_25), [26](#_ENREF_26)]. The negative regulation of STAT3 is mainly executed by suppressor of cytokine signaling (SOCS) proteins through JAK and Src-homology protein tyrosine phosphatases (SHPs) such as SHP-1 and SHP-2, and cytokines and growth factor receptors[[23](#_ENREF_23)]. STAT3 is activated in HCC and knockdown of STAT3 had a therapeutic effect on HCC[[27](#_ENREF_27)]. It has been recently reported that sorafenib inhibited the activity of STAT3, by downregulating the phosphorylation of STAT3 at the tyrosine and serine site (Y705 and S727) through regulating PI3K/Akt pathway and MAPK pathway, respectively, but had no effect on JAK2 and SHP2 expression[[27](#_ENREF_27)]. Sorafenib displayed its inhibitory effect on STAT3 in an SHP-1-dependent manner, but not kinase-dependent inactivation of STAT3[[28](#_ENREF_28)]. Sorafenib could also overcome TRAIL resistance by inhibiting the activation of STAT3 in HCC cells[[29](#_ENREF_29)]. Several studies have also investigated the role of JAK-STAT pathway in the mechanisms of acquired resistance to sorafenib in HCC. Sorafenib-resistant HCC cells express higher levels of p-STAT3, p-JAK1 and p-JAK2, but lower levels of SHP-1 and p-SHP-1, indicating that the JAK-STAT pathway participates in the acquired resistance to sorafenib in HCC[[26](#_ENREF_26)]. Interestingly, dovitinib, another multikinase inhibitor targeting VEGFR, FGFR and c-KIT and regulating the JAK-STAT pathway, could reverse the acquired resistance to sorafenib by directly activating SHP-1, and thus downregulatingp-STAT3[[26](#_ENREF_26)]. Inhibition of SHP-1 or gene knockdown of SHP-1 blocked the effect of dovitinib, indicating that SHP-1-activating agent may provide the second-line treatment after the failure of sorafenib therapy[[30](#_ENREF_30)].

***Hypoxic microenvironment and******sorafenib resistance***

The hypoxic microenvironment is closely related to the resistance to many antitumor drugs[[19](#_ENREF_19)]. We have previously demonstrated that targeting hypoxia-inducible pathways enhanced the antitumor activity of doxorubicin in HCC[[4](#_ENREF_4), [31](#_ENREF_31)]. Although sorafenibdownregulates the synthesis of hypoxia-inducible factor (HIF)-1αin HCC cells *in vitro* and *in vivo*[[32](#_ENREF_32)], the correlation of sorafenib resistance and hypoxic microenvironment is attractive because the anti-angiogenic activity of sorafenib is speculated to lead to tumor starvation and subsequent tumor hypoxia[[33](#_ENREF_33)]. A recent study[[34](#_ENREF_34)] has shown that sorafenib-resistant HCC tissues had higher expression of HIF-1α than sorafenib-sensitive and pre-treated HCC tissues. In xenograft models, the increased hypoxia because of sustained sorafenib therapy was associated with sorafenib sensitivity. Moreover, the EF24, an analogue of curcumin, could synergistically enhance the antitumor effects of sorafenib and overcome sorafenib resistance through inhibiting HIF-1α by sequestering it in cytoplasm and promoting degradation via upregulating VHL.

***EMT and sorafenib resistance***

Epithelial-mesenchymal transition or transformation (EMT) is the transitional phenomenon of epithelial cells to a mesenchymal phenotype which participates in the embryonic development and wound healing, and recently emerged as a pivotal event in the development of the invasive and metastatic potentials of cancer progression including HCC[[35](#_ENREF_35), [36](#_ENREF_36)]. EMT is regulated by the upstream pathway such as PI3K/Akt pathway, MAPK, *etc*[[37](#_ENREF_37)]. Emerging evidence suggests that EMT is involved in, and targeting EMT can reverse, the resistance of antitumor drugs[[38](#_ENREF_38)]. Recently, the role of EMT in the resistance of HCC to sunitinib has been reported[[39](#_ENREF_39)]. A study showed that sorafenib inhibited the HGF-induced EMT in HCC, by downregulating SNAI1 expression via the MAPK signaling pathway[[37](#_ENREF_37)]. The microarray gene expression analysis showed the existence of EMT accompanied by activation of PI3K/Akt and MAPK pathway in sorafenib-resistant HCC cells[[40](#_ENREF_40)]. The above studies indicate that EMT may be involved in the resistance to sorafenib in HCC, but further studies to clarify the specific mechanisms are required.

In addition to the above-described mechanisms, some limited studies have also demonstrated that EGFR[[10](#_ENREF_10)], glucose-regulated protein 78 (GRP78)[[41](#_ENREF_41)], multidrug resistance protein (MDRP) 2[[42](#_ENREF_42)], nuclear factor κB (NF-κB)[[43](#_ENREF_43), [44](#_ENREF_44)] and autophagy[[45](#_ENREF_45)] may be involved in the acquired resistance to sorafenib in HCC.

**STRATEGIES FOR OVERCOMING THE RESISTANCE TO SORAFENIB**Although the exact mechanisms of resistance to sorafenib has not yet been fully elucidated, some approaches have been launched to cope with sorafenib resistance in HCC in clinical trials. The completed and ongoing clinical trials for overcoming sorafenib resistance are summarized in Table 1 and 2, respectively. These trials can be divided into two categories. One is to combine sorafenib with other anticancer drugs, and the other is to use other drugs or drug combinations as second-line treatments in HCC patients after the failure of sorafenib therapy.

***Combinational therapy with sorafenib***

At present, there are dozens of clinical trials ongoing, which are evaluating the therapeutic efficacy of sorafenib in combination with other anticancer agents to treat advanced HCC, according to the database of clinical trials from the United States National Institutes of Health (<http://www.clinicaltrials.gov>). Some completed clinical trials have shown the promising to some extent by combining sorafenib with other agents.

In a phase II trial with 39 advanced HCC patients, sorafenib in combination with 5-fluorouracil infusion showed an encouraging disease control rate with the stable disease (SD) rate of 46.2% for a median duration of 16.2 mo, median TTP of 8 mo, and OS of 13.7 mo[[46](#_ENREF_46)].

Metronomic chemotherapy using tegafur/uracil has been shown to enhance the anti-tumor effect of anti-angiogenic agents in preclinical models. In a phase II study with 53 advanced HCC patients, metronomic chemotherapy with tegafur/uracil was safely combined with sorafenib, and preliminarily showed the improvement of sorafenib efficacy, with median progress-free survival (PFS) of 3.7 mo and median OS of 7.4 mo[[47](#_ENREF_47)].

In a multicenter phase II So.LAR. study with 50 advanced HCC patients, the combinational therapy with sorafenib and long-acting octreotide resulted in SD rate of 66%, median TTP of 7.0 mo, and median OS of 12 mo[[48](#_ENREF_48)]. The results suggest that the combination between sorafenib and long-acting octreotide is active and well tolerated in patients with advanced HCC and could represent another efficacious chance for the management of this population[[48](#_ENREF_48)].

Doxorubicin is considered as one of the most effective cytotoxic agents, and is widely used in the treatment of HCC, especially via transcatheter arterial chemoembolization (TACE)[[4](#_ENREF_4), [49](#_ENREF_49)]. In a phaseIII trial, doxorubicinplussorafenib compared with doxorubicinalone was evaluated in 96 patients with advanced HCC[[50](#_ENREF_50)]. The sorafenibplusdoxorubicin achieved longer median TTP (6.4 mo *vs* 2.8 mo), OS (13.7 mo *vs* 6.5 mo), and PFS (6.0 mo *vs* 2.7 mo) than doxorubicin-placebo monotherapy. The only grade 2/3 adverse event of left ventricular dysfunction was seen in one patient in thesorafenibplusdoxorubicin group. However, because doxorubicin was used as controlled arm in this trial, the encouraging outcome was unable to justify that the efficacy was from sorafenib alone or the synergism with doxorubicin. Now, a randomized phase III trial aiming to evaluate the combinational therapy of doxorubicin plus sorafenib compared with sorafenib alone is recruiting participants (linicalTrials.gov, NCT01840592).

Erlotinib, an oral tyrosine kinase inhibitor of EGFR, has shown a modest antitumor activity against HCC[[51](#_ENREF_51), [52](#_ENREF_52)].To evaluate the effect of sorafenib in combination with erlotinib, a randomized, placebo-controlled, double-blind, phase III study (SEARCH trial, NCT00901901) is being conducted with sorafenib as the controlled arm. However, the preliminary results reported inthe 37th European Society for Medical Oncology (ESMO) Congress[[53](#_ENREF_53), [54](#_ENREF_54)], did not show that the addition of erlotinib to sorafenib met the primary endpoint, and the median OS and TTP was no statistically difference in the experimental and controlled arms.

***Second-line treatments***

Many anticancer drugs, most of which are MTDs, such as VEGFR inhibitors (axitinib and ramucirumab,mTOR inhibitor (everolimusand temsirolimus), EGFR inhibitor (erlotinib) in combination with VEGFR inhibitor (bevacizumab)and GC33, a recombinant humanized antibody against glypican-3are being tested as second-line treatments for advanced HCC in clinical trials (<http://www.clinicaltrials.gov>).

Sunitinib, a multikinase inhibitor targeting the similar receptors to sorafenib, such as VEGFR, PDGFR and RAF, showed a modest antitumor activity in 11 sorafenib-resistant patients with SD in 40% patients, and median TTP of 3.2 mo[[55](#_ENREF_55)]. Undesirably, sunitinib as second-line treatment did not show the antitumor activity in HCC patients with Child-Pugh class B liver cirrhosis because these patients died within 4 mo due to the clinical deterioration of liver function and tumor progression.

Brivanib, a selective dual inhibitor of FGFR and VEGFR, has a shown antitumor activity against HCC[[56](#_ENREF_56)]. A phase II open-label study assessed brivanib as second-line treatment in HCC patients who had failed prior antiangiogenic treatment including sorafenib[[56](#_ENREF_56)]. In 46 enrolled patients, brivanib was administered orally at a dose of 800 mg once daily, and the SD, tumor response rate, and disease control rate was 41.3%, 4.3%, and 45.7%, respectively. The median OS was 9.79 mo. The results show that brivanib may be of safety and efficiency in treating advanced HCC after prior sorafenib therapy. However, a press release in July, 2012 from Bristol-Myers Squibb, the manufacturer of brivanib, revealed that brivanib did not meet the primary endpoint of improving overall survival *vs* placebo in the phase III trial (http://news.bms.com/press-release/).

Recently, a multicentre, randomized, placebo-controlled, double-blind, phase II study (ClinicalTrials.gov, NCT00988741) reported the results of using tivantinib, a selective oral inhibitor of MET, as second-line treatment in sorafenib-resistant HCC[[6](#_ENREF_6)]. Among the 107 enrolled patients, 104 patients had received sorafenib treatment. Seventy-one patients were randomly assigned to receive tivantinib (38 at 360 mg twice-daily and 33 at 240 mg twice-daily), and 36 patients, to receive placebo. At the time of analysis, 46 (65%) patients in the tivantinib group and 26 (72%) of those in the placebo group had progressive disease. After the median follow-up of 5.5 mo, the tivantinib group had a longer TTP than the placebo group (1.6 *vs* 1.4 mo). The 22 (31%) patients with MET-high tumors treated with tivantinib had a median TTP of 2.7 mo, which was significantly longer than that (1.4 mo) for 15 MET-high patients (42%) on placebo. Interestingly, tivantinib at the dose of 240 mg (twice per day) showed slightly longer OS and moderate adverse events compared to the schedule of 360 mg. These results provide an option for second-line treatment of advanced HCC patients, particularly for those with MET-high tumors, after failure of sorafenib, and calling for further phase III trials. The report may also imply that Met might serve as a predictive biomarker in this case.

A drug combination of gemcitabine plus oxaliplatin has shown antitumor activity again HCC[[57](#_ENREF_57), [58](#_ENREF_58)], thus it was used as second-line treatment in HCC patients after sorafenib pretreatment. In a clinical trial with 18 patients after the failure of sorafenib therapy, gemcitabine plus oxaliplatin treatment showed an overall response rate of 18.8%, SD of 18.8 %, PFS of the median 3.2 mo, and OS of 4.7 mo with moderate adverse events[[59](#_ENREF_59)].

Erlotinib plus bevacizumab has shown an apparently synergistic effect with acceptable adverse events as first-line treatment of HCC[[60](#_ENREF_60)]. To evaluate the effects of erlotinib in combination with bevacizumab as second-line therapy after the failure of sorafenib, a phase II trial is ongoing (ClinicalTrials.gov, NCT01180959). However, another similar phase II trial executed during the same period showed disappointing interim results[[61](#_ENREF_61)]. Among the ten recruited patients after first-line sorafenib treatment, no response or stable disease were achieved, and the median TTP and OS was 1.81 mo and 4.37 mo, respectively. The reverse events were common with rash in 70%, diarrhea in 50% and malaise in 40% patients. Thus this trial was halted after the interim analysis[[61](#_ENREF_61)]. The results of the ongoing similar trial are being concerned and expected.

**CONCLUSION**

In summary, the mechanisms accounting for the resistance of HCC to sorafenib are complicated and remain unclear. The primary resistance of HCC to sorafenib is possibly due to the genetic heterogeneity. Seeking predictive biomarkers and therapeutic strategies by combining sorafenib with other anticancer agents have been launched with varying degrees of success. Sorafenib inhibits several kinase targets, but it can also simultaneously or sequentially activate the addiction switches and compensatory pathways, such as PI3K/Akt and JAK-STAT pathways, tumor hypoxia, EMT, *etc*, leading to the acquired resistance. Some other MTDs have been applied as second-line treatment for advanced HCC after the failure of sorafenib therapy, and more are under evaluation in clinical trials. Further investigation on the crosstalk and relationship of associated pathways will better our understanding of the mechanisms, and seeking effective strategies for overcoming sorafenib resistance in HCC.

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**Table 1 Completed clinical trials for overcoming sorafenib resistance**

|  |  |  |  |
| --- | --- | --- | --- |
| **Therapeutic strategies** | **Phases** | **Cases** | **Efficacy** |
| **Combinational therapy**  5-fluorouracilplussorafenib[[46](#_ENREF_46)]  Tegafur/uracilplussorafenib[[47](#_ENREF_47)]  Octreotide plussorafenib[[48](#_ENREF_48)]  Doxorubicinplussorafenib*vs* doxorubicin plus placebo[[50](#_ENREF_50)]  Erlotinib plussorafenib*vs*erlotinib plus placebo[[53](#_ENREF_53), [54](#_ENREF_54)]  **Second-line treatments**  Sunitinib[[55](#_ENREF_55)]  Brivanib[[56](#_ENREF_56)]  Tivantinib*vs* placebo[[6](#_ENREF_6)]  Gemcitabine plus oxaliplatin[[59](#_ENREF_59)]  Erlotinib plus bevacizumab[[61](#_ENREF_61)] | Phase II  Phase II  Phase II (So.LAR.)  PhaseIII  PhaseIII (SEARCH)  Retrospective analysis  Phase II  Phase II  Retrospective analysis  Phase II | 39  53  50  47 *vs* 49  362  11  46  71 *vs* 36  18  10 | SD:46.2%, median TTP:8 mo, OS :13.7 mo  Median PFS:3.7 mo, median OS:7.4 mo  SD:66%, median TTP :7.0 mo, median OS:12 mo  Median TTP：6.4 *vs* 2.8 mo，OS：13.7 vs 6.5 mo, PFS：6.0*vs* 2.7 mo  Median TTP：3.2 *vs* 4.0 mo，OS：9.5 *vs* 8.5 mo  SD:40%, median TTP:3.2 mo  SD: 41.3%, RR: 4.3%, DCR: 45.7%, median OS :9.79 mo  Progressive disease: 65% *vs*72%, TTP: 1.6*vs*1.4 mo  Overall RR:18.8%, SD:18.8 %, median PFS:3.2 mo, OS:4.7 mo  No response or SD, median TTP: 1.81 mo, OS:4.37 mo |

SD: Stable disease; TTP: Time to progression; OS: Overall survival; PFS: Progress-free survival; DCS: Disease control rate; RR: Response rate.

**Table 2 Ongoing clinical trials for overcoming sorafenib resistance**

|  |  |  |  |
| --- | --- | --- | --- |
| **Studies** | **Therapeutic strategies** | **Phases** | **Primary outcomes** |
| **Combinational therapy**  NCT01271504  NCT01033240  NCT01539018  NCT01272557  NCT01015833  NCT01214343  **Second-line treatments**  NCT01507168  NCT01273662  NCT00717756  NCT01545804  NCT01567930  NCT01180959  NCT01140347  NCT01108705  NCT00825955  NCT01035229 | E7050 plus sorafenib *vs* sorafenib  CS-1008plus sorafenib *vs* sorafenib  Tegafur-uracil plus sorafenib *vs* sorafenib  Doxorubicin plus sorafenib *vs* sorafenib  Doxorubicin plus sorafenib *vs* sorafenib  Cisplatin/Fluorouracil plus sorafenib *vs* sorafenib  GC33 vs placebo  Axitinib  Lenalidomide  Lenalidomide  Temsirolimus  Erlotinib Plus Bevacizumab  Ramucirumabplus BSC *vs* placebo plus BSC  Brivanib plus BSC *vs* placebo plus BSC  Brivanib plus BSC *vs* placebo plus BSC  Everolimus plus BSC *vs* placebo plus BSC | Phase II  Phase II  Phase II  Phase II  PhaseIII  PhaseIII  Phase II  Phase II  Phase II  Phase II  Phase II  Phase II  PhaseIII  PhaseIII  PhaseIII  PhaseIII | Adverse Event  TTP  TTP  TTP  OS  OS  PFS  SD  RR  SD  Disease Progression  PFS  PFS  OS  OS  OS |

TTP: Time to progression; OS: Overall survival; SD: Stable disease; PFS: Progress-free survival; RR: Response rate; BSC: Best supportive care.